Informing the Future of Genomic Medicine in Scotland
Scottish Science Advisory Council Report  
Informing the Future of Genomic Medicine in Scotland

Table of Contents

Chapter 1  General Introduction and Recommendations ..........................................................2

Chapter 2  Introduction to Genomic Medicine ........................................................................4

Chapter 3  Structure and organisation of Genomic Medicine in Scotland ................................ 8

Chapter 4  Rare Genetic Diseases, Congenital Abnormalities and Prenatal testing ....................15

Chapter 5  Cancer ..................................................................................................................19

Chapter 6  Pharmacogenetics ..................................................................................................23

Chapter 7  Data storage and Bioinformatics ............................................................................25

Chapter 8  Workforce planning, Education and Training............................................................28

Chapter 9  Patients at the Centre: Involvement and Engagement ............................................31

Chapter 10  Industry-facing activity ......................................................................................33

Annex 1  Recommended Actions ..........................................................................................36

Annex 2  International Perspective .........................................................................................41

Annex 3  Expert Contributions ..............................................................................................42
CHAPTER 1 – General Introduction and Recommendations

The Scottish Science Advisory Council (SSAC) was asked by the Scottish Government’s Chief Scientist Office to review the development of Genomic Medicine in Scotland in order to support long-term planning and investment in this fast-evolving area of healthcare.

This report, “Informing the Future of Genomic Medicine in Scotland” focuses on implementation of genomic technology in the clinic, beginning with rare diseases and cancer, and then extending to other commoner diseases affecting our society which will guide medicine prescribing (pharmacogenomics). The platform for Genomic Medicine requires investment to maximise these opportunities and benefits.

In summary, this report:
- provides an overview of the current Genomic Medicine capabilities in Scotland;
- compares developments elsewhere in the UK and internationally;
- summarises opportunities and benefits for the NHS, research and life sciences sectors in Scotland; and
- recommends where action and investment are needed to realise this potential.

The report has been developed alongside the broader Science & Innovation Audit: Precision Medicine Innovation in Scotland: Accelerating Productivity Growth for Scotland and the UK, due to be published in 2019 by the UK Department for Business, Energy and Industrial Strategy. The two documents are complementary in recognising the many strengths and capabilities of Scotland in supporting rapid advances in healthcare, improved patient outcomes and driving sustainable economic growth. With many of the foundations now in place, additional investment in the areas highlighted in this report will enable scientists and clinicians in Scotland to play a bold and innovative role in the vanguard of Genomic Medicine, realising its full potential for the health of the Scottish people as an integral part of Precision Medicine, and making the most of future innovation and economic growth opportunities.

The Recommendations have been drawn from across the report and focus on six core areas of Leadership, Clinical Implementation, Workforce, Digital Health, Research and Innovation, and Industry-Facing activity; together they provide suggested next steps to shape the future direction of Genomic Medicine in Scotland. Proposed actions in support of the Recommendations are provided in Annex 1. An international perspective on genome projects and government investments in other countries in Europe, Asia and North America is given in Annex 2.

The content and recommendations for this report have been developed by a group of experts from across Scotland spanning NHS clinics, NHS laboratories, NHS commissioning, academic research and industry representatives. All contributors are listed in Annex 3 and we thank them all for their expert knowledge and the significant time they have given to the writing group.
Recommendations

1. Leadership
The Scottish Government should convene a Scotland-wide Leadership Group to advise how best to support the development of Genomic Medicine in Scotland; challenge barriers to progress; maximise impact for the benefit of healthcare, research and life sciences in Scotland; engage and involve the public; and increase Scotland’s influence at UK and international levels, positioning Scotland as a world leader in genomics in the wider context of Precision Medicine.

2. Clinical Implementation
With Scottish Government support, NHS Scotland should expedite the evaluation and adoption of genomic testing strategies into clinical pathways where there is good evidence that these lead to improved patient outcomes. Clinical applications are evolving rapidly with incorporation of genomics into routine care closest for rare disease diagnosis, followed by patient stratification for targeted cancer therapy, followed by safer and more effective prescribing. The Scottish Government should also enable NHS Scotland to remain agile regarding latest genomic tool developments; to test, validate and contribute to the creation and implementation of international best practice in clinical governance of medical genomics; engaging with appropriate regulatory bodies at UK and international level. Failure to support best practice genomic capabilities in NHS Scotland will deprive Scottish patients of the benefits this cutting edge technology can provide and lead to Scotland lagging behind the rest of the UK and other high income countries.

3. Workforce
NHS Scotland, working with NHS Education for Scotland, ScotGEN, Skills Development Scotland and academic institutions should lead in co-ordinating the development and delivery of the training courses and educational resources required to develop essential expertise to support and drive world-class Genomic Medicine capabilities in NHS Scotland. Investment will be required in training, recruitment and retention of laboratory, clinical and clinical academic staff, in different specialisms and at a range of levels.

4. Digital Health
When delivering on its Digital Health and Social Care Strategy, the Scottish Government should take full account of the digital infrastructure needed to enable genomics within clinical pathways and to support the use of genomic data for research and innovation. This infrastructure includes: digital skills, supercomputing hardware, high capacity connected networks, and systems for data management and security.

5. Research and Innovation
The Scottish Government, working with research funders, industry, enterprise agencies and higher education providers, should consider how best to support genomic research and innovation in Scotland, including patient and public involvement and engagement, and maximise the opportunities for inward investment, building on Scotland’s current position of excellence.

6. Industry-Facing Activity
The Scottish Government, working with enterprise agencies, should build on the strengths of Scotland’s “triple helix partnership” between academia, the NHS and industry and consider how best to position assets across Scotland to maximise future engagement and partnership opportunities which will accelerate genomics development as an integral part of Precision Medicine.
CHAPTER 2 – Introduction to Genomic Medicine

Chapter 2 Summary
This chapter provides background information on genomics, the technologies being used in genomic research and how these are already making a significant impact on healthcare. The decision by many Governments globally to invest in Genomic Medicine is due to the prospects for more precise, individually targeted healthcare strategies. Scotland has begun to invest through the Scottish Genomes Partnership, leading to opportunities to improve diagnosis and management of rare diseases and transform models of cancer care. Data innovation and integration must be integral to efforts going forward. Scotland has an exceptional opportunity to take advantage of its strengths in genome technology alongside excellent electronic health records, to ensure that its state-of-the-art genome sequencing facilities are put to best use and integrated with strengths in data innovation to underpin the development of Genomic Medicine in Scotland and beyond. This will require Government support, significant investment and effective long-term planning to keep pace with developments elsewhere in the UK and to take advantage of global opportunities for healthcare, research and the life sciences sectors.

Genomics is the study of the complete genetic material, or instruction book, of an individual. Genomic Medicine can be defined as the use of genome technology and information in healthcare and related research and innovation. It seeks to understand genes, their interactions and the consequences of genetic variations to provide new methods for disease diagnosis and targeted treatment. It is a vital component of the broader aspirations of Precision Medicine (providing the right treatment for the right person at the right time by tailoring to individual characteristics¹).

The first two decades of the 21st century have seen a revolution in genome technology and information. A project to decode the first human genome, which was completed in 2001, was a worldwide 15-year project costing more than £2 billion. We can now decode – or sequence – an entire human genome in a few days. The core cost of sequencing is around £800 per genome and expected to fall in the next 2-3 years. Analysis of genome data, clinical interpretation and data storage are an additional cost, with leading edge work still happening mainly in a research setting, but translation into clinical practice is an important driver for this. The one million-fold reduction in sequencing costs and one thousand-fold increase in the speed of genome sequencing, epitomised by the term "Next-Generation Sequencing" (NGS) (Box 1) is already revolutionising healthcare. Genome-based technology is used across all healthcare specialties, across most fields of health-related research, and is key to industry-led research and innovation in biomedicine and biotechnology. It therefore has enormous reach for effective delivery of healthcare, research, innovation and economic development.

NGS can contribute to healthcare in many ways. In rare diseases caused by a glitch in a single gene, genome sequencing can pinpoint the exact molecular change underlying the disease. In common diseases usually caused by an interplay of genetic variation and the environment, genome sequencing can identify the instances where the disease is caused by an abnormality in a single gene. When a precise molecular diagnosis is made in this way, it means that further investigations into the cause of the disease are unnecessary, that closely related family members can be easily screened for the same genetic abnormality, and that accurate advice can be given about the risk of recurrence in other family members or future pregnancies. One of the major diagnostic impacts of genomics is the identification of de novo variants which are by definition those caused by an error in the DNA replication process rather than inherited from the parents. A diagnosis also means that the prognosis

of affected individuals can be clearer and a more effective management plan can be put in place. Additionally, in a small but growing proportion of cases, specific therapies can be initiated to relieve symptoms or prevent disease progression. Pilot programmes in partnership with the NHS, such as that undertaken by the Scottish Genomes Partnership (see below) are delivering genomic sequences for patients, enabling them to access innovative clinical trials.

Box 1. Next-Generation Sequencing (NGS)

Next-generation sequencing permits the reading of single genes, panels of genes, component parts of the genome, or the whole genome, in large numbers of patients or healthy subjects, in hours or days, at affordable cost.

- **Single genes or gene panels.** Useful in patients where clinicians believe their disease is caused by a single gene or a panel of small or large numbers (2-250) of genes. Cost: £100-£500
- **Whole exome sequencing (WES).** The protein-coding part of the genome - the exome - is the commonest component part of the genome to be sequenced and makes up around 2% of the entire genome. Cost: £200-£800
- **Whole genome sequencing (WGS).** This is the most comprehensive method of screening large numbers of genes for all types of abnormalities. These include changes in single “letters” of the genome; insertions and deletions; and structural variations including changes in the number of copies of a gene or a re-arrangement of chromosomes. Cost: £750-£1500
- **Clinically actionable genomes.** A targeted genomic assay which screens for complex genomic changes known to be prognostic, predictive or diagnostic in cancer, where alterations to the genome are several orders of magnitude more complex. It is more specific and faster than WGS, and data can be stored more cost-effectively, making it ideal in a cancer diagnostic setting. Cost: £200-300

NGS is seen as one of the major opportunities for advances in healthcare and wealth generation in Scotland’s Ecosystem for Precision Medicine. The quoted costs vary by provider and by additional services provided with the core sequence.

Genome sequencing has also had a major impact on cancer diagnosis and management, and is playing an increasingly central role in cancer prevention and treatment. Inherited genetic variation can be detected by sequencing the "constitutional" or germline genome - the genes that we inherit from our parents. But cancer develops through changes or "mutations" that occur in the genomes of the cells and tissues of our body - somatic mutations. These alterations determine, to a large extent, how the cancer grows and behaves, including its response to treatment. By sequencing the cancer genome – the genome of the tumour – scientists can identify the genetic changes that have led to the development of that person's tumour. Our recent understanding of the molecular diversity that underlies tumours that look the same but behave differently is challenging traditional models of cancer care. This complexity provides explanations for why systemic therapies provide effective treatment for only a small proportion of patients with disseminated cancer. Predicting which patients will benefit ahead of time, using information from an individual’s cancer genome to improve overall outcomes and minimise toxicity and cost, is the clear path forward. To achieve these goals, health systems need to evolve from their current state, to a more personalised model of cancer care with targeted therapies, driven by more precise and genome-driven research and diagnostics. This is a central tenet of Precision Medicine.

Medical genomics programmes are underway in several countries, with more than 20 countries having programmes that plan to sequence the genomes of 100,000 subjects (Ginsburg, Keystone Million Genomes meeting, Hannover, June 2018; see also summaries of international activities at
Annex 3). Genomics England was established in 2013 with the 100,000 Genomes Project to sequence and analyse 100,000 whole genomes for rare diseases and cancer patients within NHS England.

By December 2018, following an investment of more than £550m, the project had reached its 100,000 target with all sequencing expected to be complete early in 2019. Genomics England is now working to embed genome technology into the English NHS: the 2016 Annual report of the Chief Medical Officer in England “Generation Genome” made clear recommendations for modern state-of-the-art healthcare delivery and a new Genomic Medicine service was launched for NHS England in 2019. Thirteen EU member states, including the UK, recently signed a declaration of cooperation towards shared access to at least a million genomes by 2022, to facilitate advances in research and healthcare. Support for Genomic Medicine enables Precision Medicine in the NHS as genomic analyses can begin to happen synergistically with other technologies such as proteomics (the large-scale study of sets of proteins) and digitisation of data and imaging.

