Genetic & Genomic Medicine in Wales

A Vision Document from Welsh Scientific Advisory Committee

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This document proposes the development of a dedicated center for genetic and genomic medicine for Wales that will combine NHS services, Research and Development (R&D) and Innovation and Engagement (I&E) activity.

Contents

Summary

Genetic and genomic technologies, notably those for high throughput DNA sequencing, are central to contemporary life sciences. In health research and health care they inform the understanding of disease and its diagnosis, treatment and prevention. For patients, these technologies enable earlier and more accurate diagnosis and more individualised treatment ("personalised" or "stratified" medicine). Genetic and genomic technologies can also identify those who are currently well but at high risk of specific diseases, enabling prevention and early intervention for many otherwise serious disorders. In addition to the economic benefits of improved health genomic activities create opportunities for economic benefit by attracting externally funded biomedical research and enabling provision of diagnostic services to the UK and internationally, licensing and spin out of intellectual property (IP) and knowhow and development of commercial databases relating genetic variation to disease and health outcomes.

Strengths in genetics and genomics already exist in Wales and there is a track record of collaborative working in this area between NHS, Higher Education Institutes (HEIs) and the commercial sector. Current and projected changes in scale and scope of genomic medicine mean that for Wales to benefit fully from the development of genomic medicine there is an urgent need to develop estate, equipment, the workforce and databases of genetic and clinical data as well as agile systems and processes if it is to be competitive at a UK and international level.

This document proposes the development of a dedicated centre for genetic and genomic medicine for Wales that will combine NHS services, Research and Development (R&D) and Innovation and Engagement (I&E) activity. Government, University, charity and commercial investment could support different elements of the centre as it is developed.

1. Background

Current genetic and genomic applications in healthcare involve the identification and characterisation of inherited and somatic (acquired) human genetic variation and the characterisation of pathogen genes and genomes. These technologies enable the diagnosis of a very large number of individually rare inherited disorders, the more precise diagnosis and treatment of an increasing number of common disorders – notably cancers, the diagnosis and tracking of infectious diseases, better targeted treatment of individual patients to increase efficacy and reduce toxic effects and the identification of those at high genetic risk of specific disorders for prevention and early intervention.

Many elements required for the development of effective genomic medicine are in place in Wales. These include the All-Wales NHS Genetics Laboratory and Medical Genetics Service (both hosted by Cardiff and Vale UHB), expertise in genetics and genomics within the HEIs, particularly Cardiff University, and a strong track record of effective joint working between these organisations. There is existing support for genetics and genomics R&D from Welsh Government (via NISCHR) including the Wales Gene Park, a Biomedical Research Unit and Biomedical Research Centre supporting cancer genetic and neuropsychiatric genetic research respectively and the Wales Cancer Bank. Genomic medicine could be a flagship development to fit within the strategic agenda set out in Science for Wales for life sciences and health. However, in Wales the facilities for high throughput DNA sequencing are currently underdeveloped. A coherent plan for integration and further development of capacity and capability is required including dedicated space, lab equipment and associated Information Technology (IT) infrastructure and the availability of skilled laboratory and bioinformatic staff.

By comparison with the situation in Wales there has been considerable investment at the NHS/HEI interface in major centres in England and further significant commitments have been made very recently in England and Scotland e.g. £100M in England for sequencing genomes in 100,000 NHS patients and development of a new £20M centre for stratified medicine in Glasgow, , with the aim of ensuring that the UK remains at the forefront of this rapidly evolving field (Human Genomic Strategy Group Report, *Building on our Inheritance; Genomic Technology in Healthcare, 2012*; https://www.gov.uk/government/news/dna-tests-to-revolutionise-fight-against-cancer-and-help-100000-nhs-patients; http://www.gla.ac.uk/news/headline_275904_en.html

