

## **Executive Summary**

- **The Scottish Genomes Partnership (SGP) is a major Scotland-wide research programme between the Universities of Edinburgh, Glasgow, Dundee and Aberdeen, and NHS Scotland.**
- It is a unique synthesis of academic and clinical research expertise in genomics from across Scotland, to improve clinical practice, diagnosis and treatment and to establish optimum ways in which genome technology can be brought into routine clinical care
- The **overall aims of the SGP programme** are:
  - the sequencing of more than 2500 Scottish genomes to understand more about the causes of rare genetic disease and cancer;
  - the diagnosis of rare genetic diseases in a strategic collaboration with the Genomics England 100,000 Genomes Project;
  - the sharing of genetic and genomic information with parallel national and international genome projects; and
  - the development of expertise and awareness of the impact of whole genome sequencing in Scottish healthcare and society.
- There is a broad sense that in the last year SGP has moved successfully from the setting up and early delivery of projects to full implementation, detailed analysis and in 3 cases publication. With much of the sequencing now complete, the focus is changing from recruitment and sample collection to analysis, clinical interpretation, data federation and data sharing. Sharing outcomes, exploring future research opportunities and maximising use of SGP and other data will be an important part of the next phase.
- **Significant achievements during the last year include:**
  - Submission of data to GeL for the first 309 samples with no sample swaps or data entry errors. GeL has emphasised that this is a major achievement when entering such complex information, and not accomplished by any other centre. It is a reflection of the many systems and processes in place (some new, some existing) to ensure accurate flow of samples from clinic to sequencer. Dr Sandi Deans (Director, UK NEQAS for Molecular Pathology) emphasised our success saying, “the view in England is that the Scottish system is a high quality, good approach – well done!”
  - REC and NHR&D approval for recruitment of Adults with Incapacity to the GeL study is a landmark decision in Scotland. This paves the way for future genetic research studies.
  - A publication from the SGP cancer programme for the McNeish *Squamous Cell Carcinoma* study.
  - Early analyses in the Jackson *Microcephalic dwarfism* study implicating bi-allelic mutations in POLE, the catalytic subunit of polymerase epsilon in IMAGE syndrome and *de novo* mutations in COG4. Publications from this work are anticipated.
  - Establishing a Scottish Variant database which will allow interrogation of Scottish genomic data as a direct comparator with other datasets such as GeL.
- At the second meeting of the Scientific Advisory Board in April 2018, Board members enthusiastically endorsed the programme of work, stating that SGP has “an exceptionally strong team doing cutting edge work and working well as an integrated whole that continues to be an outstanding programme of science”. They also stated that the scale of activity is impressive.

- **The strategic collaboration with the Genomics England 100,000 Genomes Project has made considerable progress with recruitment across all 4 study sites almost complete, sequencing well underway and initial analysis in progress.**
  - In addition to REC approval to recruit adults with incapacity to the study, approved telephone and postal consent processes were put in place and a complete review of documentation and processes has increased participation.
  - Governance approvals are in place to perform analysis of data within Scotland for clinical diagnostic purposes and to pilot a questionnaire for collection of data to support health economic analyses. Health Economics data collection will provide essential evidence for NHS Scotland service development.
  - Recruitment for all of Scotland will close at the end of September 2018, in line with GeL deadlines for completion of the 100,000 Genomes Project and transition to the NHSE Genomic Medicine Service.
  - All processes for transfer of data & results between SGP and GeL are in place and working well. All data entering the analysis pipeline at GeL is complete at the time of submission and of high quality. 522 FASTQs from 201 families have been transferred to GeL for analysis and 100% have met the minimum QC requirements.
  - The NHSS Genetics Clinics, Laboratory leads and Edinburgh Genomics Clinical Division have ensured joint working to develop robust sample handling protocols. Retrospective checks of the first 309 samples from Scottish centres raised no queries which might indicate sample swaps or data entry errors, which GeL emphasised is a major achievement when entering such complex information.
  - Of the 201 Scottish families submitted, a list of tiered variants is available for review by NHSS genetics laboratories for 104 families, with the remainder queued for analysis. No Clinical Interpretation Partner has been allocated yet to the Scottish sites, so all clinical interpretation is currently through the Scottish NHS laboratories.
  - A minimum of 4 families from 36 will receive a diagnostic result from the first batch of analyses. All families from the first batch without a positive diagnostic report will undergo additional interpretation.
  - The project has established joint working between SGP bioinformatics expertise and NHS Scotland clinical scientists. Following a successful joint workshop in December 2017, plans have been developed for local analysis of data for clinical diagnostic purposes. Various processes to support this have been developed, including the transfer of and access to data within the secure project area at the Edinburgh Parallel Computing Centre, identifying families for analysis and the analysis pipeline itself.
- **In the cancer work strand, the SGP is providing comprehensive genomic profiling of clinically important and recalcitrant cancers from Scottish cohorts.**
  - The Glasgow Precision Oncology Laboratory has worked closely with the Glasgow Biorepository and Molecular Genetics Laboratory at NHS Greater Glasgow & Clyde to maximise the success of DNA extractions, leading to complete cancer genome profiles from FFPE samples.
  - Further work is being undertaken to optimise the pan-cancer bioinformatics platform developed through SGP, with the aim of characterising tumour samples for clinical and clinical trial use.
  - One study is complete and published (Cooke *et al* Clinical Cancer Research 34:7633-40). This found that mutation profiles for mature cystic teratoma (MCT)-associated squamous

