Delivering a Globally Competitive Precision Medicine Ecosystem for Scotland

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On behalf of Health Science Scotland

22nd October 2015

Purpose of Paper:

Following the meeting hosted by the First Minister and Cabinet Secretary for Health, Wellbeing and Sport on 22nd September, 2015, [REDACTED], [REDACTED] and [REDACTED] were invited to provide details on the proposal that would accelerate the development of a Precision Medicine Ecosystem for Scotland.

Outline Proposal:

We request strategic investment for the Stratified Medicine Scotland Innovation Centre (SMS-IC). Specifically the investment will secure:

- An outstanding precision medicine platform that will "join up" the broad field of informatics to link detailed biology with human health and disease across Scotland
- Further investment in two flagship nationwide programmes on precision medicine of pancreatic cancer and multiple sclerosis
- A more powerful SMS-IC that aligns outstanding NHS, academic and business assets to drive beneficial change and efficiency.

This proposal is timely as it resonates with Scottish Government's Economic Strategy and the new CSO's Strategy for Health Research in Scotland. Specifically it:

- Fosters a culture of innovation and research and development within NHS Scotland
- Makes best use of public sector levers and funding to drive change
- Will develop a truly collaborative approach to precision medicine across the whole of Scotland
- Promotes Scotland on the international stage to boost our trade and investment, influence and networks
- Is consistent with Programme for Government 2015/15 that committed to support Innovation Centres to use academic expertise to address real world business issues, helping them to raise their profile with businesses in Scotland and beyond.

Introduction

Recently, there has been substantial global investment in public/private collaborations designed to accelerate the development of precision medicine for health and wealth benefits. Scotland is well positioned internationally to lead precision medicine. But several cutting-edge organisations and initiatives

must optimally coordinate to realise our potential and thus fulfil the scope and economics of each precision medicine programme, whether for academic, NHS and/or industrial output. These organisations include:

- *Stratified Medicine Scotland Innovation Centre (SMS-IC)* – a national collaboration between NHS Scotland, the Universities of Aberdeen, Dundee, Edinburgh, Glasgow, Scottish Funding Council, Scottish Enterprise, Thermo-Fisher and Aridhia. SMS-IC now has its permanent base at the Queen Elizabeth University Hospital Campus with University of Glasgow as administrative lead.
- *The UK Precision Medicine Catapult* – the Scottish National Precision Medicine Centre of Excellence (one of several UK centres to accelerate SME growth in the precision medicine market), to be based at the Queen Elizabeth University Hospital to create synergies with SMS-IC.
- *Scottish Genomics Partnership* - Universities of Edinburgh and Glasgow with Illumina (£15M), affording cutting edge technology and leadership in population and clinical genetics, cancer genetics and rare diseases.
- *Glasgow Polyomics* – state-of-the-art metabolomics, proteomics and transcriptomics.
- *Edinburgh Parallel Computing Centre (EPCC)* – the UK's supercomputing facility with advanced compute and storage capabilities.
- *NSS/Public Health Intelligence* (previously ISD) - health data services including longitudinal 'deep phenotyping' from electronic patient records, including Scotland-wide prescribing, imaging and hospitalisation data.
- *The MRC Farr Institute* – six Universities and NHS Scotland leading health informatics research.
- *NHS Research Scotland (NRS)* – biorepositories, clinical trials network and the federated network of regional safe havens in Aberdeen, Dundee, Edinburgh and Glasgow.
- *NHS Clinical Genetics* – diagnostic genetic services for cancer and rare genetic diseases.
- *Generation Scotland* – a rich resource of high-quality, consented samples and data for genetic and health-related research.
- *SMEs* in life sciences and informatics, both independent and supported by regional incubators at Bioquarter, Glasgow Biocorridor, Biocity Scotland and BioDundee.
- *MRC Molecular Pathology Hubs* in Glasgow (£3.4M) and Edinburgh (£2.0M).

Scotland thus has already invested heavily and is poised to compete effectively for leadership and commensurate funding within the global market for precision medicine services.

What is the problem?

With activities across academia, NHS and industry our greatest risk is fragmentation leading to: duplication of effort and infrastructure. This makes long-term sustainability less likely and Scotland may fail to provide a platform for SME growth. There is also the danger of confusing external customers as to how to engage with Scotland as a single destination for precision medicine programmes. Scotland currently has the ability to take a global lead in the implementation and commercialisation of precision medicine, this opportunity is time-limited due to the growth of investments elsewhere. Therefore there is an urgency to this proposal.

