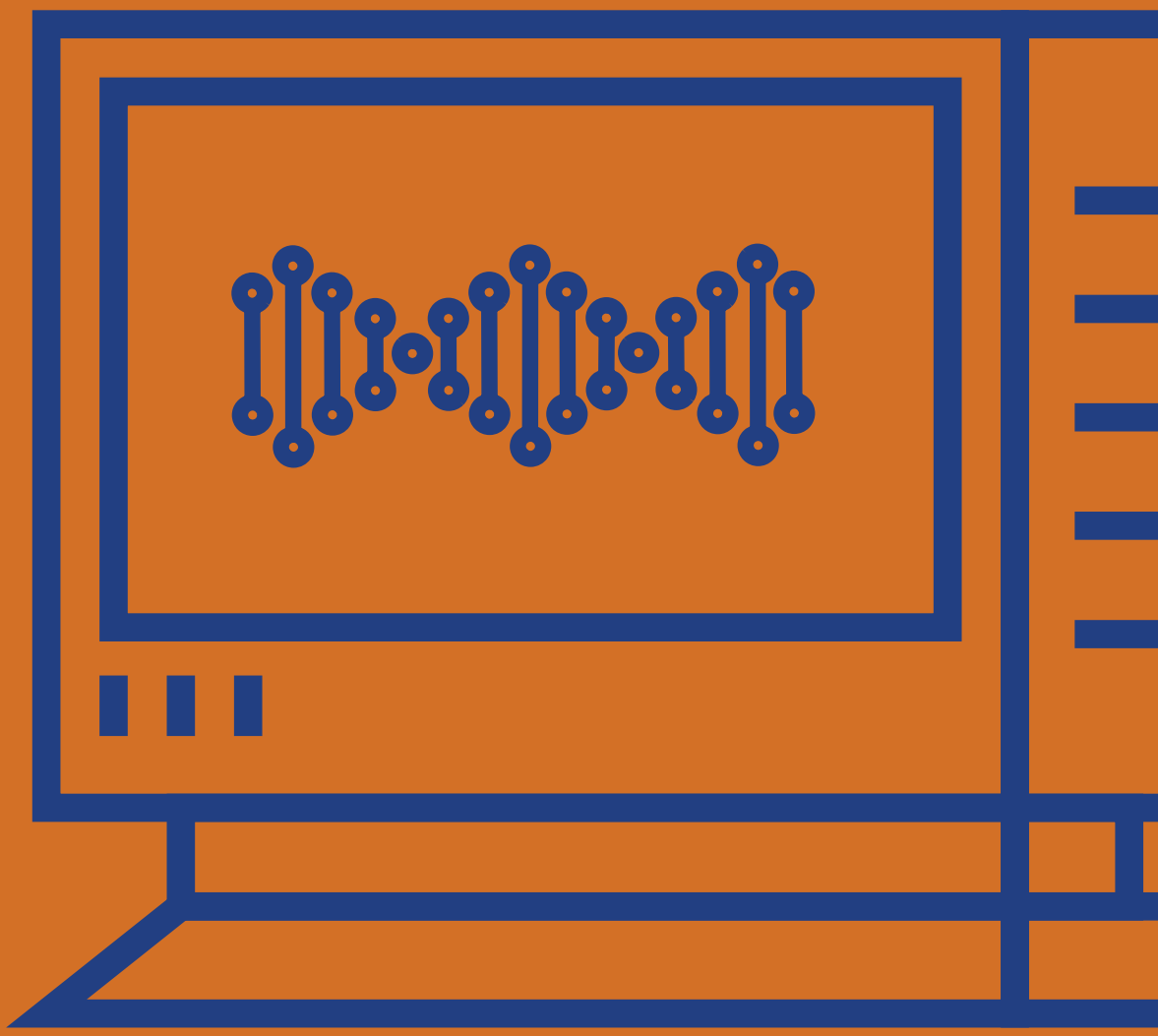


GENOMICS EXPLAINED

A guide to genomics and UK excellence in the field

UK BioIndustry Association

October 2018

Foreword

The 21st century is proving to be one of the most exciting and prolific periods of innovation in biosciences and healthcare. Advances across biology, technology, engineering and data science are converging to help create new, potentially life-changing solutions for individuals and societies across the globe.