cell carcinoma (SCC) of the ovary are similar to SCC found in other organs, indicating the possibility of similar treatments.

- The six remaining studies include retrospective pancreatic, oesophageal and ovarian cancer samples, with all remaining sequencing nearing completion. Genomic profiling of glioblastoma for a new phase 1 clinical trial cohort is also underway.
- Whole genome sequencing and analysis of tumour-normal pairs are well underway for the AstraZeneca ovarian cancer collaboration.
- **SGP Rare Disease academic studies are building on Scotland’s outstanding academic track record in gene identification and functional analysis of single gene human disorders.**
  - Six studies are underway, seeking new information about unknown molecular influences on motor neurone disease, eye malformation, microcephalic dwarfism, disorders of sexual development, primary ciliary disorders and nervous and immunological systems.
  - One study is piloting rapid whole genome sequencing in Scottish Neonatal Intensive Care Units as a collaboration between academic research and NHS Scotland.
  - A total of 689 whole genomes have been sequenced through Edinburgh Genomics Clinical Division for these studies, with extremely high quality data produced.
  - The first 2 publications from these studies have been submitted for publication.
- **An SGP population cohort study – the Shetland based Viking Health Study – is providing a different approach to understanding how the genome influences health and disease.**
  - Whole genome sequencing has been completed by Edinburgh Genomics Clinical Division for 500 participants and analysis of these data is underway with linkage to NHS health records.
  - As would be expected for a genetic isolate cohort, there is an enrichment in rare and very rare variants; preliminary results show a higher number of ultra-rare variants than would be expected.
- **Data sharing has been established as a central principle of SGP, to make best use of resources and expertise.**
  - All SGP’s bioinformatics work is underpinned by a commitment to common, optimal informatics solutions for genomics, with standardised data formats and analysis pipelines.
  - A Scottish genomic variant repository has been established through SGP. This provides decisive information for making sense of genomic data, will underpin future genomic interpretation in clinical and academic environments, and allows researchers to run the same query easily across different databases which run the same API.
  - All SGP data are being lodged into the European Genome-phenome Archive (EGA) under their controlled access framework to ensure that data is available for further research in line with the consent and ethical approvals for each sample set.
- **Translating research into practice is a key aim of the SGP, and much progress has already been made with this.**
  - The placement of SGP within world class centres for rare diseases, cancer and population genomics, working closely with clinical colleagues, has led to strong integration. New joint working practices are a clear strength emerging from SGP.

- SGP activities are shaping the policy direction for genetics in NHSS. Key milestones have been the SGP submission to the House of Commons Science & Technology Committee Inquiry on Genomics; the visit to Edinburgh Genomics by the Cabinet Secretary for Health and Sport; front page coverage in *The Scotsman* about genomics as a vital part of future NHS transformation; and significant contributions to the Government-commissioned Scottish Science Advisory Council (SSAC) review of Genomic Medicine.
- **Future plans are being configured for sustainable funding that builds on the SGP progress.**
  - The NHS across the UK is considering how to make the most of genomics for healthcare.
  - The NHS Scottish Diagnostic Steering Group and the Scottish Government Rare Disease Implementation Oversight Group are both monitoring SGP progress to consider how the outputs may be used to develop NHSS services.
  - The next phase of the International Cancer Genome Consortium (ICGC), known as the ARGO project, is being led from Scotland by SGP's Biankin, placing Scotland at the centre of the development of a unified strategy for managing and sharing cancer genomics research data.
  - New research funding proposals are being shaped with a view to using genomics to make further advances in understanding the molecular basis of cancer and rare diseases.