Genomic Medicine in Scotland

Scottish physicians and scientists have made world-leading research contributions in rare disease and cancer genomics in the past three decades and there is a well-established network of clinicians and clinical scientists working with NHS Scotland (NHSS) who have been delivering Genomic Medicine since at least 2013.

In 2015/16, the Scottish Genomes Partnership was established, from a £15 million investment by the Universities of Edinburgh and Glasgow, and a £6 million joint investment by the Scottish Government Health Directorate and UK Medical Research Council. This generated infrastructure for establishing Genomic Medicine in Scotland, has permitted the sequencing of over 12,000 whole genomes for a range of health-related and scientific cohorts at two centres of excellence for genomic sequencing (Edinburgh Genomics and the Glasgow Precision Oncology Laboratory), has attracted more than £20 million of additional funds from industry and other sources, and enabled the integration of genomic testing in cancer clinical trials and some aspects of cancer care. A primary aim of the Scottish Genomes Partnership is the improvement of national health, through disease prevention, precise diagnosis and rational targeted therapies, focussing predominantly, at the present time, on rare diseases and cancer. The University investment in sequencing technology was highlighted at the JP Morgan Investors Conference in January 2015 as putting Scotland amongst the first 20 research centres worldwide to install world-leading whole genome sequencing (WGS) equipment.

Scottish researchers have also played a pre-eminent role in "big data" curation and analysis through the Farr and Usher institutes. Alongside this we have enviable informatics facilities and research skills which are being further developed through investment in data innovation by UK and Scottish Governments as part of the Edinburgh and South East city region deal. Scotland’s world class electronic health records are recognised as a unique resource for health research, presenting significant opportunities for research and clinical care if integrated effectively with genomic data. These records are defined by the Community Health Index (CHI) number which unifies health events and records for Scottish patients back to the 1970s (including all primary and secondary healthcare visits, drug prescriptions, International Classification of Diseases (ICD) codes, digitised radiology, and birth, death and cancer registrations).

Improving Rare Disease Diagnostics

Scotland has played a leading role in UK and international programmes for diagnosing rare disease, such as the pioneering work of the UK10K and Deciphering Developmental Disorders (DDD) studies. The UK10K project began in 2010 and studied the genetic code of 10,000 people to explore rare

variants in different types of disease. The DDD study began in 2011 collecting DNA and clinical information from more than 4,000 families in the UK – including more than 1,000 from Scotland. These families have at least one child affected by a severe developmental disorder that was undiagnosed using existing diagnostic testing. The DDD study has identified more than 30 new genes for developmental disorders and has now studied more than 13,000 families with these conditions.

In a collaboration with Genomics England, the Scottish Genomes Partnership had sequenced 1,000 genomes of Scottish NHS patients with a rare disease and their relatives by December 2018. Genomics England anticipates that a disease-causing genomic change will be identified in 35-40% of patients. A better patient experience, improved care for patients and their families, and potential cost savings are anticipated through increased availability of precise, rapid molecular diagnoses, reducing the often prolonged need for invasive and expensive clinical investigations, and providing accurate reproductive counselling and pre-symptomatic diagnosis to reduce the risk of familial disease recurrence.

Transforming Models of Cancer Care
Scottish physicians and scientists have made world-leading research contributions in leadership of international cancer programmes such as the International Cancer Genomes Consortium and in clinical trials with industry that stand to benefit patients as well as growing the Scottish economy. The ICGC Secretariat was based at the Ontario Institute of Cancer Research in Toronto from its inception until May 2018, when its base of operations moved to the University of Glasgow under the leadership of its new Executive Director and Chairman, Professor Andrew Biankin. Today Scotland is ideally positioned to use Genomic Medicine to improve the specificity of cancer care through national efforts such as Scotland’s Ecosystem for Precision Medicine, of which the Scottish Genomes Partnership is a key pillar; these provide the research excellence required to enable this new model of healthcare. The SGP studies have developed some of the most advanced cancer assays and associated analysis platforms in the world. The clinically actionable genomes developed through new targeted analysis pipelines will be used for future cancer clinical trials and can facilitate rapid turnaround genomic screening for cancer. This is different to the whole genome approach trialled by Genomics England, but increasing numbers of scientists and oncologists both in the UK and internationally are reaching the conclusion that targeted sequencing panels are a better choice for the foreseeable future, for both the patient and the NHS. Scotland has the opportunity to move to Real World Therapeutic Testing, where treatment response and other important data for the >95% of patients that are not in clinical trials will inform and improve healthcare strategies.

Opportunities Provided by Digital Health in Scotland
As highlighted by the External Expert Panel on Digital Health and Care in Scotland³, the opportunities for research and care improvement through better use of data are huge. Efforts include the NHSS “Safe Havens” for secure and approved data usage. The availability of innovative medicines will build value for the health system, attract significant industry investment and drive the health service to the ultimate goal of a “Self-learning Health System”, where robust data acquired through routine care and use of innovative medicines inform future treatment decisions. Due to the modest size of Scotland, it should be possible to combine routine healthcare information as well as genetic and genomic data to obtain relatively complete data for the entire Scottish population, to take forward a data driven approach to public health that is unlikely to have been attempted at a national scale elsewhere internationally.

Chapter 3 Summary

This chapter summarises the structure of Genomic Medicine in NHS Scotland, how the different elements operate within NHSS and how NHSS benefits from working closely with world-leading Scottish research programmes and industry to translate cutting-edge developments into clinical care. Scotland has excellent academic-NHSS partnerships and the Scottish Genomes Partnership has supported further collaboration between healthcare and biomedical research. Genomic Medicine is evolving rapidly with an extraordinary increase in NHSS testing in recent years alongside modest budgetary increases. This pattern is not sustainable and a clear forward strategy with appropriate significant investment is now required to ensure that Scottish Genomic Medicine can continue to play a significant role in the rapidly evolving landscape in the UK and elsewhere. Health economics data will be vital to help guide investment decisions.

Within the NHS, the two areas using Genomic Medicine most intensively are Clinical Genetics and Cancer services including wider Pathology and Oncology. However, other mainstream specialties, including Neonatology, Paediatrics, Neurology, Cardiology, Ophthalmology and Nephrology, rely increasingly on genome-based testing to identify single-gene causes of common diseases such as epilepsy, immunodeficiency, neurodegenerative disease, cardiomyopathy, aortopathy, retinal dystrophy and cystic kidney disease.

Clinical Genetics and Molecular Pathology NHSS Services

NHSS genetics services are delivered through 4 regional genetics centres in Aberdeen, Dundee, Edinburgh and Glasgow. Each offers a closely integrated laboratory and clinical service. Clinical services are funded by host health boards and the 4 centres work closely together through the Scottish Clinical Genetics Forum.

National Services Division (NSD), a division within NHS National Services Scotland (NSS), commissions Genetics and Molecular Pathology laboratory services nationally through a consortium arrangement. National commissioning is reserved for those very specialist services where local or even regional commissioning is not appropriate. It ensures equity of access, the best possible clinical outcomes and avoids unnecessary duplication of services. The Molecular Genetics Consortium is concerned with the diagnosis of inherited and rare diseases, while the Molecular Pathology Consortium investigates molecular markers or their surrogates for malignant tumours (cancer). These consortia provide a forum for clinicians, scientists and commissioners to identify, evaluate and implement the most clinically- and cost-effective approaches to genetic testing consistently across Scotland, taking advantage of national expertise and developing clinical management pathways that serve across specialties.

Genetics and Molecular Pathology services are evolving rapidly, with workload increasing each year alongside significant advances in the range of possible tests. Common core tests are delivered in each laboratory while specialised testing is distributed across Scotland or requested from recognised specialist centres in England, Wales and Northern Ireland. Scottish laboratories specialising in specific tests also receive test requests from centres across the UK. Testing of main cancer types is provided by all 4 molecular pathology laboratories. Molecular Pathology growth is being driven by approvals of companion diagnostics – biomarkers that guide decision-making for prescription of appropriate drug therapies.
Governance Structure of the Consortia
A 2016 review of the Nationally Designated Genetic Laboratory Testing Services recommended a revised governance structure including the establishment of a National Genetics Laboratory Management Committee (GLMC) and the appointment of 3 national leads for Clinical Genetics, Laboratory Science and Molecular Pathology to drive forward strategic development of genetic services within NHSS Board priorities. The GLMC ensures coherent development and delivery of high quality genetic and genomic diagnostic services based on proven clinical utility. It leads strategic planning and decision-making across the 4 regional centres within the strategic direction of the Health and Social Care Delivery Plan and the National Clinical Strategy.

Cost of Service/Funding
The Genetics and Molecular Pathology consortia have delivered an extraordinary increase in testing volume and complexity in the last 5 years with only small increases in staffing budgets. The total NHSS expenditure on genetic laboratory testing (molecular, cytogenetic and molecular pathology) including testing obtained from outside Scotland was £16.6 million in 2017/18, an increase of 7% on the previous year (Figure 1). In addition a rolling capital budget of £300,000 has been provided to the consortia to allow replacement equipment to ensure sustainability of the service. A more detailed appraisal of costs and testing rates is provided in the NHSS National Services Division Review of Genetic Laboratory Testing Services (February 2017).

Figure 1. Total costs by Board
(Includes staff, overhead costs, consumables and capital charges)

Joint NHSS working across clinical disciplines
A key strength in NHSS has been the development of joint approaches to patient care for downstream follow-up of patients after a genetic test result. The NHS Greater Glasgow & Clyde Ophthalmology Genetics pathway is an excellent example of joint working practices. This shared “holistic” management approach between Genetics and Ophthalmology has improved access to treatments and clinical trials (Figure 2).

NHSS collaboration with academia and industry
Alongside NHSS services, experts in universities and industry are playing a vital role in developing and delivering Genomic Medicine in Scotland. Figure 3 provides a summary of key contributors who have been integral to this, and shows the importance of joint working to bring new research developments into the clinical care setting. It is this close collaborative approach which has underpinned the excellent progress made in Scottish Genomic Medicine over the last decade.
World-leading research

The Medical Research Council Human Genetics Unit (HGU) at the University of Edinburgh. This is the major current MRC UK investment in human genetics and genomics (£53M) with Principal Investigators who have been developing genomic approaches to diagnose and understand ultra-rare disease in a clinical setting.

The Deciphering Developmental Disorders (DDD) study. The DDD study established a network of skilled clinicians, bioinformaticians and research scientists throughout Scotland focussed on the diagnosis and molecular understanding of severe and extreme developmental disorders. Innovative analytical approaches to trio-based whole exome sequencing in this study were derived from a bioinformatics research pipeline developed in Scotland (FitzPatrick; MRC Human Genetics Unit), leading to a definitive diagnosis in >40% of families, including the identification of 14 previously unreported developmental disorders.

The Scottish Genomes Partnership (SGP). This flagship Scotland-wide programme developed with government support4 is a close working partnership between Universities of Edinburgh, Glasgow, Dundee, Aberdeen and the NHSS genetics services and laboratories. A recognised strength has been the emergence of a strong interdisciplinary genomics team across research and NHSS, bringing together NHSS genetics with University genome sequencing facilities, experts in data storage/supercomputing, bioinformatics, genome interpretation and health economics. A key benefit of joint working is that quality assurance is seamless across the entire pathway from clinic through NHSS laboratories and onwards to academic sequencing centres; this is evidenced in recent quality feedback from Genomics England and UK NEQAS (National External Quality Assessment Services) where there were no queries, sample swaps or data entry errors. SGP has spawned an important collaboration between NHSS and the Genomics England 100,000 Genomes Project. The partnership also includes vital academic research to find new genes in rare and common diseases, alongside pioneering sequencing and analysis for clinically important and recalcitrant cancers.

The Stratified Medicine Scotland Innovation Centre (SMS-IC). Established in 2013, this national collaboration is developing Scotland’s Ecosystem for Precision Medicine, bringing together NHS Scotland, the Universities of Glasgow, Edinburgh, Dundee and Aberdeen with industrial partners such as ThermoFisher and Aridhia.

Significant exemplar projects include NSS / Public Health Intelligence which aims to enable longitudinal ‘deep phenotyping’ from electronic patient records, including Scotland-wide prescribing, imaging and hospitalisation data; the UK Precision Panc project which aims to speed up scientific discovery in order to improve the survival rates of patients with pancreatic cancer; and the Scottish Molecular Ovarian cancer collaboration with AstraZeneca and SGP to determine the clinical consequences of ovarian cancer molecular subgroups.
Future Challenges
The NHSS NSS-NSD review of the Nationally Designated Genetic Laboratory Testing Services (Feb 2017) highlighted the following strategic development requirements:

- Continued development of NGS panels.
- Development of targeted sequencing using the clinical exome.
- Introduction of trio-based whole exome sequencing for diagnosis of developmental delay.
- Evaluation of WGS in patient care.
- Implementation of NGS techniques for molecular pathology of acquired disease and primarily the areas of cancer diagnosis, predictive and prognostic testing.