Genomics – the study of our genetic material, or DNA – is enabling truly personalised medicines, designed to effectively address particular patients' disease with as few side-effects as possible. It is also paving the way to more accurate, convenient diagnostic products that help characterise and potentially prevent disease, by picking up signs much earlier.

> **The 21st century is proving to be one of the most exciting and prolific periods of innovation in biosciences and healthcare."**

As engineers and biologists join forces to build ever-more sophisticated gene-editing tools, new classes of medicines are emerging, including **cell and gene therapies**. These involve altering cells or genes, usually outside the body, to provide a patient-specific therapy that is re-injected into the patient. Scientists' growing understanding of how genes exert their influence, and of the crucial impact of multiple environmental factors on those genes ("epigenetics"), is opening up new frontiers of drug research. It has led to an explosion of activity around the gut microbiome – the colonies of micro-organisms residing in our gut – and its role in health and disease.

Genomics, **engineering biology** and related data and analytics tools are also helping fuel innovative approaches to tackling pathogenic bacteria. These may provide new, more effective and less toxic medicines for a range of life-threatening infections. Importantly, they may also help address the growing global challenge of **antimicrobial resistance**.

UK bioscience companies are at the forefront of these innovative, converging disciplines. These companies are a key part of the UK Bioindustry Association (BIA)'s membership and as the trade association for innovative life science companies in the UK, the BIA provides a home for these groups through our Advisory Committees and working groups on antimicrobial resistance, cell and gene therapy, engineering biology and genomics.

Given both this focus of our membership and the increasing external interest in how these innovations can tackle key challenges that society faces and contribute to the growth of a 21st century economy, the BIA is delighted to publish this series of four explainers on antimicrobial resistance, cell and gene therapy, engineering biology and genomics.

Within these explainers, we describe what these areas are all about, the important contributions made by UK bioscience firms, and the external environment required to ensure that these innovative approaches continue to benefit patients, the economy and society as a whole.

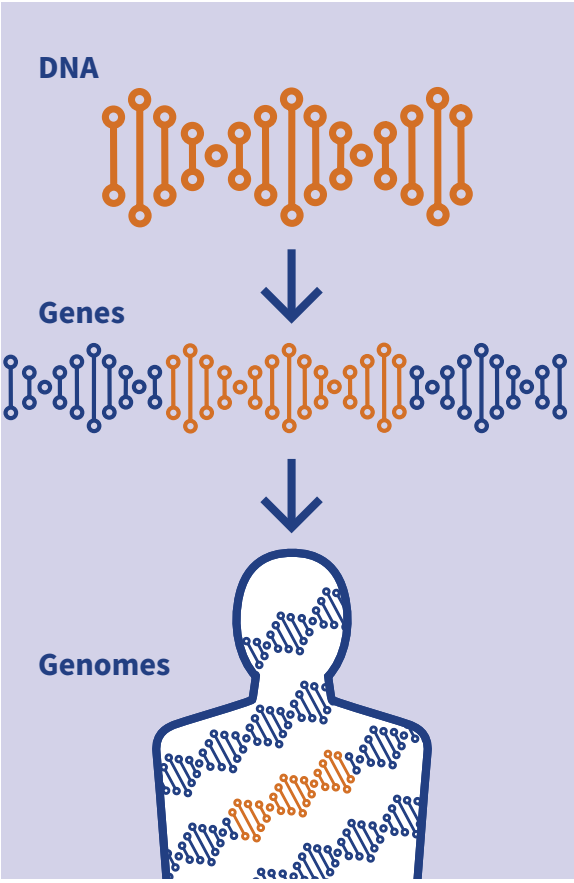
I hope you enjoy reading them.

Steve Bates OBE
CEO, UK Bioindustry Association

What is genomics ?

The sequencing of the human genome at the start of the 21st century uncovered the series of letters – chemical codes – that make up our genetic material. That was an important step. But learning how to interpret and, in some cases modify, that genetic code is even more significant.

That's genomics – reading, understanding and editing the genetic instructions, or DNA, that make up each one of us. DNA, deoxyribonucleic acid, is a chain of four types of molecule, called nucleotides, arranged in a spiral, ladder-like structure called a 'double helix'. (This structure was, famously, uncovered by Cambridge scientists Francis Crick and James Watson in 1953 – with some unacknowledged help from Rosalind Franklin.) Each nucleotide is represented by a letter – A, G, C or T. A gene is a specific sequence of these four letters, whose arrangement contains information about how to make a particular molecule (protein). These proteins, in turn, determine what we look like, how we develop and how we function. Human DNA, contained in the nuclei of every single one of our cells, contains about 20,000 genes and about 3 billion nucleotides, or bases.