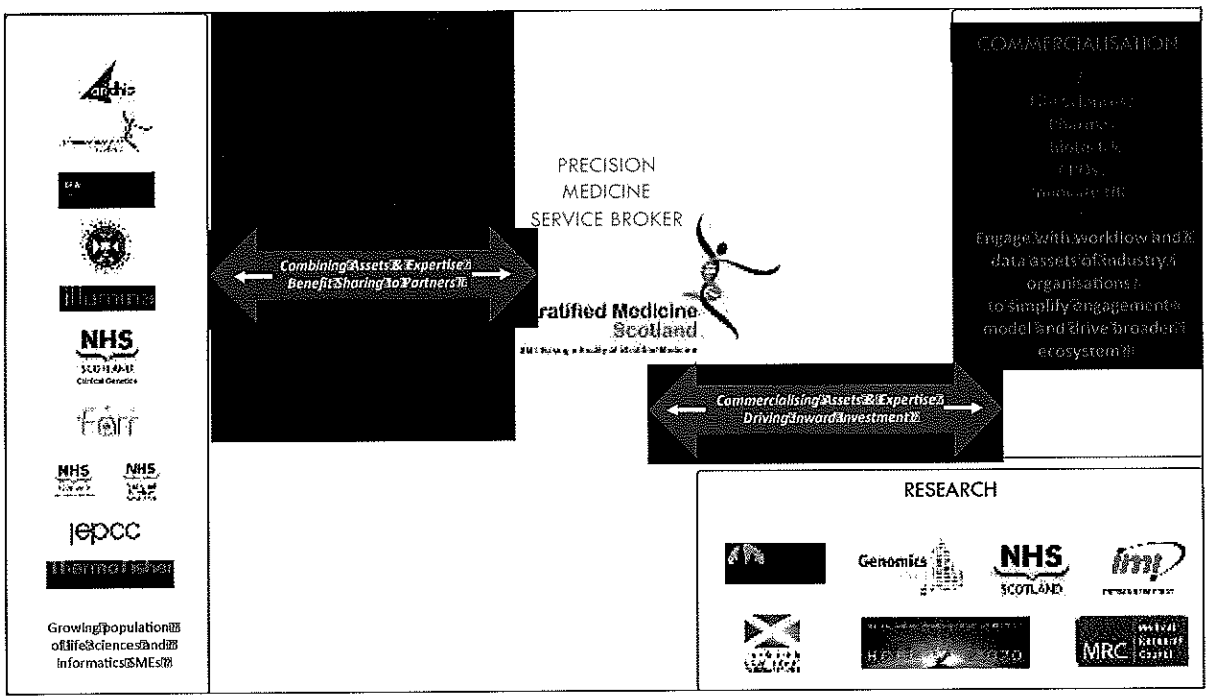
The Solution

We propose a solution that facilitates Scotland's leading position in precision medicine. SMS-IC will build a business model and service catalogue to facilitate a Precision Medicine Ecosystem in Scotland, including specification of benefit sharing across partners ('The Precision Medicine Service Broker Model'). This business model would leverage and incorporate appropriate existing assets and capabilities within Scotland

via technology partners (such as EPCC in Edinburgh), and enable a route to market for genomic service providers (including *the Scottish Genomics Partnership, Generation Scotland, Glasgow Polyomics* and the broader Scottish SME community). Engagement with the NHS would be enhanced through ever closer collaboration with NRS and the Farr Institute.

In essence, the opportunity and intent would be to use SMS-IC to provide the necessary coordination (1) to build on the discrete capabilities and assets that exist, and (2) to use those assets to configure precision medicine solutions that are optimised for purpose for commercial engagement and enable a business model of revenue sharing amongst Scottish partners. Through this model, we would accelerate adoption and speed to market for genomic services, and enable broader academic, industrial and NHS participation across Scotland.

This joined-up approach and single point of access to our ecosystem will enable Scotland to punch well above its weight as an international destination for precision medicine through clear engagement models, service level agreements, transparent pricing, rapid responsivity and the ability to interoperate with forthcoming global standards for federated analysis.



It is proposed that SMS-IC becomes the governance vehicle by which this vision may be achieved since it is already (1) an existing contractual collaboration between the interested parties and/or their parent institutions, (2) central to existing initiatives in Scotland in this space, and (3) has established relationships with the necessary stakeholders and their networks to ensure broad engagement. We are now further strengthening the governance, leadership and inclusivity of SMS-IC to ensure that all relevant components of Scotland benefit from our leadership of the rapidly growing precision medicine market.