2. Opportunities for Improving Health in Wales via Genetics and Genomics

2.1 Rare Diseases

Rare diseases are defined in the European Union (EU) as those affecting less than 1 in 2000 of the general population. There are thousands of these disorders and cumulatively they affect 1 in 17 people (European Commission estimate) and most are genetically determined and in Wales services for their diagnosis are provided largely by the NHS All Wales Genetics Laboratory in conjunction with the UK Genetic Testing Network (http://www.ukgtn.nhs.uk/gtn/Home). Genetic and genomic technologies enable rapid and accurate diagnosis and have the potential to reverse the delays in diagnosis that have been a longstanding problem for affected patients and families (Optimising Lives, Optimising Resources: A Vision for the UK Rare Disease Strategy - at www.raredisease.org.uk). Service-ready Next Generation Sequencing (NGS) approaches to diagnosis include tests for panels of many different genes that determine similar clinical disorders (e.g. familial cancer syndromes, retinal degenerations). Tests of all genes or of all chromosomal DNA ("Exome Sequencing" and "Whole Genome Sequencing") are mainly research applications at present but will become service-ready within the next few years making NGS approaches truly comprehensive.

Increasingly, specific treatments for rare diseases are emerging based upon precise genetic diagnosis and an understanding of the genetic basis of these disorders (e.g. approved treatments including ivacaftor for cystic fibrosis, mTOR inhibitors for tuberous sclerosis and enzyme replacement therapy for Fabry disease). This scenario will become the norm rather than the exception. Cardiff University researchers at the Institute of Medical Genetics have been at the forefront of research into molecularly targeted treatment in this type of context. Consideration should be given to including treatment of inherited disease within the remit of a genomic medicine centre in Wales. A centre for genomic medicine could form a major plank of Wales' plan in response to the UK Strategy for Rare Diseases that is to be launched this month.

2.2 Cancer

Cancer medicine is the area in which application of genetics and genomics is currently most highly developed in common disease. The testing of tumours for changes in cancer-associated genes enables selection of therapies that will confer most benefit and least harm (side effects) for individual patients (stratified or personalised medicine). Clinical trials of new anticancer drugs are increasingly designed to include genetic stratification. Cardiff is an important UK centre for the development of stratified cancer medicine, being one of only 3 centres selected by Cancer Research UK to develop and evaluate this approach (the others being in London and Birmingham). There is potential to offer these skills and technology not only to the NHS and HEI sectors but also to Pharma in relation to commercial clinical trials. Researchers at Cardiff University's Institute of Medical Genetics have also established a track record in basic pharmacogenetic research, exploiting DNA samples and clinical data collected in association with UK-wide cancer clinical trials.

2.3 "Mainstream Medicine"

Diagnostic and pharmacogenetic applications of genetics and genomics are emerging across mainstream medicine. Major examples include in 1) **cardiovascular** medicine e.g. the diagnosis of cardiomyopathies, disorders of cardiac rhythm, familial hypercholesterolaemia 2) **neurology** e.g. diagnosis of neuromuscular disorders and neurodegenerative disorders 3) **paediatrics** e.g. metabolic disorders, learning difficulties/intellectual handicap, congenital anomalies 4) **obstetrics and antenatal care** e.g. screening for Down syndrome and single gene disorders including free fetal DNA analysis in non invasive prenatal diagnosis 5) **pharmacology** – genetic determinants of efficacy and drug safety in personalised medicine. These developments are reflected in a rapid growth of requests for DNA diagnostics from outside of traditional clinical genetic services and an accelerating year on year increase (currently 25% year on year) in genotyping workload in the NHA All Wales Genetics Diagnostic Labs. Opportunities are also beginning to emerge for applications in **psychiatric medicine**, an area of international strength in Cardiff University.

2.4 Infections & Microbiology

NGS enables the rapid characterisation of variation in pathogen genomes. This provides information that is helpful in individual patient management, for example in relation to drug resistance, and in the public health setting – for example in tracking and linking infection outbreaks and monitoring the evolution of genetic variation associated with changes in pathogenicity or transmissibility. Many of the technological applications and bioinformatics challenges are shared with human genetics. So far developments in human genomics and in genomics of pathogens have not been co-ordinated in Wales but opportunities for joint working should be explored as part of the strategy for genomic medicine.