When cells divide and multiply, errors can occur as the long, highly-repetitive DNA code is copied. These coding errors, known as 'mutations', can lead to disease. The mutations may be inherited, or caused by environmental factors, such as exposure to toxins or even certain stress hormones. Many cancers, for example, result from damage to cellular DNA incurred over a lifetime. Cystic fibrosis occurs when children inherit two copies of a faulty gene called cystic fibrosis transmembrane conductance regulator (CFTR).

Few conditions are so neatly associated with a single gene. Some, like certain cancers, are found to be associated with a range of possible genetic mutations, at multiple sites. The discovery of these mutations is leading to new disease sub-categories, such as HER-2 positive breast cancer. Women with this version of the disease have a faulty gene that encodes for too much of a protein called HER-2, leading to excessive cell-division.

The promise of genomics goes well beyond human genomes. Genomics has helped uncover the workings of many other organisms that co-exist with, and inside us. The combined genomes of the trillions of micro-organisms that reside in our gut, for instance – the gut microbiome – has opened up an exciting new frontier of health-related research. These organisms are intricately involved in our health, and disease, in ways that we are only just beginning to unravel.

Personalised medicine

Scientists' growing understanding of the human genome, and those of other organisms, is already transforming healthcare. Genomic analysis has uncovered that the genetic signature of many diseases may be unique to small groups of patients, or even to individuals. This knowledge has enabled the development of more personalised therapies, or therapy combinations, that can more effectively treat particular patients, potentially with fewer side-effects than their less-targeted counterparts.

Accurate diagnosis is key to personalised medicine (and to any effective treatment). Genomics-based diagnostic tests can now rapidly assess mutations across multiple cancer-associated genes, for example, allowing patients and clinicians to make the most appropriate treatment choices. Genome sequencing approaches are leading to more rapid and accurate diagnosis of infectious diseases, helping identify particular bacterial, fungal or viral culprits via their DNA, rather than cultivating them in a petri-dish. The spread and virulence of infections in hospitals and communities can be more effectively measured, monitored and even predicted using genomics-based techniques.

Screening and prevention

Scientists are also using genomics in disease screening tools. Several groups are working on a blood test that may be able to detect signs of cancer very early on, before symptoms appear. The approach looks for bits of mutated DNA shed into the blood by cancer cells, as well as other substances associated with the disease. These 'liquid biopsies' could one day enable earlier treatment that is more likely to be effective.

Genomic-based insights are already helping prevent certain diseases altogether, by better understanding the associated genetic risk factors. Angelina Jolie, the Hollywood actress, famously underwent a double-mastectomy in 2013, after learning that she carried a faulty version of a gene called BRCA1. The mutation significantly increases the risk of contracting breast and ovarian cancer.

Beyond the Gene: Epigenetics

Only a tiny portion of our DNA comprises protein-encoding genes. (And we only understand the function of a few of those.) The rest – an astounding 95% of the string of nucleotides – is involved in *controlling* which genes are expressed, when, how much and how fast. Chemical modifications in this vast gene 'control panel' can occur as a result of our daily activities (such as sleep, diet, stress and exercise), our environment, as well as disease. Epigenetics is the study of these changes in gene on-off switches and volume dials, and indeed any modifications to gene expression which do not involve changes to the underlying sequences of nucleotides.

Epigenetic changes are many and widespread. Scientists are only just beginning to uncover their role in complex conditions including cancer, auto-immune diseases and neurological disorders. Yet already, epigenetics research is leading to potentially more accurate, earlier diagnostic tools, and helping identify new avenues for drug development.

Epigenetics explains why genomics data on its own is not enough to predict how long, or how healthily, we will live (despite the emergence of consumer-focused DNA sequencing services). Genomics can tell us some very useful things, however, such as how our bodies are likely to respond to certain medicines, or, in some cases, whether they will work at all. Such pharmacogenomic testing is already used for some cancers and other conditions, where medications are targeted at patients with specific gene mutations, or where there are known drug-gene interactions that may be dangerous.