Investment description

Essential to delivering the ecosystem is an informatics infrastructure and portfolio of services that allows SMS-IC to engage with the market in an efficient and highly supported manner. Much of this has already been built at SMS-IC. However, there are a small number of key capabilities requiring additional early

investment which are summarised below. Detailed work stream descriptions, individual budgets and intellectual property allocations are available for review.

Informatics Budget request (£2.9M)

The core informatics budget request (£2.9M) would enable the delivery of the workstreams highlighted below and the operation of these services, with the expectation that the Precision Medicine Ecosystem would become financially self-sustainable in the shortest possible time. SMS-IC will be extended to support these 3 crucial informatics functional deliverables to enable the ecosystem's rapid development:

1. Service Broker Model

Enabling Scotland's Precision Medicine Ecosystemd, through the initial establishment and maintenance of a participant programme and service catalogue. This would be followed by the setup of a business development/sales and solution definition function, to define the combined service offerings for specific projects, and to generate a pipeline of customers/programmes. Service delivery and project governance frameworks will be established to deliver integrated solutions to the customer, having back-to-back service level agreements with participating service providers, and agreed data access and interchange mechanisms.

Rationale

- Scotland as a precision medicine destination: customers can combine capabilities from across the precision medicine assets, programmes and domain expertise within Scotland to create their specific solution. There is a clear need, validated in industry engagements, for a streamlined contracting procedure. SMS would be the prime contracting authority and sub-contract/benefit share to other providers within the ecosystem.
- Business development/sales/marketing capability to help drive new revenue streams to Scotland under a coherent brand and business model designed for delivery and customer satisfaction.
- Underpinned by the capacity to deliver precision medicine services at service levels acceptable to the NHS, pharma and biotech industries.

Method

- Delivery of a market facing web portal into the SMS informatics platform. Principal purpose is to enable the informatics workflow, analysis, governance and reporting to be delivered in a manner that is aligned with customer expectations – degree of self service, provision of metadata tools and services on-line, automated reporting, collaboration tools.
- Resourcing a responsive team for business development and project delivery that compliments the existing Scottish domain-specific expertise, particularly in the NHS and academia.
- Development of outbound marketing programmes through the SMS-IC web site that presents the value proposition of the Precision Medicine Ecosystem, its process for engagement, case studies, and service catalogue.
- Implementation and operation of the virtual informatics environment that 'joins up' the disparate compute facilities available within the eco-system (SMS-IC, EPCC, Farr, others as the system grows) as required for individual customer programmes.

Budget Requirements 18 months (Jan 16 – Jul 17) £900K

- 4 SMS-IC FTE resources (Programme Manager, Business Analyst, Product Manager, Marketing Executive)
- Informatics build and operate - web portal, virtual informatics environment (collaboration with NHS, NRS, EPCC, others)

Key Deliverables

The expected outcomes of this part of the investment is a business development and delivery function that can reach out to the market for new clients, streamline opportunities that arise directly with members of the ecosystem, and enable delivery through an integrated informatics environment.

2. *Platform Services*

The validation of new diagnostic tests based on complex bioinformatics processing pipelines is currently problematic. These rely on 'big data' infrastructures which are not readily available to, for example, NHS customers. Existing capability at SMS-IC will be extended to support a development, test, validation, production and deployment workflow. This will support comparison of multiple genomic pipelines to inform procurement decisions, clinical/regulatory validation and subsequent use of novel tests for NHS patient care.

Rationale

- Precision medicine generates a fundamental shift in the scale that sequence data needs to be analysed and interpreted. Clinical organisations such as the NHS wishing to integrate genomics are faced with varying levels of maturity in the annotation products they are offered. Universities and companies have existing capabilities to develop and test pipelines in R&D environments but these do not scale and integrate well with clinical requirements. At the same time, the variety of health conditions, and the disparate know-how required to analyse the specific aspects of those conditions, means that multiple annotation providers (i.e. new and existing Scottish SMEs) will be required to support a broad-based clinical genomics service within the NHS.

- The NHS will be faced with the requirement to manage multiple annotation analysis pipelines and multiple interpretation tools and integrate these into their IT estate. Currently there is no clear framework for multiple annotation services to be procured or integrated into NHS systems. To ensure the NHS can support and benefit from the clinical adoption of genomics a new approach to on-board pipelines and operate them at scale in production mode is required. Services to support this must offer a set of guarantees around the provenance and repeatability of annotation services, and yield instrumentation data that is richer than may be supported by R&D infrastructure; in many cases information governance requirements and clinical accreditation (especially in the EU) would preclude the adoption of annotation services without those guarantees.