Workforce development
The continued evolution of genetic and genome-based testing, including increased mainstreaming, has highlighted the need for specific workforce and infrastructure development both within NHSS and academic career pathways. These are discussed in detail in Chapter 8.
Wider UK NHS service changes

NHSS should offer NGS tests in line with best practice and agreed clinical priorities. Provision of tests should be guided by the rapidly evolving research landscape, NHS genetics and genomics services across the UK and recent service reviews in Scotland. Forward-planning activities are exploring how to adapt Scotland’s services within this landscape. One example is the current reconfiguration of NHS England laboratory testing services and the dissolution of the UK Genetics Testing Network (UKGTN) following the publication of the ‘Generation Genome’ report in 2016. Scotland has a single national commissioner for Genomic Medicine through NSD, which is a clear advantage when responding to these types of change. A Devolved Nations Working Group has been established with representation from NSD and the Scottish Molecular Genetics and Molecular Pathology consortia, to support dialogue and forward planning.

Economic evidence base

The focus to date has been on biomedical and clinical advances in Genomic Medicine, with almost none on economics. Health economics is important in guiding decisions about adoption of new tests and clinical pathways into the NHS and therefore there is a pressing need to establish the evidence base around costs and benefits for Genomic Medicine. While there is potential for genomics to lower overall costs to the health system by providing faster diagnosis and avoiding unnecessary or ineffective treatments, this is not proven.

Standard and value-based health economic models should be used to compare efficacy, cost-effectiveness and patient perspectives. The Health Economics Research Centre at the University of Oxford has concluded that there has been limited work to date in this area. A very recent systematic literature review of health economic evidence for WES and WGS suggests that full costs of WGS (including sequencing, analysis, clinical interpretation and clinical reporting) may be anything from £1,312 to £17,243. However, the quality of the costing exercises varied considerably with small sample sizes, modelling (rather than real-world costs), variation across clinical areas, and a lack of clarity about the costs included. It is clear that the methodology to conduct suitable health economic evaluations is underdeveloped and research is needed to develop this. The Scottish Government core-funded Health Economics Research Unit (HERU) at the University of Aberdeen and The Health Economics and Health Technology Assessment (HEHTA) Research Group at the University of Glasgow are both working on research which will directly contribute to the economics evidence base.

HERU has pioneered the development and application of valuation methods beyond clinical outcomes which are necessary to assess the full range of benefits from Genomic Medicine and relevant to the Scottish Chief Medical Officer’s commitment to Realistic Medicine. Examples of benefits beyond clinical outcomes include:

- the value of a diagnosis even without treatment options;
- avoidance of ineffective treatments; and
- removal of uncertainty about genetic risk factors and clarity for future family planning.

Costing is also required for other genetic conditions such as cancer treatment. For example, rolling out a cancer genomic profiling platform and analysis pipeline for all cancer patients could help avoid unnecessary treatments. Given the side effects of many cancer treatments there is potential to reduce costs further, for both NHSS and social care, through reduction of morbidity due to ineffective but aggressive treatments.

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5 https://www.herc.ox.ac.uk/downloads/herc-database-of-health-economics-and-genomics-studies
6 https://www.nature.com/articles/gim2017247
Financial
A major barrier to implementing the positive outcomes from genomics research into routine clinical care is the investment required alongside the growing costs of maintaining the current service provision. The NHSS genetics service has not seen significant investment for development since the Calman review in 2008. In contrast, as highlighted in Chapter 2 and Annex 3, the Department of Health and NHS England invested >£350 million in the Genomics England 100,000 Genomes Project and further undisclosed investment will underpin the development of a new Genomic Medicine Service in England from 2019. In 2017, NHS Wales committed investment of £6.8 million for a Precision Medicine Strategy, with Genomic Medicine forming a key part.

So far the increases in service costs in Scotland have been managed through service redesign, maximising use of automation and the implementation of NGS for gene panel testing, but this is not sustainable. Realising the longer term benefits of Genomic Medicine for Scottish patients requires strategic investment now in both research and NHSS genetics / genomics services. The immediate challenges include NHSS IT infrastructure, data storage, data sharing, workforce development and succession planning as highlighted in subsequent chapters of this report. An announcement from the Scottish Government in September 2018 of £4.2m over 2 years has been welcomed as a starting point to address these challenges, but a longer term strategic vision with the necessary financial commitment to deliver it is now required urgently. Only through strategic development with parallel underpinning investment will NHSS be able to ensure that its future standards of care for inherited diseases and cancer are equitable when compared with the rest of the UK, as well healthcare systems across Europe and internationally. Links between the NHSS Genetics services, the SMS-IC and the SGP genome sequencing laboratories should be strengthened as part of this, to provide economies of scale, for example for exome and genome sequencing, and increase the speed and frequency of genetic diagnosis for patients in Scotland.
Chapter 4 Summary
This chapter covers the impact of Rare Diseases and Congenital Abnormalities in the Scottish population and sets priorities for improving diagnosis. NGS is already having a significant diagnostic impact in NHSS with greater clinical effectiveness than traditional gene tests. NHSE is now establishing a Genomic Medicine Service to offer a range of genetic tests to patients including the analysis of WGS as part of routine care. More evidence is still required to inform the most appropriate use of different genetic tests (panels, exomes, genomes) in NHSS services. NHSS Boards should be supported to adopt best practice from Genomics and Precision Medicine research, and encouraged to push the boundaries and increase diagnostic yield from NGS tests.

The Impact of Rare Diseases in Scotland
The Scottish Government’s Implementation Plan for Rare Diseases in Scotland, “It’s Not Rare to Have a Rare Disease” highlights that up to 300,000 people in Scotland may be affected by a rare disease at some point in their lives. The recognition that a baby or young child has severe intellectual disability and / or other disorders of development has life changing and life-long impact for a family. Parents typically ask health professionals:

“Why did this happen?”
“Will it happen again if I have another child?”
“How will the condition affect my child through their life?”
“Is there any treatment?”

An accurate answer to these questions requires a precise genetic diagnosis. Without this, families face a long and traumatic sequence of investigations and referrals over many years – the so-called ‘diagnostic odyssey’ – with multi-disciplinary clinical teams making iterative suggestions of new possible diagnoses which require further tests and which may or may not lead to answers about their condition.

A rare disease is defined as one that affects less than 5 in 10,000 of the general population.
7% of the population (1 in 17) will be affected by a rare disease at some point in their lives.
80% of rare diseases have a genetic component.
75% of rare diseases affect children.
Often rare diseases are chronic and life-threatening.

They include rare cancers such as childhood cancers and some other well-known conditions, such as cystic fibrosis and Huntington’s disease.

Source: Rare Disease UK website

Congenital Abnormalities in Scotland
Congenital anomalies can be defined as structural or functional anomalies, or conditions which can affect metabolism, which occur during the pregnancy and can be identified either during the pregnancy, at birth or later in life. They are also known as birth defects, congenital disorders or congenital malformations. Of the 3% of pregnancies in which a congenital anomaly is identified, the cause is unknown in 50%. 25% are secondary to a chromosomal change, 20% are due to a genetic change and 5% are due to environmental factors. Of the approximately 55,000 babies born in Scotland in 2016, approximately 1,650 would have had a congenital anomaly. Congenital anomalies can contribute to long-term disability, which may have significant impact on individuals, families, health-care systems, and societies.

7 https://www.gov.scot/publications/rare-rare-disease/
The need to transform models of care in Rare Diseases
Improved and more rapid diagnosis of rare diseases is a cornerstone of the Scottish Government’s 2014 Rare Disease Implementation Plan\(^7\), which sets out priorities such as identifying and preventing rare diseases; diagnosis and early intervention; and the role of research. Current clinical challenges include:

- Recognising rare disease and identifying patients who would benefit from genetic testing;
- Supporting patients with a rare disease, establishing effective diagnostic pathways and ensuring appropriate follow up;
- Using genomics and clinical genetic services to guide management of rare disease patients; and
- Establishing national rare disease registers to identify patients for clinical studies.

Genomic subtypes of Common Diseases: an opportunity for Precision Medicine
Improved diagnosis and management of rare diseases is an important driver for NHS practice, but some families exhibit multiple cases of more common diseases (e.g. diabetes, Alzheimer’s disease, cardiomyopathy and several types of cancer) due to a pathogenic variation in a single gene. To date, around 4,000 Mendelian disease genes (those where a characteristic is under the control of a single genetic locus) have been identified of a total of 7,000 Mendelian diseases, mostly by NGS. Identifying the subtypes of common diseases where the cause is a variation in a single gene is increasingly important because the treatment is often different from the large majority of cases where multiple genes and the environment are the cause of the disease. This Precision Medicine-based management will benefit the patient in such cases, as well as reducing the number of unnecessary interventions for the NHS.

Optimising diagnosis with Genomic testing
Over 1,500 gene variants are already known to cause rare diseases and further new disease-causing gene variants are being identified at pace through research. Current NHSS diagnostic practices for rare diseases use gene panels and, in some circumstances, clinical exomes (partial genome sequencing). Whilst screening single genes or defined parts of the genome can be helpful, it is widely agreed that WGS, alongside effective clinical-laboratory and clinical-academic coordinated working practices, gives more complete answers. Current research is focused on understanding when WGS would be a more appropriate test than exome sequencing.

The House of Commons Science and Technology Committee’s inquiry into Genomics and Genome Editing in the NHS, which included written and oral evidence from SGP, concluded in April 2018 that “there is great potential for WGS to improve patient care, particularly for diagnosing rare diseases and for more personalised targeting of medicines and treatments\(^8\). However, the inquiry also noted a lack of available evidence to inform a full assessment of clinical- and cost-effectiveness of routine WGS in the NHS, saying that “research and evidence-gathering will need to be continuing processes.”

New developments in Genomic Medicine are improving identification of genetic causes of congenital anomalies, giving couples more information about the condition affecting their child and what this may mean for future pregnancies. Invasive testing, such as amniocentesis and chorionic villus sampling have been in place for 30+ years, but a prenatal microarray is more sensitive, picking up small chromosome changes and increasing the diagnostic rate from approximately 40% to 60%. A UK guideline for the use of microarray in pregnancy has been accepted as best practice by the Association of Clinical Genetics Science (ACGS) and has led to new NHSS patient pathways. Advances in non-invasive prenatal testing (NIPT) allow identification of chromosomal and genetic disorders during a pregnancy by using a maternal blood sample containing foetal DNA. NIPT can identify

\(^8\) https://publications.parliament.uk/pa/cm201719/cmselect/cmsctech/349/349.pdf
A child born with paralysed malformed legs and severe developmental delay was first seen in the genetic clinic at the age of 2 years. Over the following six years they underwent a large number of investigations to identify the underlying cause of the problems. These included MRI scans and electrophysiological testing of muscle and nerves. These required general anaesthetics as well many targeted genetic blood tests. With all standard avenues exhausted and no explanation, the child’s parents decided to enrol them in the DDD research study for trio-based whole exome analysis. This identified a mutation in a gene not present in either parent and which indicated a very rare genetic condition. The diagnosis from this research study gave the family an answer to the cause of the child’s problems, reassured them that they – and other family members – were unlikely to have another child with the same condition, and allowed them and their doctors to learn from children worldwide with similar problems in terms of clinical outlook and appropriate care.

An opportunity for NHSS to deploy resources better

Although further evidence-gathering continues to be required through research, it is widely agreed that the traditional NHSS diagnostic pathway without NGS lacks clinical effectiveness. It leads to a diagnosis in <10% of rare disease patients, while ongoing research (DDD, SGP and Genomics England) indicates a diagnostic rate of 35-40% for most diseases with NGS. Furthermore for the patient, a single NGS genomic test would provide a one-stop-shop that avoids the need for other sequential and lengthy diagnostic tests, and is thought likely to save money through more rapid diagnoses and safer, more effective management plans.