Data, data everywhere

Although genomics is rooted in biology, it is fundamentally about data. Genomics, and the study of related epigenetic, molecular and cellular mechanisms involved during the cascade from gene to protein to physical characteristics, are generating vast swathes of data.

Collecting, analysing and making sense of those huge data-sets is a multi-disciplinary challenge. It requires data scientists, bioinformatics experts and engineers alongside biologists, chemists and clinicians. These experts are collaborating to enable, for instance, efficient, precise, cheaper and more convenient DNA sampling, sequencing, analysis, interpretation and application. They're building systems that combine genetic, epigenetic and other kinds of molecular data with clinical, behavioural and other kinds of information to help paint a fuller picture of human health and disease, and to help identify new drugs and diagnostics.

Genomics is still a relatively new field. But, alongside advances in data sciences and engineering biology, it is already significantly impacting healthcare and other areas.

UK excellence in genomics

The UK is a leader in the genomics-driven transformation of healthcare. The country boasts an unrivalled mix of world-leading research and medical institutions, biopharmaceutical companies, digital technology start-ups and investors, packed tightly within a relatively small area. This provides the perfect environment for genomics-based R&D and its commercialisation.

The Wellcome Genome Campus, situated just outside Cambridge, was a founding member of the human gemome project and was the single largest contributor of data to this project. It has the largest concentration of genomics scientists in the world and it is expected to at least double in size in the next 20 years. It's home to one of the biggest data repositories, the EMBL's European Bioinformatics Institute, the Wellcome Sanger Institute and the Biodata Innovation Centre, an incubator for genomic and biodata companies, many of which are featured in the following case studies. These organisations not only benefit from their own co-location, but also their proximity to the broader life science expertise concentrated in Oxford, Cambridge and London and beyond.

100,000 NHS patients

13 dedicated NHS Genomic Medicine Centres

2,500 researchers

Genomics England's sequencing facilities are also now located at the Wellcome Genome Campus. Genomics England was established in 2012 to sequence the genomes of 100,000 NHS patients with rare diseases and cancer. The project has been integral to ensuring that the NHS has the infrastructure and systems in place to deliver genomic medicine, with many thousands of diagnoses made which previously would not have been possible. Diagnostic yields have been increased many-fold, improving patient care, treatment choices, and disease management on an unprecedented scale. NHS England has created a network of 13 dedicated NHS Genomic Medicine Centres across the country to deploy this UK leading technology into front-line clinical care. Genomics England is facilitating new medical discoveries and innovation by giving over 2,500 researchers, NHS clinicians and trainees access to the data it has collected via its disease specific Genomics England Clinical Interpretation Partnerships (GeCIPs). Alongside this, Genomics England has played a key role in kick-starting and building a UK genomics industry by allowing industry to access its data, identifying opportunities for collaboration and creating demand for analysis and interpretation services. Genomics England will continue to prioritise this function following the completion of the 100,000 Genomes Project in order to reap the benefit obtained from this data and provide new and better treatments.

Sitting at the interface of life sciences and data science, genomics drives two of the most highly-skilled and high-growth sectors, both of which have been prioritised by the UK government's Industrial Strategy via various incentives and funding opportunities. In the Life Sciences Sector Deal, the government committed to investing £210 million in data technologies that will support earlier diagnosis and the development of precision medicines. It has been announced that some of this funding will be used to sequence the genomes of all 500,000 Biobank participants, with additional financial support from industry, and to create a network of Digital Innovation Hubs. The hubs will be overseen by Health Data Research UK and will link NHS health and care information with biomedical data in secure and controlled environments. NHS clinicians, health researchers, data scientists,

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computer scientists, ethicists and social scientists will be encouraged to use the data collaboratively to discover and develop new treatments more quickly. The prominence given to artificial intelligence via the AI and Data Grand Challenge and AI Sector Deal also provides a welcome boost to the genomics sector and will help drive the development of key technologies for genomic data analysis, interpretation and application.

This level of scientific activity and government support makes the UK an excellent location for start-ups, spin-outs and more mature companies specialising in genomics and bioinformatics.