2.5 Mental Health

Currently, the major clinical application of genetics and genomics is in diagnosing the causes of intellectual disability. Genomic approaches offer great advantages in terms of specificity and have enabled precise diagnosis in a rapidly increasing proportion of those affected. Cardiff University scientists have been at the international forefront of advances in genetics of the major psychoses (e.g. schizophrenia, bipolar disorder), neurodevelopmental disorders (e.g. autism, ADHD) and dementias (e.g. Alzheimer's disease). Some of these advances are now ready for pilot studies of clinical application. For others, the underlying genetic heterogeneity and complexity mean that the timeline to clinical application will be longer, but there is great potential for applied research.

3. Opportunities for Creating Wealth in Wale via Genetics and Genomics

3.1 External Research Income

In the year to April 2013 researchers in Wales won >£20M in new external (non-Wales) funding for R&D in genetic and genomic medicine. The vast majority of this funding relates to the areas of cancer, mental health and rare diseases, reflecting areas of genetic and genomic research strength in Wales. R&D income won for Wales comes from diverse sources including large and small charities e.g. Wellcome, CRUK and from UK Government via research councils with a small proportion (5% approx.) coming from pharma and technology companies. With appropriate infrastructure this income can be increased.

3.2 Commercial Income

Commercial opportunities in genetics and genomics that have been realised to date include licensing of IP, delivery of diagnostic services for the non-Welsh NHS and for international health care providers, provision of genetic and genomic services to pharma/trials and license income from commercial genetic databases (total >£1M in year to April 2013). Wealth generation through spin out companies based upon genetic and genomic R&D in Wales is in its infancy but has significant potential (e.g. in the year to April 2013 researchers from the NISCHR Cancer Genetics Biomedical Research Unit won investment to develop a spin out company for cancer prognostic tests based upon their patent “Method for using telomere length for prognostication”).

4. Realising the Vision

4.1 Estate

There has been no co-ordinated long-term plan for development of facilities for genomic medicine services in Wales. Current clinical and laboratory facilities for the NHS are fragmented at the University Hospital of Wales site. They do benefit from some co-location with academic medical genetic researchers at Cardiff University School of Medicine in the Institute of Medical Genetics and the adjacent BARRI Building. However, these buildings were developed prior to the genomic era, are full and include significant clinical/patient and administrative areas that are not segregated appropriately for a modern laboratory facility. Cardiff University has developed estate for research including genetic and genomic medical research including Biosciences 2 (city centre campus) for pre-clinical work, the Cancer Genetics Building (University Hospital site, opened Dec 2011) and the Haydn Ellis Building (Maindy Road site, opened 2013).

Possible scenarios for development of a centre for genomic medicine include a new build of combined NHS service and HEI R&D laboratory facilities, possibly in conjunction with facilities for out-patient clinical assessment. Planning for 150-200 laboratory staff to include the NHS All Wales Genetics Laboratory, Wales Gene Park Genomics Facility and Cardiff University researchers in genomic medicine from the University Hospital site would require floor space of approximately 3000 m^2. Facilities for long-term, large-scale DNA sample storage and automated retrieval will be an important component of the plans. An additional 1500m^2 could be needed if provision for clinical genetic services were also to be made. IT facilities for secure data storage and connectivity with bandwidth adequate for very large data sets will be required. Such a development could be considered at the Cardiff University Maindy Road campus (where other Health Science developments include the Institute of Ophthalmology, The Haydn Ellis Building including the neuropsychiatric genetics researchers and the European Cancer Stem Cell Research Institute and the planned CUBRIC2 brain imaging centre) or at the University Hospital of Wales site.