Plans to commission and embed Genomic Medicine into routine care pathways in England began in 2016. Work is underway in NHS England to establish a new Genomic Medicine Service, which will offer a range of genetic tests including the analysis of WGS as part of routine NHS care alongside single genes, gene panels and exome sequencing. A newly commissioned network of Genomic Laboratory hubs is delivering a standard set of genomic tests. A central data repository will be connected to the wider NHS digital infrastructure. NGS testing for genetic disorders identified in pregnancy is also being evaluated. The interim analysis of 620 trios in the UK study of Prenatal Exomes and Genomes (PAGE) in different types of foetal abnormalities has been accepted for publication in The Lancet and NHSE is aiming to roll out prenatal and new born exome tests as a diagnostic service in 2019.

Common chromosomal trisomies such as Down syndrome and some single gene disorders, allowing more accurate screening with fewer false positives. NIPT to screen for Down Syndrome is increasingly taken up through private clinics and is available in other countries such as the Netherlands as part of routine pregnancy screening. Its introduction in NHSS is currently under discussion.

Pre-implantation genetic diagnosis (PGD), a procedure which involves the removal of a tissue sample from embryos followed by genetic analysis of the tissue sample to detect chromosomal abnormalities, allows couples to choose to have a child without the chromosomal or genetic condition which has occurred in the family, without testing during pregnancy. The Human Fertilisation and Embryo Authority (HFEA) regulates when PGD is available in the UK. Introduction of NGS into PGD is likely to improve this service further and pilots are underway in NHSS Molecular Genetic Laboratories.

**CASE STUDY**

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With all standard avenues exhausted and no explanation, the child’s parents decided to enrol them in the DDD research study for trio-based whole exome analysis. This identified a mutation in a gene not present in either parent and which indicated a very rare genetic condition.

The diagnosis from this research study gave the family an answer to the cause of the child’s problems, reassured them that they – and other family members – were unlikely to have another child with the same condition, and allowed them and their doctors to learn from children worldwide with similar problems in terms of clinical outlook and appropriate care.
The proposed way forward for Scotland

Links between the Scottish Universities and NHSS created by DDD and SGP have put in place world-class infrastructure and expertise in genomics and bioinformatics that provide a potential framework for future genetic and genome-based diagnostics for Scottish patients. In 2017 Scotland’s Genetics Consortium quinquennial review set out the aim of developing targeted panel and exome testing as a short-term priority, working towards WGS in due course if cost-effective. With the announcement of the new 2-year £4.2m funding package for Genomic Medicine by Scottish Government in September 2018, there is support to begin to deliver these objectives, with results from the DDD and SGP research informing the mix of genomic testing and enabling further evaluation of which patients are likely to benefit from which tests:

- It will be possible to offer whole exome sequencing in NHSS clinics routinely for patients presenting with severe developmental disorders, using evidence-based systems developed for the DDD study; and
- There will be continued WGS research in NHSS using the SGP mechanisms with Genomics England.

However, these can only be seen as a “bridge funding” mechanism to meet immediate needs. Genomic Medicine continues to evolve rapidly and a longer term funded strategy must be developed as a matter of priority by Government to assure NHSS as a world-class comprehensive genetics service, ensuring that Scottish patients will continue to have equitable treatment options alongside the rest of the UK and other developed countries throughout this 2-year period and beyond.

Implementation of Genomic Medicine will also require a national informatics/data structure with clinical, audit and research functionality to facilitate eventual mainstream delivery of analysis and interpretation of WGS for a wide range of disorders with suspected genetic causes.

In relation to congenital abnormalities and prenatal testing:

- NIPT for routine screening should be made available nationally in NHSS in line with NHSE.
- Plans should be developed by NHSS for NIPD for genetic diagnosis in at-risk pregnancies.
- Chromosomal microarray testing and NGS technologies should be added to the diagnostic tests available in NHSS for pre-implantation genetic diagnosis (PGD).

At a time of significant budgetary challenge for the NHS, any decision for funding of NGS testing needs to be based on clinical outcomes and cost-effectiveness. As seen in England, such evidence-gathering is still at an early stage, but with economies of scale and increased efficiency of the patient diagnostic journey, it is expected that costs can be saved through fewer expensive/invasive diagnostic tests and earlier interventions.
CHAPTER 5 – Cancer

Chapter 5 Summary
This chapter covers the impact of Cancer in the Scottish population and why current models of cancer care are outdated and do not work in most patients. A more personalised model of cancer care is needed in NHSS to tailor treatments to specific genomic markers. High-quality clinical outcome data linked to genomic profiles would greatly inform cancer research and improve future treatment strategies, building the foundations for a self-learning healthcare system which could rapidly identify which patients are most likely to benefit from a particular treatment and support delivery of appropriate care pathways.

The impact of cancer on Scotland
There are over thirty thousand new cases of cancer diagnosed each year in Scotland. 40% of the Scottish population will be diagnosed with cancer at some point in their lives and cancer is the registered cause of death for 25-30% of people in Scotland. Approximately £140 million per year is spent on cancer medicine in Scotland and one third of Scottish genetics laboratory funds are now spent on cancer testing.

The need to transform models of cancer care
Our recent understanding of the molecular diversity that underlies tumours that look the same but behave differently is challenging current models of cancer care. This new understanding of the complexity present within and between different cancers provides explanations for why systemic therapies provide effective treatment for only a small proportion of patients with disseminated cancer. Predicting which patients will benefit ahead of time, and as a consequence improving overall outcomes and minimising both the toxicity and cost of ineffective treatment is the clear path forward.

To make the necessary transformation, health systems need to evolve from their current state to a more personalised model of cancer care. Scotland is ideally positioned to do this, with national efforts such Scotland’s Ecosystem for Precision Medicine providing the excellence required to enable this new model of healthcare. However, beyond such platforms, Scotland needs to position itself to move to the ultimate goal of Real World Therapeutic Testing. This would allow important treatment response and outcome data for the >95% of patients that do not get onto clinical trials to inform improved healthcare strategies. The availability of innovative medicines in this environment will build value for the health system, attract significant industry investment and drive the health service to the ultimate goal of a “Self-learning Health System”, where robust data acquired through routine care and use of innovative medicines informs future treatment decisions. Having defined the challenges and the strategic direction, what is the path to achieving this goal?

CASE STUDY
KYT is a US program for pancreatic cancer patients. Pancreatic cancer has a median survival of 6 months and only 10% patients survive for a year after diagnosis. In KYT, patients have their tumour profiled using genomic and other molecular technologies. Half of patients profiled to date have had an “actionable change” identified in their cancer, meaning that a specific treatment is available. Patients who had a treatment that was matched to their actionable change survived more than twice as long as patients who had unmatched treatment.
Optimising cancer therapy with Genomic testing
NGS techniques should be implemented for molecular pathology of acquired disease and primarily the areas of cancer diagnosis, predictive and prognostic testing. The range of therapies available to patients with cancer has expanded considerably in recent years. Alongside traditional chemotherapy drugs there are now a wide range of targeted agents and therapies designed to enhance the anti-tumour immune response. The mechanisms of action of tailored therapies are much better understood than those of traditional chemotherapy. As a result, patients who are more likely to respond to tailored therapies can often be identified by genomic profiling of their cancers. For example, genomic alterations affecting individual genes or collections of genes may predict a higher likelihood of response to a specific therapy.

Whilst this new generation of tailored therapies brings great opportunities for cancer patients, meaningful clinical responses are limited to a subset of patients receiving any given drug. As such, many patients receive therapy that is ineffective but can have severe side effects. An increasing proportion of the health budget is therefore spent on ineffective therapies, and then managing the resulting toxicity and complications. Whilst Precision Medicine promises to identify the optimal therapy for a patient, almost more importantly, it has the potential to identify which intervention strategies will not work. This improves quality of life and creates opportunities for patients to access clinical trials of novel therapeutic strategies, which in turn attracts external investment into the NHS.

An opportunity exists for public healthcare providers to deploy resources better
Despite an increase in the number of tailored anti-cancer therapies being brought to market, pharmaceutical companies have largely failed to incorporate response prediction into their routine drug development processes. This is despite pressure from both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). A significant amount of information already exists that could inform matching cancer patients with therapies that are more likely to benefit them; however, use of this information is yet to be integrated into clinical practice. There is, therefore, an opportunity for healthcare systems to leverage existing knowledge in order to deploy resources more effectively. This approach would provide benefits to patients by providing the most effective therapy, whilst delivering financial benefits to healthcare providers through the avoidance of ineffective therapy.

The current companion diagnostic model is out-dated
Underpinning a better utilisation of cancer therapy is the ability to perform complex genomic analysis of the patient’s tumour. At present, only a limited number of tailored therapies are covered by a specific biomarker with regulatory approval. In such cases, the model in the EU and the US is for regulatory bodies to mandate testing for the presence of the biomarker using a specific approved assay. These assays, referred to as companion diagnostics, generally provide only very limited information relating to the specific marker of interest. Given the wide array of emerging therapeutics, there are benefits in moving away from the current model of iterative testing using scope-limited assays towards the deployment of a single broad genomic assay, available for all at diagnosis, that informs on the entirety of the clinically actionable genome. An additional advantage would be the potential to include identification of inherited mutations in single genes causing significantly increased cancer risk. Such inherited cancer-predisposition mutations have implications for the patient and their relatives, and enable cancer prevention strategies by directing surveillance and intervention to those most likely to benefit. The expected outcomes of this approach include improvements in patient outcomes and a more parsimonious and efficient use of healthcare resources.
Clinically actionable genomes in cancer care: towards a self-learning healthcare system

The routine collection of high-quality outcome data, linked to cancer genomic profiles, would enable real-time hypothesis testing in the NHS to rapidly identify novel biomarkers of treatment response and refine treatment strategies. This is a particularly pressing problem for immunotherapy, a relatively new approach that can induce long-term remission in previously untreatable tumours. However, immunotherapy agents are expensive (c.£50,000 per annum), response rates are low, and they carry a material incidence of serious complications. The integration of genomic profiling, possibly alongside immune function assays, into a self-learning healthcare system would allow for the rapid identification of patterns that identify patients most likely to benefit.

Current strengths and assets in Scotland

- Scotland already has sufficient sequencing capacity to sequence the cancer genomes of all cancer patients, through its centres of excellence for genomic sequencing with associated research bioinformatics capabilities (see Chapter 2). Both facilities are moving towards quality management systems and regulatory standards that would allow them to support clinical trials and clinical practice.
- A strong commitment to Precision Medicine initiatives, such as the flagship Precision Panc clinical trials platform. This incorporates comprehensive genomic screening of a patient’s tumour into their care pathway, allowing rapid recruitment to any clinical trial being opened under the Precision Panc umbrella.
- NHSS’s Scottish Genetic Laboratory Consortium co-ordination of an efficient and comprehensive genetic testing for a wide range of conditions, including some cancer biomarkers. As highlighted in Chapter 3, this is a rapidly evolving field and the Scottish laboratories are at the forefront of deploying state-of-the-art assays in routine clinical diagnostics, already offering several NGS-based assays to patients.
- Exceptional electronic health records with national datasets including: the Scottish Cancer Registry; the Picture Archiving and Communication System (PACS) for all cross-sectional imaging (CT scans and MRIs); a unified cancer treatment prescribing system (Chemocare) and Scottish Care Information (SCI) Store. Such data is essential for linking genomic profiles to cancer phenotype, therapeutic response and outcome in a self-learning healthcare system. It also adds value to Scottish health cohorts from a commercial perspective.

Scotland is poised to become a world leader in clinical cancer genomics

The combination of sequencing capacity, Precision Medicine expertise, engaged and committed NHS laboratories and a wealth of recorded treatment and outcome data for patients, places Scotland in an ideal position to offer world-class genomic profiling of all cancer patients, in a timely manner, for the improvement of patient care. The biggest opportunity is the potential to attract clinical trials to Scotland, which would maximise patient benefit in the shortest timeframe whilst bringing investment in to Scotland.

A key outcome of the cancer workstrand of SGP is a cancer genomic profiling platform and analysis pipeline that could be deployed in the NHS for c.£140-£600 per cancer patient. Pharmaceutical companies currently pay commercial providers in the region of £3700-£6000 per patient for a standard whole genome profile as part of a clinical trial. If NHSS rolled out genomic profiling across the cancer patient population it would match NHSE’s commitment to Genomic Medicine but using a much more cost-efficient testing strategy, which would also provide a powerful incentive for companies to run clinical trials in Scotland. The benefits of this SGP-developed clinically actionable genomic assay for newly-diagnosed cancer patients in Scotland should be validated by NHSS and adopted where appropriate.
Although the cost of a genomic test may seem high compared to current diagnostic tests, there is a significant difference between the cost of tailored anti-cancer therapies (£30,000–£50,000 per annum) and the cost of clinically actionable genome analysis. Saving just one unnecessary year of treatment would pay for the profiling of more than 60 other patients, yet current data suggests that up to 85% (fifty-one out of every sixty) patients would be eligible for treatment tailored to their genomic profile. There is also potential to reduce costs, for both the NHS and social care, through reduction of morbidity due to ineffective but aggressive treatments.