In 2015, a report published by the UK government and Deloitte[1] valued the UK genomics industry at £0.8bn and predicted rapid growth. By reviewing the revenues of UK genomic companies, the Deloitte report identified 5 elements to the genomics value chain:

- **Sampling** – The process of collecting and packaging samples
- **Sequencing** – Decoding the nucleotides in a genome
- **Analysis** – The process to identify disease-causing variants, often run by bioinformatics software
- **Interpretation** – Taking analysed information and providing clinically useful interpretations and results
- **Application** – The process of directly using genomic information to improve targeting of clinical services

Sequencing is currently the largest part of the value chain, generating revenues in the UK of around £500 million. However UK companies specialising in analysis, interpretation and application are growing in size and number, as shown by the following case studies.

To find out more about the BIA's Genomics community please visit:

www.bioindustry.org/bia-membership/advisory-committees/genomics-advisory-committee.html

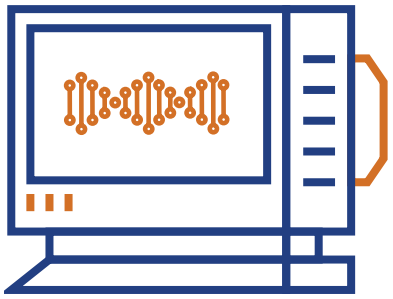
1 *Genomics in the UK: a study for the Office of Life Sciences* https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/464088/BIS-15-543-genomics-in-the-UK.pdf

A snapshot of UK companies driving excellence in genomics

The **Wellcome Genome Campus** is home to research institutes, spin-out and start-up companies, academic-industry partnerships and Genomics England; all dedicated to driving and leading genomics research and innovation and houses the largest concentration of genomics scientists in the world. **The Wellcome Sanger Institute**, a major contributor to the Human Genome Project which celebrated its 25th anniversary in 2018, is built to think big: among its latest projects is the Human Cell Atlas, an ambitious, international consortium seeking to define and map out the exact characteristics of every single cell type in our bodies. Located just outside Cambridge, the Wellcome Sanger Institute sits next to one of the biggest life sciences data repositories, EMBL's European Bioinformatics Institute. This innovation and data-rich infrastructure is expanding, for instance with the BioData Innovation Centre, opened in 2016 at the Wellcome Genome Campus to house emerging genomics and biodata companies.

Largest concentration of genomics scientists in the world

Among those is **Congenica**, whose genome-analysis software filters raw genomic data and extensive clinical information to generate insights to help clinicians diagnose and treat patients with inherited diseases. Congenica's Sapientia platform is designed to provide genome sequencing, annotation, interpretation and customisable clinical reports, with the added flexibility of allowing genetic and relevant clinical data to be uploaded in a variety of formats. Using sophisticated data analysis tools Sapientia interprets the genetic and clinical "phenotype" information of the patient and also interogates previous diagnosis or disease relationships seen at the population level to rapidly deduce the most accurate diagnosis for the individual patient. Validated as part of the UK 100,000 Genomes Project, Sapientia is being used by the NHS today to make important diagnosis and improve the lives of patients. The company is also partnering with clinical and research organisations across the world. In China, it is supporting whole-genome sequencing as part of the country's 100k Wellness Pioneer project, seeking to improve health through understanding the genomes and other molecular and clinical information gathered from 100,000 Chinese citizens.