Method

The Precision Medicine Ecosystem platform services will comprise enhanced informatics capability to analyse clinical genomes (or exomes, gene panels) in a robust operational setting:

- The requirements for the platform services have been validated through extensive preparatory work with NHS, industrial and academic customers and users.

- Genomic repository - interim operational store of genomic data for clinical, research and industrial use is envisioned as a shared facility with EPCC. We envisage separate genomic repositories for research, NHS and industry in the medium term. An interim implementation will allow different stakeholders to iterate a clear set of requirements for the procurement for their specific needs.

- Clinical API - generic layer on top of clinical database to allow annotation pipelines and other apps to access specific datasets required to ensure patient-specific clinical analysis is undertaken as part of generating genomic reports.

- Annotation platform - allows 3rd parties, including NHS sites, to run multiple annotation pipelines against the genomic repository under controlled conditions, including as part of time-critical diagnostic and treatment stratification services. This platform will provide customers with the ability commission and manage multiple providers.

- Define input data standard for annotation pipelines so that NHS sites can submit cases for diagnosis/analysis of treatment options. This will standardise the interface for annotation providers, and reduce the cost for NHS customers to adopt the emerging technologies.
- Interoperability of annotation reports by defining NHS-acceptable report format/standard and providing adapters for annotation providers to deliver reports in that format. This will also reduce variation and waste when NHS commissions multiple annotation providers.
- Definition of bioinformatics and clinical quality measures for NHS customers to validated third party and internal annotation pipelines.
- This project requires some build, test and deployment to production. This will be done incrementally in partnership with NHS, industrial and academic customers.
- NHS pilots – including Genetic Testing Services at NHS GG&C. In order to demonstrate the utility of the platform services and their integration with new services.

Budget Requirements 18 months (Jan 16 – Jul 17) £1100K

- 2 NHS FTE resources - blend of skills including knowledge about service design, implementation, validation and applicability of annotation services for clinical decision-making.
- Informatics build and operate – multiple parties (NHS, Farr, EPCC, SMS)

Key Deliverables

The implementation of the platform services will incrementally create a world-leading market place for new genomic services that are integrated with healthcare provision. There will be clear incentive for companies to offer their services to the NHS community and Scottish start-up organisations will be able to validate their services with a reduced cost base.

3. *Federated Analysis*

Having a single entity act as the governance vehicle for interoperability and service level definition will enable and simplify local and international collaborations. Those collaborations will require low level access to genomic data, which must be balanced against the need to maintain patient and research participant privacy. Work will be undertaken to develop protocols and supporting systems for such analyses, based on emerging standards from the Global Alliance for Genomics and Health that SMS-IC and others are actively engaged in supporting.

Rationale

Federated analysis promises larger sample sizes, more comparison to get better insight and drive improvement. This has been highlighted in a couple of health-related domains:

- Genomics: given the high cost of data, its low mobility, and high privacy constraints
- Health Improvement where partnerships share data to drive up standards of care

In general, federated analysis is seen as supporting partnership models of collaboration, where parties agree in principle to cooperate but are reluctant or unable to pool resources for a variety of reasons – governance, cost, practicality. As genomics hubs increase in size and as the volume of data within large pharma/biotech hubs increases, it will become necessary to have data remain in situ and bring the analysis to the data.

Layered protocols allow a user to build up a federated analysis or report incrementally. At each stage a contributing party may check their willingness to participate in a subsequent layer.

A range of technologies are required to implement federation. At the time of writing, these are not in widespread use or even production quality. These might include:

- Open standards for query definition
- Agreed data sets
- Shared configuration management specification for (bioinformatics) compute
- Disclosure risk assessment (for 'filtering' PHI or identifiable data from results)

The Global Alliance for Genomics and Health has pioneered a number of the technical pre-requisites, including the data sets and query mechanisms to the extent that a meaningful test can be constructed to raise confidence in the approach.

SMS-IC is beginning a pilot on behalf of the Global Alliance to test (PoC) some of those federated analysis techniques. We have participation from England, Russia, Australia, US, China and Singapore. For Scotland, the Farr Institute is participating. We expect the results to build a specification for production services and adoption by the Genomics Alliance.