The future of genomic profiling technology for cancer applications

International research efforts have demonstrated the importance of a wide range of complex genomic features in cancer outcomes and therapeutic responsiveness. This, combined with the nature of cancer samples and the way they are processed in routine pathology workflows, means that the most appropriate assay is a technique called sequence capture, for which there are a number of competitors in the market place. However, for the required downstream genome sequencing, the market place is dominated by a single company, with limited competition that would otherwise drive down costs. The need for genomic results to be returned and acted upon relatively quickly (the cancer waiting time target is 62 days from urgent referral to starting treatment) and the difficulty in data transfer given the data sizes involved (see Chapter 8) mean that the capability for running genomic assays would be best placed within Scotland rather than being commissioned as a remote service.
CHAPTER 6 - Pharmacogenetics

Chapter 6 Summary

This chapter looks at the potential for genome-based testing to improve prescribing, with more targeted drug therapies (increased benefit) and a reduction in side effects (reduced harm). Existing research strengths in Scotland, and the potential to use patient data, including whole genome sequence data, to explore pharmacogenetic variation, should generate new opportunities for academic and industrial research partnerships with the NHS in this emerging area.

Pharmacogenetics and adverse drug outcomes
Pharmacogenetics is the study of how individual genetic variation impacts on individual drug responses. Drug treatment regimens usually treat the ‘average’ patient based on studies of benefit versus harm in drug trials during licensing. Individual genetic variation means that some patients are inadequately dosed despite being at low risk of harm, others are at such high risk of harm from a particular drug that they could never expect to benefit, and others can expect no benefit at all. By December 2017 the FDA had included pharmacogenetic information in the drug label for 330 drugs, including 144 oncology drugs, with this information highlighting genes involved in drug metabolism or immune-related adverse drug reactions. The Clinical Pharmacogenetic Implementation Consortium (CPIC)\(^9\) and the Dutch Pharmacogenetics Working Group (DPWG)\(^{10}\) provide guidelines on how drug-gene interactions should be used to guide clinical care in patients known to carry a particular gene variant. The evidence base for these guidelines varies but although much of the clinical evidence is very robust with clear, clinically important implications, there are limited examples that establish the cost-effectiveness of genetic testing prior to prescribing.

Pharmacogenetic testing in Scotland
Despite the robust evidence for the clinical impact of pharmacogenetics on harm or benefit for many drugs, pharmacogenetic testing is rarely offered in Scotland. It is mandatory or strongly recommended for Abacavir (anti-HIV) and Azathioprine (immunosuppressant) prescribing, but in practice testing is sparse and when carried out it is outsourced to a private company.

Given the increasing use of genome sequencing and genotyping in healthcare and the increasing evidence for effectiveness in pharmacogenetics testing, NHS England/Genomics England established a short-life working group to evaluate what drug-gene pairs should be offered for genetic testing in NHSE. The focus was on drugs that are relevant to the NHS, where efficacy can be clearly established. The Scottish research community should continue to contribute to, review and evaluate the outputs from this working group where they relate to implementation of pharmacogenetics into the NHS. One implication may be for people who have already undergone WGS, for any indication, to ensure that they can benefit from prescribing that takes into account any clinically actionable variants already identified in their genomes.

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\(^9\) https://cpicpgx.org/
\(^{10}\) https://www.pharmgkb.org/page/dpwg
Barriers to implementation

Barriers to the implementation of pharmacogenetics tests have been both logistical and financial. Physicians are resistant to the inconvenience of ordering a bespoke test before making a prescribing decision even in well-justified circumstances, and initial health economic analysis suggests that development of convenient point-of-care tests for individual gene-drug interactions is unlikely to be cost-effective. However, the potential of leveraging the scale and economy of whole genome analysis has raised the possibility of pre-emptive genotyping being used to guide prescribing using electronic clinical decision support.

Panel genotyping, pre-emptive testing and clinical decision support for pharmacogenetics

A new generation of genotyping microarrays can capture most relevant ADME (absorption, distribution, metabolism and elimination) drug information as well as known disease-causing variants in a single test for under £30 per sample. This opens the opportunity for pharmacogenetic testing to become routine in the next 5-10 years: a panel genotype could be undertaken on all individuals at their first health care encounter, stored in a secure repository and linked to their medical ID. A continually updated clinical decision support tool would then be able to query this stored information and guide prescription of the most effective and least harmful drug for a particular patient. Similar information could also be gleaned from individuals who have undergone WGS.

Current strengths and assets in Scotland

Scottish Government investment in SMS-IC is helping to develop a Scottish Ecosystem for Precision Medicine that will support further academic and industry-led research in pharmacogenetics. Scotland is also a substantive site in the Health Data Research UK initiative, which includes a “precision therapeutics” research initiative specifically aimed at identifying pharmacogenetic variants and implementing pharmacogenetics into clinical care. It is important that the Scottish research community continues to develop this work, including working with international initiatives piloting pre-emptive genotyping for pharmacogenetics, such as the EU-Horizon 2020 funded consortium “Ubiquitous Pharmacogenetics”.

Scotland already captures all prescription and health outcome data, including hospitalisation and death, which will enable the capture of drug outcomes and evaluation of parallel drug prescribing in the context of multiple long term health conditions. The NHSS SHARE platform facilitates participation in health research, with the option to consent for storage of spare blood and use of genetic information for clinical care. To date over 200,000 people have signed up to SHARE, with blood on >60,000 individuals in the biobank, offering an important test bed to evaluate pre-emptive genotyping within the NHS. Using SHARE, researchers should develop a collaboration with NHSS Genetics laboratories for a careful step-wise implementation of pre-emptive genotyping for pharmacogenetics, generating clinically accredited data making this available for future research. Feedback from this work should be reported back to the new Scotland-wide Leadership Group (see Recommendation 1) to ensure that the Scottish Government is fully briefed on new evidence, appropriate steps are taken by NHSS and research opportunities are taken forward.

11 http://www.goshare.org.uk
CHAPTER 7 - Data Storage and Bioinformatics

Chapter 7 Summary

This chapter describes the challenges around managing, processing and storing genomic “big data” in effective and secure ways that preserve privacy whilst developing patient care and enabling cutting-edge research. Scotland’s 2018 Digital Health and Care Strategy commits to using technology to reshape and improve health and care services. It is vital that genomic data processing and workflows are considered when delivering on the commitment to build a national digital platform to record and deliver real-time health data at point-of-care. Suitable information governance arrangements will also be critical to ensure public confidence in genomic data. Ultimately the delivery of effective genomic analyses for NHSS will require investment in hardware, software and skills and a commitment to a self-learning healthcare system.

Genomics produces big data

Modern genomics sequencing technologies produce data on a scale comparable to other big data generators such as social media and astronomy. A standard laptop would spend more than three days processing a single WGS experiment compared to a few hours or less on dedicated state-of-the-art servers. Using genomics to benefit patients and the healthcare system is therefore dependent on our ability to store, analyse and access large volumes of data. Genomic informatics requires three specialist infrastructure aspects:

- High-performance computing hardware for data processing
- High capacity networks to allow data access and movement
- Large volume data storage to archive data

Genomic data is only useful if it can be used to direct patient care and drive continual improvement in NHS service delivery and population health. Utilisation of genomic data requires 3 specialist software themes:

- On-line ordering of tests and delivery of results in routine healthcare
- Analytic pipelines (an organised series of data processing steps) for converting large-volume raw data into clinically-useable information to help direct treatment and care
- Integration with other health and social care datasets to enable service evaluation and improvement, and research and innovation

Medical genomics can be delivered via centralised or distributed service strategies

Most of the national efforts underway to roll genomics out into healthcare involve the creation of a national centre, or a limited number of regional centres, for data generation and analytics. While such efforts are required to deliver some of the higher content and throughput genomic tests, there are a range of smaller volume genomic tests, particularly for oncology applications, that are amenable to being adopted by local genetics laboratories. The organisational arrangements adopted for the relative locations of data generation, analysis and long-term archiving place different requirements on the IT solutions for processing, networking and both temporary and permanent data storage. It is likely that a combination of both a small number of high-capacity processing and several more modest-capacity compute systems will be needed, with the total number of sites and location of storage at either a single central repository or at each processing location determining the network connections and bandwidth needed.
Sufficient sequencing capacity exists already in Scotland, within academia
Scotland has established 2 major sequencing centres through SGP (Chapter 2): Edinburgh Genomics and the Glasgow Precision Oncology Laboratory. Between them they have sufficient capacity to deliver large-scale Genomic Medicine for oncology and rare diseases across the Scottish population. The major barrier to doing so is that under current information governance arrangements they are not permitted to hold or process patient data, such as genomic sequencing results, outside of specifically consented research studies and clinical trials. One solution would be to build a high-capacity sequencing facility within NHSS for routine service provision, but the cost of doing so suggests that the national interest may be better served by finding a way to utilise the existing assets as service providers for NHSS. An IT infrastructure that supported the submission of pseudonymised samples to the sequencing centres and streaming of data straight from sequencers into a secure NHS cloud may be one way to achieve this.

Scotland’s Digital Health and Care Strategy is well-configured to support genomics
Scotland’s Digital Health and Care Strategy, published in April 2018\(^\text{12}\), sets out a commitment to use technology to reshape and improve health and care services. It identifies several key areas that will be critical for enabling the delivery of genomics in NHSS and its use to underpin Precision Medicine. It will be important to ensure that the NHSS Genomic Medicine bioinformatics capacity – including hardware and software infrastructure, staffing requirements, digital leadership and the national digital platform – is a key part of delivering the Digital Health and Care strategy. The Scottish Genetics Consortium should be resourced to work with eHealth, academic partners and the national data governance team to scope and deliver a national strategy for the hardware and software infrastructure needed to deliver genomics as part of routine care.

Of particular relevance for the development of Genomic Medicine are recognition of the need for dedicated senior leadership in digital delivery and the intention to build a national digital platform that will record and deliver real-time health data at point-of-care. This will enable both the ordering of tests and return of results, which is a major barrier at the present time especially across Health Board IT boundaries, as well as supporting appropriate use of health and care data for innovation and improvement. It is vital that considerations about design of this platform encompass genomic and other biomedical data processing and workflows i.e. to develop NGS capacity in NHSS laboratories that is supported by integrated solutions for test management, data processing, storage and data interpretation. In order to deliver these elements successfully, it will be necessary to have key genomics front-line stakeholders represented, including the Scottish Genetic Laboratory Consortium, oncologists, haematologists, histopathologists, germline geneticists and medical genomics subject matter experts.

Genomic technologies raise a multitude of both real and perceived risks and issues. The intrinsic identifiability of genomic data in conjunction with publicly available records, plus the large amount of health information about an individual that can be extracted from some of the larger genomic tests, make it a particularly sensitive form of data. Privacy concerns are paramount to the genomics research community, both scientists and study participants. The Information Governance and Cyber Security strand of the Digital Health Strategy will be key for building confidence in Scotland’s ability to deliver genomics safely whilst making sure the power of such data can be fully unlocked, and hence development of information governance arrangements needs to encompass genomic and other biomedical as well as clinical patient-level data.

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Further consideration on how to deliver analytic pipelines is needed
Genomic data analysis (bioinformatics) uses complex pipelines consisting of series of different computer programs. All of the methods in widespread use for handling and analysing genomic data were originally developed in the research space. These are increasingly available as commercial re-implementations, which are often more computationally efficient and provide user-friendly graphical interfaces, although they contain essentially the same functionality and give similar quality results to their research-grade predecessors. The analytical pipelines that are deployed in routine clinical pathways will need to be standardised and validated across NHSS. Such efforts can build on the experience in existing academic pipelines but further development work is needed to optimise them for clinical applications.

The rapid progress in applications for sequencing means that the regulatory space is struggling to keep up and strategies to make bioinformatics safe for routine clinical use are still being developed. It is important for Scotland to have its say in these debates and engagement at a national level with regulatory bodies such as the National Institute of Biological Standards and Controls (NIBSC), UK National External Quality Assessment Service (UK NEQAS), the Medicines and Healthcare products Regulatory Agency (MHRA), UK Accreditation Service (UKAS) and NHS England should be encouraged to define and coordinate appropriate strategies for regulating the analytics associated with genomic testing.