4.2 Equipment and IT

The rapid pace of technology development in genomics means that equipment for sequencing becomes out-dated very quickly. In Wales, some investment has been made in NGS technology via Wales Gene Park and the All Wales NHS Genetics Laboratory (>£1M).
Robotics and automation underpin DNA extraction and laboratory analysis. A step change in automation will be required to service a competitive facility for genomic medicine.
Genomic NGS technologies cannot be fully implemented within the current NHS IT infrastructure available to the All Wales NHS Genetics Laboratory. The Wales Gene Park has invested in and implemented an IT infrastructure for NGS in a research setting (approx. £250K) and a further investment is being made presently for the NHS genetics laboratory. Specific further investment will be required for secure data handling and storage in the diagnostic / NHS setting.

4.3 Samples and Clinical Data for Research

Genomic health research requires a combination of DNA samples (and usually other biological samples for functional work to confirm mechanisms) and high quality clinical data. A number of linked DNA/clinical data resources exist in Wales (for example disease-specific research cohorts and the Wales Cancer Bank). A Wales development in genomic medicine could include the building of a much larger, population-based sample and linked data set, taking advantage of the relatively stable population and the NHS in Wales. However, collection of comprehensive and high quality clinical data from the NHS remains very challenging and realising the potential value of such a resource is a long-term venture.

4.4 Personnel, Skills and Knowledge

4.4.1 Core Personnel

Joint working between academia and the NHS is critical to the development of skills and knowledge in technology and bioinformatics for genomic medicine. These relationships exist across organisations at the University Hospital of Wales site. Notably, the NISCHR supported Wales Gene Park and Cancer Genetics BRU have invested in technologists (3) and bioinformatics posts (2) for NGS research and the CRUK funded Experimental Cancer Medicine Centre (ECMC) supports a further NGS technology post within the NHS. Skills and expertise in NGS and bioinformatics are also present in research groups within Cardiff University, notably in the MRC Centre for Neuropsychiatric Genetics and Genomics, the NISCHR Cancer Genetics Biomedical Research Unit and NISCHR National Centre for Mental Health and, in relation to model organisms, in the School of Biosciences. These organisations are key stakeholders in the vision for genomic medicine in Wales and represent one potential mechanism for revenue support for capital investment in genomic medicine.

In the NHS, the AHSC clinical research time competition has resulted in awards to release small amounts of time for NHS Genetics Laboratory staff to develop NGS, but these awards are short term and cover only very small amounts of time for small numbers of personnel. Further technical support and especially leadership to develop bioinformatics for NHS diagnostics is required. No dedicated NHS bioinformatics support exists at present. This should be a priority for the NHS in Wales. In addition, medical charities for which development of genomic medicine in Wales represents a major opportunity (e.g. Cancer Research Wales) should be engaged to support these areas.

4.4.2 Expertise across Wales

Although most research relevant to genomic medicine in Wales is located in Cardiff, some medial genetic and genomic research is undertaken in other HEIs, for example genomic epilepsy research is well developed in the Institute of Life Sciences (ILS) at Swansea University. This work is linked to and supported by the Wales Gene Park and diagnostic applications are being made by transfer of know-how to the All Wales NHS Genetics Laboratory. The development of a centre for genomic medicine could provide support for research at HEIs across Wales, technical aspects of which would otherwise be outsourced from Wales.

There is potential to add significant value to databases and biobanks in Wales through development of associated genomic data. This includes enhancement of biological and data resources that can attract funding for externally funded research and increase their value to the commercial and pharmaceutical sectors. Examples include the Wales Cancer Bank at Cardiff University for which research funding for limited genotyping has already been established and HIRU at Swansea University. However, issues surrounding anonymisation in the face of significant genomic data need more detailed exploration.

4.4.3 Wider Links

The development of a centre for genetic and genomic medicine in Wales would generate new opportunities to engage the commercial and pharmaceutical sectors, attract and retain high quality and skilled personnel and compete more effectively for UK and European funding. It would provide a focus for working with similar centres in England and Scotland.

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