Method

- Develop second iteration implementation of GA4GH standard server reusing existing components
- Extended to clinical data (SMART/FHIR compatible)
- Engage with the NRS and University communities via Farr to capture requirements/controls on its use
- Run pilot projects with collaborating institutions

Budget Requirements 18 months (Jan 16 – Jul 17) £900K

- 3 FTE resources - blend of skills from multiple parties in the ecosystem; technical design and implementation, governance and audit, performance and reporting.
- Informatics build and operate – multiple parties (NHS, NRS, Farr, EPCC, SMS)

Key Deliverables

The Federated analysis workstream is expected to deliver a production service that is compatible with world leading institutions (e.g. EBI, Broad Institute) that implement local variants

Support multiple data sharing models for clinical and R&D use cases: commercially curated databases, private cohorts, networks of domain specialists (e.g. via the Matchmaker API)

Exemplar Projects (£1.1M)

To lead the international market Scotland critically needs to exemplify delivery of some high profile projects, thus bringing *Precision Medicine into Practice.* We propose two pivotally poised projects to be accelerated for this purpose:

Precision Panc

Clinical Context

The significant molecular heterogeneity, the lack of effective therapies, and the almost uniform mortality of pancreatic cancer (PC) provide an ideal opportunity to explore models of molecular phenotype-guided cancer care. Our increasing understanding of the molecular pathology of PC, the co-location of world-leading expertise in genomics, cell biology and pre-clinical therapeutics with substantial clinical trial

expertise and networks within Scotland and the UK, advanced health information systems, and the willingness of major pharmaceutical companies to share their assets, make the Scotland uniquely positioned to advance stratified therapeutic strategies for PC.

Response

A key deliverable of Precision Panc, a national initiative led by [REDACTED] which is developing mould-breaking molecular diagnosis and the consequent multi-disciplinary treatment of pancreatic cancer, is the establishment of at least one clinically approved molecular phenotype directed therapeutic target. This will make molecular phenotyping part of routine clinical practice and thus transform current clinical care and accelerate stratified therapeutic development. This needs to become part of routine clinical services for NHS Scotland patients.

An informatics architecture and set of informatics services has been developed between SMS-IC, Aridhia and NHS Greater Glasgow and Clyde. The funding would enable the deployment and operation of these services for a two-year period. This will be key to establish a viable product that can be exported to other healthcare providers and be adapted to other cancer types within the NHS. **(£550k requested)**.

FutureMS

Clinical Context

Multiple sclerosis (MS), a chronic and incurable neurological disorder, is the leading worldwide cause of non-traumatic disability in young adults. With over 10,000 prevalent cases and 650 new diagnoses annually, Scotland is the global capital for MS. Uniquely, and in contrast to all the other major progressive neurological disorders including the dementias, there are now many disease modifying treatment (DMT) options for newly diagnosed people with MS (pwMS). MS can thus be considered the pathfinder disease for therapeutics in neurology.

Aside from the emergence of DMTs, two recent advances in knowledge drive the current potential for positive change: (i) improved understanding of the two pathological processes that drive clinical outcomes in pwMS and (ii) objective and quantifiable surrogate measures of disease activity with respect to these processes. Although both pathological processes occur throughout disease, early disease is dominated by inflammatory mediated relapses and late disease is characterised by irreversible progressive disability due to neurodegeneration. Widespread availability of brain MR imaging surrogates of inflammation (T2 hyperintense lesion load) and neurodegeneration (cerebral volume loss) now allows accurate measurement of disease activity in both these dimensions without the limitations of poor sensitivity and specificity inherent in exclusively clinical measures.

Response

To increase adoption and implementation of stratification in MS, the need in Scottish neurological practice is therefore to link and align multiple and disparate "piecemeal" data sets in a single customised platform that enables implementation of personalised "point of care" decision / stratification tools.

The project has 'many elements of the eco-system in place: academic leadership, [REDACTED], sequencing from SMS-IC and the *Scottish Genomics Partnership*, clinical engagement through NHS Scotland, buy-in from the charitable sector and clinical community, industry partnership with Biogen, and a growing interest from other healthcare providers.

Existing investments in MS research and clinical integration will be enhanced through 2 key areas for development:

- Development and validation of standardised and automated analytics for clinical, imaging, laboratory, and prescription data sets that will support clinical stratification decisions in MS.

- Generation & validation of a point of care "clinical dashboard" with built-in stratification support tools.

These services will form the basis for a world-leading product that could be marketed to healthcare providers. The opportunity exists to accelerate both the commercial scope and the number of sequenced patients and market this exemplar globally during 2016. **(£550k requested)**.

Summary

In summary, a total funding of £4 million is requested, comprised of £2.9M for the Scottish Precision Medicine core informatics and £1.1M to accelerate two exemplar programmes. This will be pivotal to accelerate Scotland's progress to lead in precision medicine globally. The investment will enable us optimally to drive and exploit the opportunity afforded by stronger collaboration between existing partners, including NHS Scotland. It will enable alignment with the goals and aims of industry partners, including large diagnostic and pharma companies as well as Scottish SMEs.