Skills and staff needed to deliver genomic analyses within NHSS
Maintaining the hardware and software required to deliver genomic analyses in routine service requires a diverse set of skills. While some of this may be delivered by upskilling existing staff to operate bioinformatics pipelines, and through the National Digital Strategy for Health and Care, new staff may also need to be recruited into NHSS, for example bioinformaticians, data scientists, software developers, database developers, web developers and software testers. As with the introduction of any new system, the roles needed for initial design and development and the roles for ongoing operation, maintenance and support are very different and some stages may lend themselves to being contracted out. As medical genomics is still a relatively young discipline, the number of clinical medical genomics experts who can act as key stakeholders for system development strategy, planning and delivery is an independent potential point of failure.

Enabling genomic data to support a self-learning healthcare system
The philosophy of a learning healthcare system is to use the wealth of data generated in routine clinical care to improve outcomes for patients and the efficiency of operation of the health service. By continually analysing and learning from the information collected by the healthcare system, knowledge is accumulated rapidly and can be used to inform subsequent decisions in both patient care and resource provision. The need to embed ways of supporting this type of work throughout NHSS systems is recognised in the NHS Digital Health and Care Strategy and must be included in subsequent plans and developments such that Genomic Medicine can be a key element of that vision. Further integrating NHSS genomics with the existing Ecosystem for Precision Medicine across industry and academia in Scotland would create opportunities for both research programmes in Scottish Universities and also attract business to Scotland, as long as appropriate data protection strategies can be developed.
This chapter highlights an urgent need for strategic workforce planning in Genomic Medicine – current skills mix and future workforce needs vs skills predicted from existing training – with necessary actions taken. Many of the building blocks to fill education and skills gaps already exist in Scotland, although these require additional resources. Development of additional bioinformatics and data science skills will be required, with a particular focus on use of these skills in clinical service delivery. Education providers need to be identified to ensure that current and future staff have the appropriate skills to build the capacity and capability for Genomic Medicine across specialist digital, IT and data platforms, aligning with Scotland’s Digital Health and Care Strategy. Further collaboration between academic and NHS disciplines will encourage the transfer of academic expertise into patient care.

Current Landscape
During the last 10 years, genetic and genomic testing has become increasingly embedded in patient care pathways, but development of the capacity and expertise of the workforce for genome-based testing has not kept pace. To realise the potential to transform patient care, the Genomic Medicine workforce must be robustly supported and appropriately trained. The current workforce is facing significant challenges in training, recruitment to vacant posts and succession planning, and these problems will be exacerbated by projected high retirement rates. There is a need to enhance the training provision for Consultants in Clinical Genetics; 57% of the consultant workforce is predicted to retire within 6-8 years and the current allocation of 6 training posts will not be enough to fill these vacancies. There is an urgent need to establish a funded training programme in Scotland for Genetic Counsellors; they are facing a 24% decrease in workforce over the next 5 years through retirement. There is also an urgent need to enhance the allocation of funded training posts for Laboratory Clinical Scientists; the current allocation is inadequate to cope with the increasing workload and requirement for genome analysis, and will not be sufficient to fill anticipated vacancies through retirement.

Genetic/genomic analysis is new to routine oncology, so the equivalent of the Consultant Clinical Geneticist does not yet exist for cancer. Healthcare has been slow to appreciate the significant differences in the detection, validation and interpretation of somatic (acquired by the cancer) versus germline (inherited) genomic variants. As yet, there is no clear consensus on which medical specialty should take responsibility for the development of the appropriate skills required for the curation of somatic genomic data. In the US, it is largely oncologists who have driven this process, whereas in many European countries the responsibility has fallen to pathology. In the UK, there remains a requirement to bolster postgraduate training in cancer genomics in both oncology and pathology.

Individuals skilled in data science are critical for exploiting genomic data but they remain in short supply across the UK. In Scotland, the vast majority of expertise in bioinformatics is concentrated within academic institutes and consortia, many of whom have established track records in providing world-class genomic analysis. An important open question is the extent to which laboratory Clinical Scientists require specialist training in bioinformatics. It seems evident that the Clinical Scientist training pathway would benefit from more in-depth exposure to the principles of both germline and somatic genomics. What remains uncertain is the need for Clinical Scientists to be trained in bioinformatics (including software development). There is much focus at present on harmonising variant calling and annotation pipelines, and the provision of informatics expertise at individual sites may run counter to this. A more appropriate model would be the central development and
deployment of automated gene variant calling pipelines, which would obviate the need for individual establishments to develop and maintain deep bioinformatics expertise.

Finally, the provision of genomic education and training to staff in other areas of healthcare varies across Scotland with no national oversight or coordinated delivery, which is in marked contrast to the situation in England. This educational gap needs to be rectified as it will become even more acute as genomic testing becomes embedded in a wider range of patient care pathways. The online genomics modules developed by Health Education England for use by NHSS staff (genetics, molecular pathology and across healthcare including trainees and students) should be promoted.

Gaps and Opportunities
To utilise fully NGS-based testing in healthcare, a new breed of staff is needed for effective service delivery and future development, as well as re-training of established staff whose skillsets are in less demand. In recognition of the importance of genomics in modern healthcare delivery, NHSE has invested up to £30 million in the Genomics Education Programme (GEP) to upskill existing staff and support the integration of genomic technologies into wider healthcare. As well as offering online resources and self-directed learning packages in genomics, bioinformatics, consent and ethics to NHS staff, the GEP also contributes to formal academic-based training programmes and supports research fellowships in genomics and bioinformatics.

Many of the building blocks to fill education and training gaps already exist in Scotland and can be utilised to achieve similar outcomes to those in England but with more modest investment:

- Training programmes in laboratory medicine funded by NHS Education for Scotland (NES) exist for medical professionals in Pathology, Medical Genetics, Haematology, Microbiology and Immunology as well as for clinical scientists in Genetics and Molecular diagnostics.
- High-quality postgraduate academic training in Molecular Pathology, Medical Genetics, Informatics and Precision Medicine is being delivered in Scotland through a variety of routes including longstanding MSc programmes as well as more recent, time-limited initiatives such as the MRC/EPSRC-funded Glasgow and Edinburgh Molecular Pathology Nodes. The MSc programmes include: Glasgow University for Medical Genetics and Genomics (MedSci), Clinical Genetics, Genetic and Genomics Counselling, and Molecular Pathology; MSc in Medical Informatics and Postgraduate Certificate of Education (PGCert) in Molecular Pathology and Genomic Medicine at the University of Edinburgh; MSc in Genetics at the University of Aberdeen; and MSc on Data Science at the University of Dundee. A number of these include research project components that are embedded within NHS Genetics Services.
- There is a successful pan-Scottish MSc in Stratified Medicine and Pharmacological Innovation, funded by Scottish Funding Council and involving partners of SMS-IC; and a combined Edinburgh/Glasgow MRC Doctoral Training Programme in Precision Medicine.
- Health informatics training via the Farr Institute is available, as well as broader bioinformatics and health economics provision.
- Outside of formal educational programmes, cross-disciplinary training is available across multiple institutions at post-doctoral level, including in translational bioinformatics, health informatics and health economics.

Thus, Scotland already has a number of excellent training opportunities but these will require additional resource to ensure sustainability and increase capacity for greater reach across the workforce. Funded access to existing high-quality University courses should be a priority. There is support within Scotland for the Royal Colleges, including the Royal College of Pathologists to enhance molecular pathology and genomic medicine provision within training curricula, to which postgraduate education can be aligned.
Delivery of the Genomic Medicine agenda across Scotland will require staff experienced in data science and IT infrastructure with the skills to rapidly translate research findings into clinical service. Mechanisms are needed to support high level bioinformatics skills and career pathways which support the transfer of research knowledge from genomic technology, bioinformatics and data science to NHSS staff. Bioinformatics and data science analytical training is generally delivered by Universities as undergraduate modules, MSc courses or topic-based workshops. However, very few focus on the specific analysis challenges involved in clinical service delivery. With respect to cancer genomics, there is a parallel need to develop a postgraduate training programme covering the clinical implementation of genomic analyses and their interpretation in routine practice. Such training should be made available to both pathologists and oncologists. Research and development of genomics and associated other -omics and bioinformatics as well as integration with other “big data” including clinical and diagnostic imaging datasets is required to fully realise the patient benefit from implementing Genomic Medicine. Again training will be key, and there is a particular need for data scientists: individuals with a detailed understanding of biological processes and disease mechanisms who can apply that knowledge to data analysis.

Collaboration between academic researchers and NHS staff through SGP has resulted in innovative solutions to patient recruitment, genomic sequence provision, data analysis and reporting. Further support will be required for both academic and NHS staff when this programme ends, to continue the transfer of research innovations and expertise into patient care, particularly at the interface between NHSS Clinical Science and University bioinformatics and data science. The creation of a new Consultant-level post in Genomic Medicine in each of the regional centres would significantly help with the development of critical mass and expertise in this field.
CHAPTER 9 – Patients at the Centre: Involvement and Engagement

Chapter 9 Summary
This Chapter highlights the importance of Patient and Public Involvement and Engagement (PPIE) to help us learn what patients understand and expect from Genomic Medicine. Increasingly, there is a blurring of boundaries between research and care pathways, with patients often donating data to research while they are receiving care. The public is also being offered direct-to-consumer genetic testing which will change expectations. Research is needed on patient experiences, their expectations and wider social and ethical issues to ensure that health and research policy recognises societal views.

Introduction
Genomic Medicine has the potential to transform the patient experience: it raises expectations of more effective, personalised treatment; more precise and earlier diagnoses; new approaches to ongoing monitoring for signs of disease progression and novel strategies for prevention through screening programmes targeted to those at risk of disease. The pace of developments is accelerating and the healthcare system must adapt alongside. To ensure that the benefits of Genomic Medicine are realised equitably, that patients can understand and engage in developments and that patients’ needs are at the centre, it is crucial to build an infrastructure that can involve them in decision-making. An evidence base for understanding both patient experience and the wider social and ethical issues which are part of Genomic Medicine is also needed.

Genomic Medicine: Research and Care
The novel technologies and applications involved in Genomic Medicine are leading to new patient pathways for rare conditions, as well as different pathways for patients who appear to have the same condition but where there is a different underlying cause. Increasingly research is embedded alongside care pathways, so patients may be simultaneously contributing to research while receiving care. Health professionals and researchers are often involved in both, as the collection and analysis of genomic information forms part of decisions about diagnosis and treatment.

This presents challenges for all involved. Meaningful communication, involvement and engagement about genomics, their limitations and benefits, is needed so that we can all help shape an Ecosystem for Precision Medicine that keeps patients at its core. Research on patient experiences is essential to use this information in shaping care and policy, including how to manage ever more complex information in the context of shared decision-making. Research is also needed to identify and offer solutions to wider social and ethical issues, particularly in the collection and use of genomic information beyond an individual patient’s care pathway and, for optimal implementation, the results of such research should be embedded in Government strategy for the governance of Genomic Medicine research and practice.

Involving Patients – PPIE
Public and Patient Involvement and Engagement (PPIE) is a key component of effective health service design, health care policy and health-related research. PPIE can contribute to shaping each of these arenas for patient and public benefit, and more generally to improve medical science-society relations: it can help strengthen confidence in both research and care. PPIE should not be seen as an ‘add on’ or ‘nice to have’ element of developments in Genomic Medicine, but as something that is built in and iterative. It should be as much a part of ‘upstream’ developments and discussions as it is about ‘downstream’ point-of-care decisions. In Scotland the success of the NHSS SHARE platform (see Chapter 6) indicates an enthusiasm to take part in research and this is a potential resource for
PPIE activity. The benefits of good quality PPIE include research and health service changes that are responsive to, and co-produced by, those involved and affected; and, health and research policy that includes recognition of societal expectations and patient views and experiences.

**Approaches to PPIE**

While there are multiple approaches to PPIE, these can be distilled into 3 main processes: consultation, awareness raising and empowerment (Figure 4). These elements overlap: for example, the provision of accessible information (awareness raising) is a pre-requisite for informed deliberation (empowerment).

Engagement methods that are well-utilised include patient and public panels, deliberative events, including citizens juries, focus groups, patient representation on key decision-making bodies. Wider methods of consultation such as surveys can also be used, or specific methods for setting priorities or assessing trade-offs in terms of resources and choice.

In relation to Genomic Medicine, multiple methods will be required for effective and meaningful PPIE, including at different levels, with different groups, paying particular attention to those least likely to engage. A network for Genomic Medicine PPIE could be developed along the lines of Gengage (The Scottish Healthcare Genetics Public Engagement Network - a previous network created to support public and stakeholder engagement in developments genetics and medicine).

**Figure 4:** Public and patient involvement and engagement (adapted from Davidson, S., McLean, C., Treanor, S., Aitken, M., Cunningham-Burley, S., Laurie, G., Pagliari, C., Sethi, N., (2013) Public Acceptability of Data Sharing Between the Public, Private and Third Sectors for Research Purposes. Scottish Government Social Research)

**Horizon-scanning**

The direct-to-consumer genetic testing market is growing. It is recognised that more and more people are interested in having their genome sequenced for ancestry testing as well as to predict common diseases and make related lifestyle choices. The predictive algorithms for such tests are becoming more powerful and clinically relevant. PPIE activities should explore what this will mean for patients and the public. Regulation may be required to ensure that where testing is done outside a medical setting, appropriate pre- and post-test counselling are provided as part of the service.
CHAPTER 10 - Industry-facing activity

Chapter 10 Summary

This Chapter highlights the existing strengths of Scotland’s ‘triple helix’ partnership between industry, NHS and academia in Genomic Medicine as part of Scotland’s Ecosystem for Precision Medicine. The establishment of SMS-IC has created a focal point for industry engagement to translate research capability into valuable products and services. Scotland’s state-of-the-art genome sequencing centres are creating additional opportunities to engage commercially, including clinical trials being an important market. An area of specific interest currently is in the integration of data from diverse sources to improve clinical decision-making and attract industry projects. New commercial opportunities for big data projects and clinical interpretation have also arisen from the SGP research.

Scotland’s life sciences cluster is already one of the largest in Europe, and it is recognised that there are significant opportunities for economic growth in Scotland in this area. The University of Glasgow has led a Science and Innovation Audit on behalf of BEIS (Precision Medicine Innovation in Scotland: Accelerating Productivity Growth for Scotland and the UK), to evidence Scotland’s life sciences business base and the opportunities for generating economic growth in Scotland in Precision Medicine. The Science and Innovation Audit will be published by BEIS in 2019 and will provide recommendations to enable Scotland to deliver productivity across Precision Medicine, including growth in Genomic Medicine. The establishment of the Stratified Medicine Scotland Innovation Centre (SMS-IC) has already attracted inward investment by several overseas companies. The ‘triple helix’ partnership between industry, NHS and academia is a significant strength across Scotland, but needs to be carefully nurtured and supported to ensure maximum benefit.

SMS-IC is one of a network of Innovation Centres in Scotland, created by Scottish Funding Council (SFC) as an investment in Scotland’s economic capabilities. Alongside support from SFC, SMS-IC had significant financial support from two industry partners – Thermo Fisher Scientific and Aridhia. SMS-IC works in close collaboration with clinical academics from within its partner Universities (Aberdeen, Dundee, Edinburgh and Glasgow) to translate early stage research into valuable products and services to compete in the global Precision Medicine market. Since it was established in 2013, SMS-IC has worked with many companies including Canon Medical Systems, Aridhia, Fios Genomics, Cohesion Medical, Kajeka, Pharmatics, Sistemic, Destina Genomics, Biopta (ReproCELL Europe), BioClavis, ThermoFisher Scientific and Arrayjet.

SMS-IC has worked with other life sciences organisations to provide a one-stop-shop for collaboration through a service broker model. For example, SMS-IC’s collaboration with industry partner Aridhia enabled the development of an innovation platform for Precision Medicine projects, but has diversified the platform offering through collaboration with organisations such as Eagle Genomics and Cohesion Medicine.

Over recent years, working with industry partners, SMS-IC has performed exemplar projects in several disease areas (Multiple Sclerosis, Rheumatoid Arthritis, ovarian, oesophageal and pancreatic cancer). One example is the collaboration highlighted in Chapter 3 between SMS-IC, SGP and AstraZeneca, to sequence genomes of 100 tumour-normal pairs in a clinical trial study design to stratify ovarian cancer treatment. The recently funded Steatosite project will integrate data from different sources (transcriptome, digital pathology, longitudinal clinical data) to build a data commons with a focus on the chronic liver disease NASH.
Data Commons co-locate data, storage and computing infrastructure, and commonly used tools for analysing and sharing data. They integrate data from diverse sources: genetic and sequence information from patient biopsy samples, imaging, histological data and clinical data from electronic patient records. They will become an important resource for generating actionable and life-changing information about a patient that could be used ultimately by doctors, researchers and their patients. These combined data will enable improved selection of patients for Precision Medicine clinical trials, facilitate the rapid development of companion diagnostics and enable biomarker discovery. The SMS-IC-led NASH data commons has generated a great deal of interest from the pharmaceutical industry: they are interested in accessing longitudinal patient data and samples.

SMS-IC is located within the Clinical Innovation Zone in the Queen Elizabeth University Hospital campus and has a high performance Ion Torrent Cluster with several NGS sequencers attached. Collaboration with the SGP WGS sequencing capability across both the Glasgow and Edinburgh sites ensures that the most appropriate NGS technique is used for each project. Typical sequencing projects and runs consume large amounts of storage (100s Tbytes to Pbytes) and CPU processing for large (1000+) sequencing runs. This scale of projects is well catered for by the SMS-IC and EPCC clusters, with over 2,000 computing cores and 6 Pbytes of fast and tape storage dedicated to genome sequencing projects.

Edinburgh Genomics has dedicated servers for clinical data that have been optimised for secure transfer of WGS data to clinical, academic and industry users. The facility has multiple quality checkpoints in place across the entire sequencing workflow, from sample reception to data delivery, and participates in the annual EMQN/UK NEQAS external quality assessment (EQA) germline mutation scheme, which provides an independent assessment of data quality. Results from 2016 and 2017 EQAs showed equivalent or better quality compared to similar service providers within the scheme. In the past year, the facility has also developed a Quality Management System and following an audit by the UK Accreditation Service (UKAS) in August 2018, it is being recommended for full ISO 17025:2005 accreditation, providing it with an industry standard for clinical trial and other commercially-commissioned data.

SMS-IC has a Scottish Wide Area Network (SWAN) connection linking Glasgow and Edinburgh\(^{13}\). Due to the sensitive nature of the data this has safeguards and governance steps to minimize the risk to patients and their data. The SMS-IC Data Stewardship Board has membership from across Scottish Academics, NHS Boards and Influential SME’s who assess the data use cases, impact of patient data, provide a wealth of experience around ethics and successful outcomes with patient data.

Other ‘big’ data projects in collaboration with industry will facilitate better access to biorepository tissues and linkage to clinical and other data. Examples include population and disease isolates and cohorts that are being sequenced as collaborations with Regeneron and AstraZeneca. Sequencing for these projects is through Edinburgh Genomics, with analysis in collaboration with SGP partners at the University of Edinburgh. The SGP collaboration with Genomics England has led to new discussions with a commercial clinical interpretation company for development of a commercially-based Scottish Centre for Clinical Genome Informatics located at the University of Edinburgh.

\(^{13}\) http://www.stratmed.co.uk/media/1172/sms-hosting.png
**Horizon-scaning**

There is a need to identify further opportunities for which the Scottish infrastructure, expertise, population cohorts and NHS capabilities provide a particular competitive advantage for industry engagement. For example, the establishment of cancer genome testing in Scotland has attracted biopharma, UK government and other funder investment because of a world class ability by researchers to integrate genomics in clinical trials and advance therapeutic development. There have been remarkable advances in gene editing in recent years. At the present time these methods are being developed in a research context and are outside the scope of clinical practice. However this field is developing rapidly and opportunities for translation and clinical implementation are anticipated within the next 3-5 years that may impact within this timeframe on the clinical practice in Genomic Medicine.
Annex 1 – Recommended Actions

In the course of producing this report a wide range of possible actions were proposed which could advance or go some way to fulfilling the overarching recommendations. These actions are presented here to give those who have been identified as leading on next steps suggestions about how the recommendations might be taken forward.

1. Leadership
The Scottish Government should convene a Scotland-wide Leadership Group to advise how best to support the development of Genomic Medicine in Scotland; challenge barriers to progress; maximise impact for the benefit of healthcare, research and life sciences in Scotland; engage and involve the public; and increase Scotland’s influence at UK and international levels, positioning Scotland as a world leader in genomics in the wider context of Precision Medicine.

The Leadership Group should have high-level government support, be multi-disciplinary and cross-sectoral, and include significant patient and public representation in its membership. Social and ethical issues, including public confidence in data, should be considered as part of its remit. Scotland can be more nimble and flexible in its deployment of resources than many other countries, but the scale of the challenge should not be underestimated. Genomic Medicine is already impacting on frontline healthcare through prognostic, predictive and diagnostic tests, but realising the longer term benefits alongside other components of Precision Medicine will require planning and investment.

Proposed actions include:

- Agree short, medium and long term steps with Government to take full advantage of continuing advances in genome technology and Precision Medicine;
- Ensure that Scotland’s state-of-the-art genome sequencing facilities are put to the best use to underpin the development of Genomic Medicine in Scotland and beyond (Chapters 2, 3 and 10);
- Ensure that NHSS Boards are supported to adopt best practice from Genomics and Precision Medicine research, and encouraged to push the boundaries and increase diagnostic yield from next-generation sequencing (NGS) tests (Chapters 4 and 5);
- Monitor and respond to the outcomes of the Genomics England Short-Life Working Group on implementation of pharmacogenetics in the NHS, and the EU Horizon 2020-funded consortium on Ubiquitous Pharmacogenetics (Chapter 6);
- Ensure that strategies for infrastructure and workforce development, research and NHSS-academic-industry collaborative relationships are given appropriate weight at Government level (Chapters 7, 8 and 10);
- Champion a strategic review of PPIE, ensuring that the findings are implemented to develop a programme of patient and public education and awareness-raising, using well-evaluated methods (Chapter 9);
- Play a lead role in horizon-scanning and foster cutting-edge genomics research as the major contributor to Precision Medicine as this evolves on the worldwide stage.
2. Clinical Implementation

With Scottish Government support, NHS Scotland should expedite the evaluation and adoption of genomic testing strategies into clinical pathways where there is good evidence that these lead to improved patient outcomes. Clinical applications are evolving rapidly with incorporation of genomics into routine care closest for rare disease diagnosis, followed by patient stratification for targeted cancer therapy, followed by safer and more effective prescribing. The Scottish Government should also enable NHS Scotland to remain agile regarding latest genomic tool developments; to test, validate and contribute to the creation and implementation of international best practice in clinical governance of medical genomics; engaging with appropriate regulatory bodies at UK and international level. Failure to support best practice genomic capabilities in NHS Scotland will deprive Scottish patients of the benefits this cutting edge technology can provide and lead to Scotland lagging behind the rest of the UK and other high income countries.

Provision of tests should be guided by the rapidly evolving research landscape, NHS genetics and genomics services across the UK and recent service reviews in Scotland (Chapter 3). NHSS Boards should be supported to adopt best practice from Genomics and Precision Medicine research, and encouraged to push the boundaries and increase diagnostic yield from NGS tests (Chapter 4).

Results from the DDD and SGP research should inform the future mix of genomic testing to assure NHSS as a world-class comprehensive genetics service. Research should include a detailed evaluation of which patients are likely to benefit from which tests. Standard and value-based health economic models should be used to compare efficacy, cost-effectiveness and patient perspectives (Chapters 3 and 4).

NGS techniques should be implemented for molecular pathology of acquired disease and primarily the areas of cancer diagnosis, predictive and prognostic testing (Chapter 5).

In relation to congenital abnormalities and prenatal testing (Chapter 4):

- NIPT for routine screening should be made available nationally in NHSS in line with NHSE.
- Plans should be developed by NHSS for NIPD for genetic diagnosis in at-risk pregnancies.
- Chromosomal microarray testing and NGS technologies should be added to the diagnostic tests available in NHSS for pre-implantation genetic diagnosis (PGD).

The benefits of the SGP-developed clinically actionable genomic assay for newly-diagnosed cancer patients in Scotland (Chapter 5) should be validated by NHSS and adopted where appropriate.

Links between the NHSS Genetics services, the SMS-IC and the SGP genome sequencing laboratories should be strengthened to provide economies of scale, for example for exome and genome sequencing, and increase the speed and frequency of genetic diagnosis for patients in Scotland (Chapter 3).

NHSS should continue to validate and implement best national practice, engaging with the National Institute of Biological Standards and Controls (NIBSC), UK National External Quality Assessment Service (UK NEQAS), the Medicines and Healthcare products Regulatory Agency (MHRA), UK Accreditation Service (UKAS) and NHS England for continuous improvement (Chapter 7).
3. Workforce

NHS Scotland, working with NHS Education for Scotland, ScotGEN, Skills Development Scotland and academic institutions should lead in co-ordinating the development and delivery of the training courses and educational resources required to develop essential expertise to support and drive world-class Genomic Medicine capabilities in NHS Scotland. Investment will be required in training, recruitment and retention of laboratory, clinical and clinical academic staff, in different specialisms and at a range of levels.

Workforce recommendations from the 2017 NHS NSS National Services Division Review of Genetic Laboratory Testing Services should be considered carefully, including:

(i) Upskilling current staff
(ii) Attracting more talented individuals into medical genomics
(iii) Retaining highly-skilled and qualified staff
(iv) Ensuring that there are suitable succession plans in place

In relation to (ii) more skilled people are required at all levels: Genetic Counsellors, Clinical Scientists, Cancer Genomics, Pathology, Genome Informatics and Consultants. An increase in the number of training posts is required in all areas including trainee consultants and clinical science, and there is an urgent need to establish a funded training programme in Scotland for Genetic Counsellors. A review of postgraduate medical training in clinical cancer genomics is required, with support within Scotland for the Royal Colleges to enhance molecular pathology and genomic medicine provision within their training curricula. Consideration should be given to new Consultant appointments with dedicated expertise in Genomic Medicine in each of the regional centres.

In relation to (iii) urgent action is required is to retain the excellent, highly skilled, specialist genomics workforce already developed through the SGP programme to build on current research, deliver future services, share knowledge and help train the specialists of the future.

In relation to (iv), the creation of a new Consultant-level post in Genomic Medicine in each of the regional centres would significantly help with development of critical mass and expertise in this field.

A key task will be to improve the organisation and delivery of training at undergraduate and postgraduate level as well as within NHSS. Actions by NES and ScotGEN should include:

- Funded access within Scotland to existing high-quality University courses (e.g. the existing high quality courses of the MRC/EPSRC Molecular Pathology Nodes and the Medical Genetics & Genomics MSc programme).
- Promoting online genomics modules developed by Health Education England for use by NHSS staff (genetics, molecular pathology and across healthcare including trainees and students).
- Working with partners to establish mechanisms to support high level bioinformatics skills and career pathways which support the transfer of research knowledge from genomic technology, bioinformatics and data science to NHSS staff.
4. Digital Health
When delivering on its Digital Health and Social Care Strategy, the Scottish Government should take full account of the digital infrastructure needed to enable genomics within clinical pathways and to support the use of genomic data for research and innovation. This infrastructure includes: digital skills, supercomputing hardware, high capacity connected networks, and systems for data management and security.

The Government and NHSS Boards should:

- Ensure that the NHSS Genomic Medicine bioinformatics capacity – including hardware and software infrastructure, staffing requirements, digital leadership and the national digital platform – is a key part of delivering the Digital Health and Care strategy (Chapter 8).
- Ensure that development of NGS capacity in NHSS laboratories is supported by integrated solutions for test management, data processing, storage and data interpretation (Chapter 8).
- Include representation of key front-line stakeholders in both of the above, including the Scottish Genetic Laboratory Consortium, oncologists, haematologists, histopathologists, germline geneticists and medical genomics subject matter experts (Chapter 8).
- Develop a national informatics/data structure with clinical, audit and research functionality to facilitate eventual mainstream delivery of analysis and interpretation of WGS for a wide range of disorders with suspected genetic causes (Chapter 4).
- Develop strategies to ensure that bioinformatics pipelines are safe for clinical use (Chapter 8).
- Ensure the Scottish Genetics Consortium is resourced to work with eHealth, academic partners and the national data governance team to scope and deliver a national strategy for the hardware and software infrastructure needed to deliver genomics as part of routine care (Chapter 8).
- Ensure that suitable information governance arrangements are put in place to allay privacy concerns (Chapter 8).

5. Research and Innovation
The Scottish Government, working with research funders, industry, enterprise agencies and higher education providers, should consider how best to support genomic research and innovation in Scotland, including patient and public involvement and engagement, and maximise the opportunities for inward investment, building on Scotland’s current position of excellence.

Scotland needs to build a sustainable and flexible research platform for Genomic Medicine in order to support basic and translational research and ensure future innovation in NHSS services. A sustainable research platform will increase opportunities for innovation in healthcare. The genomics research community should be supported to maximise income from national funding opportunities and work with relevant enterprise agencies to build UK and international collaborations.

The Scottish Government could provide pump-priming monies to help develop competitive funding bids from Scotland. Working with NHS Scotland, the Scottish Government should consider the case for targeted investment to:

- Provide funding for strategic research in Genomic Medicine which supports pan-Scotland activities between Universities, NHSS, industry and international collaborators, to advance knowledge of the biological mechanisms underlying rare diseases and cancer, explore and support the expansion of the clinical and cost effective application of genomics in NHSS, and the clinical and health economic evaluation of Genomic Medicine and ensure that NHSS services keep pace with the latest research (Chapters 4, 5 and 10);
• Develop a research collaboration with NHSS Genetics laboratories using SHARE for a careful step-wise implementation of pre-emptive genotyping for pharmacogenetics, generating clinically accredited data making this available for future research (Chapter 6);

• Explore patient experiences, expectations and wider social and ethical issues arising from the blurring of boundaries between research and care pathways, with a view to ensuring that policy recognises societal views (Chapter 9); and

• Work with the Scotland’s enterprise agencies and UKRI to promote innovation through pilot projects and collaborative working to build industry partnerships, UK and international collaborations, which will deliver economic and clinical benefits to Scotland (Chapter 10).

Looking further ahead to the future impact of pharmacogenetics (Chapter 6), the Scottish research community should continue to:

• contribute to, review and evaluate the outputs of the Genomics England Short-Life Working Group on implementation of pharmacogenetics into the NHS; and

• engage with international initiatives piloting pre-emptive genotyping for pharmacogenetics, such as the EU-Horizon 2020 funded consortium “Ubiquitous Pharmacogenetics”.

Feedback from this work should be reported back to the new Scotland-wide Leadership Group (Recommendation 1) to ensure that the Scottish Government is fully briefed on new evidence, appropriate steps are taken by NHSS and research opportunities are taken forward.

6. Industry-Facing Activity

The Scottish Government, working with enterprise agencies, should build on the strengths of Scotland’s “triple helix partnership” between academia, the NHS and industry and consider how best to position assets across Scotland to maximise future engagement and partnership opportunities which will accelerate genomics development as an integral part of Precision Medicine.

Experiences from the Stratified Medicine Scotland Innovation Centre (SMS-IC) and other initiatives such as Scottish Enterprise’s Genomic Medicine Industrial Catalyst and the UK Research and Innovation Industrial Strategy Challenge Fund should inform next steps.

It will be vital to co-ordinate Scotland-wide efforts that enable Scotland to attract commercial interests, secure large global contracts and attract inward investment (Chapter 10). Continued investment in SMS-IC, the hub of Scotland’s Ecosystem in Precision Medicine, and the SMS-IC Data Commons would play a vital role in this. Investment in the Scottish sequencing centres will also be a vital component of any future strategy to make the most of commercial opportunities in Scotland.
Annex 2 – International Perspective

Many governments have plans to sequence human genomes for research and clinical purposes. Some of these are summarised below, including strategic Government investments, many of which have catalysed significant additional partnership funding, including commercial funds from Pharma, universities and regional initiatives.

<table>
<thead>
<tr>
<th>Country</th>
<th>Investment Details</th>
<th>Population (million)</th>
<th>Government Investment (with co-funding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>Genomics England was established by the UK Government in 2013 for the 100,000 Genomes Project. In 2018, a new aim was announced to sequence 5m genomes in 5 years, including expansion of the 100,000 Genomes Project to have 1m genomes sequenced.</td>
<td>54.8</td>
<td>&gt;£350m (£620m) + new funds tbc for next phase</td>
</tr>
<tr>
<td>Scotland</td>
<td>The Scottish Government and MRC awarded £6m in 2015 for the Scottish Genomes Partnership. A further £4.2m from the Scottish Government in 2018 aims to develop genomic medicine in NHS Scotland.</td>
<td>5.3</td>
<td>£10.2m</td>
</tr>
<tr>
<td>Wales</td>
<td>The Welsh Government and MRC awarded £3.4m in 2016 for an All Wales Medical Genetic Service. The Welsh Government announced a further £6.8m in 2017 as part of a Precision Medicine Strategy.</td>
<td>3.1</td>
<td>£10.2m</td>
</tr>
<tr>
<td>N Ireland</td>
<td>The Northern Ireland Executive and MRC awarded £3.3m in 2015 for the Northern Ireland Genomics Medicine Centre.</td>
<td>1.8</td>
<td>£3.3m</td>
</tr>
<tr>
<td>Estonia</td>
<td>The Estonian Genome Project began in 2000 and had collected 52,000 samples by 2017. The Estonian Government invested a further €5m in 2017 to support genotyping of 100,000 people. There are plans to combine 500,000 eHealth and genotype records.</td>
<td>1.3</td>
<td>&gt;£4.5m</td>
</tr>
<tr>
<td>Denmark</td>
<td>In 2017, the Danish Ministry of Health committed DKK 100m (~£12m) for PerMed to fund a national genome centre and database. They estimate previous investment of &gt;DKK 500m (£59m) for biobanks, genome sequencing and supercomputers.</td>
<td>5.8</td>
<td>£71m</td>
</tr>
<tr>
<td>Finland</td>
<td>In 2017, the Finngen project announced the aim of genotyping 500,000 people by 2023. £18m is the government commitment in a public-private partnership with 7 Pharma companies.</td>
<td>5.5</td>
<td>£18m (£52m)</td>
</tr>
<tr>
<td>Sweden</td>
<td>Government genomics funding through SciLifeLab from 2012-2016 is estimated as SEK 186m (£25m). In 2014, the Wallenburg Foundation gifted SEK 200m (£17.5m). In 2017 Genomic Medicine Sweden was established as part of a Government Precision Medicine strategy. Funds of SEK 45.8m (£4m) were awarded in 2018 in a co-financing package of around £7.3m.</td>
<td>10.0</td>
<td>£29m (£54m)</td>
</tr>
<tr>
<td>Iceland</td>
<td>The Icelandic approach is different as it has been led by private company deCODE, not Government. deCODE was established in 1996 with $12m from US venture capital and Pharma investment in 1998.</td>
<td>0.3</td>
<td>All private funds</td>
</tr>
<tr>
<td>France</td>
<td>The France Génomique (French plan for Genomic Medicine 2025) was launched in 2016, aiming for sequencing capacity of 235,000 genomes pa.</td>
<td>67.2m</td>
<td>£400m</td>
</tr>
<tr>
<td>USA</td>
<td>The National Human Genome Research Institute (NHGRI) was established in 1989. Its 2018 budget was $400m. In 2011, the Department of Veterans Affairs began to enrol one million veterans in a new DNA bank with the aim of identifying gene-health connections.</td>
<td>325.7</td>
<td>£1913m since 2014</td>
</tr>
<tr>
<td>Canada</td>
<td>Genome Canada was established by the Canadian Government to develop the use of genomics-based technologies for the benefit of the Canadian population. Their investment is in a range of industries including health.</td>
<td>36.7</td>
<td>£880m</td>
</tr>
<tr>
<td>Israel</td>
<td>In 2018, Israel’s government committed NIS 1 billion to support a National Genomic and Personalised Medicine Initiative, to sequence over 100,000 patients’ genomes from 2019-2023 and create a national database.</td>
<td>8.7</td>
<td>£210m</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>Government established a new company as part of the Hong Kong Genome Project. Initial budget of HK$682m (£67m) with HK$87m (£8.5m) pa for 6 years from 2019-25.</td>
<td>7.4</td>
<td>£118m</td>
</tr>
</tbody>
</table>
Annex 3 – Expert Contributions

The Scottish Science Advisory Council (SSAC) would like to thank all those who contributed to the writing and peer review of this report. Contributions came from all sectors NHS clinics, NHS laboratories, NHS commissioning, academic research and industry representatives. Particular thanks goes to the writing group for their expert knowledge and significant time spent on this review.

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Special thanks go to Professor Tim Aitman, and Dr Wendy Inglis-Humphrey for their additional work in co-ordinating the production of the final report.

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