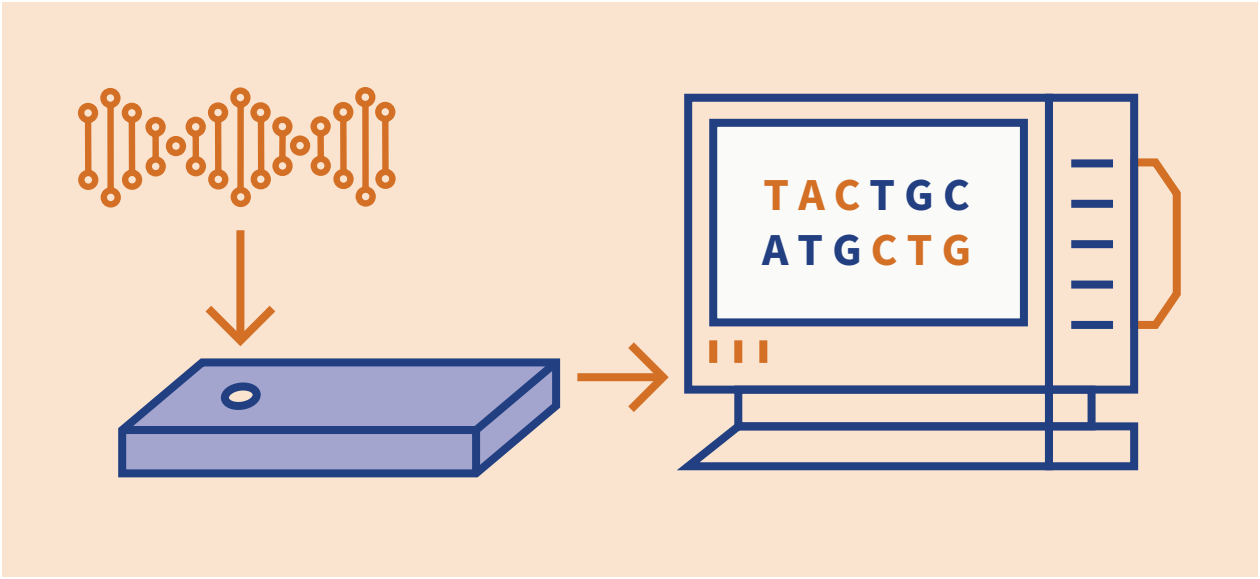
Another BioData Innovation Centre resident is **Eagle Genomics**, whose smart data management platform is designed to help researchers turn genomics data into insights that can inform the development of new solutions across a range of industries. Eagle's platform curates, annotates and organises human genome data, as well as microbiomic data – from the genomes of micro-organisms in our gut or on our skin, for instance – highlighting connections and inter-dependencies within these data sources. The approach is accelerating research and R&D efficiency across areas including healthcare, cosmetics, food safety, biofuels and agriculture. The company, sitting at the interface between biology, data science and bioinformatics, is named after the Eagle pub in Cambridge, where Francis Crick and James Watson in 1953 announced their discovery of how DNA carries genetic information.

In Oxford, **Genomics plc's** mission is to turbo-charge drug discovery by better understanding human biology and disease. The company has built one of the

largest repositories of genomic and phenotypic information, capturing the effects of millions of genetic variants on health and disease. Genomics plc applies powerful machine learning to these vast databases, seeking novel genetic and molecular pathways that may form the basis of new drugs. In October 2017, US biotech giant Biogen signed up Genomics plc to help find new drug targets for multiple sclerosis. The UK company taps into a rich pool of local expertise, including the health-focused Oxford Big Data Institute, and has recently opened offices in Cambridge to broaden their access to experts, including from the Wellcome Genome Campus.

UK-based companies are also taking genomics global – and beyond. **Global Gene Corp**. is building longitudinal genomic data sets from under-explored populations in India and South Asia. The genomics data company is working with over 50 partners worldwide to help democratise precision medicine, by ensuring that data is collected from less-studied patient populations such as those in South Asia. At the moment, 60% of the world's population accounts for only a tiny portion – less than 5% – of available genomics data. Yet certain diseases, such as cancer, may manifest differently in Indian and South-east Asian patients versus those in the US or Europe. Understanding those differences may ultimately lead to better treatments for patients everywhere. Global Gene Corp. has R&D facilities at the Wellcome Genome Campus in Cambridge, UK and offices in Boston and Singapore.

Oxford Nanopore's range of real-time, low-cost DNA sequencing devices, from benchtop to pocket-sized, are opening up biological analyses to scientists across multiple disciplines, in multiple locations. Its tiniest sequencer, which weighs less than 100g and plugs into a laptop, has been used to answer biological questions in clinical research, on farms and in food production factories, and even on the International Space Station. The technology involves passing currents through biological nanopores – small holes made by special proteins – and measuring changes as molecules, like DNA or RNA, pass through or close to the nanopore. Oxford Nanopore's technology is not only about size and convenience; it can also help make research more rapid and efficient. As a sample is analysed, data is streamed in real-time, meaning researchers can stop as soon as they have enough data to answer their question. Such rapid results mean that, for example in infectious diseases, pathogens and their drug resistance properties could be identified from their DNA in minutes or hours, rather than days or weeks.



> Genomics is already changing medicine, making it more personalised, and ultimately more effective."

Based in Oxford, with offices in Cambridge, UK and in the US, Oxford Nanopore also has a commercial presence in China, Japan, France and Germany, and is expanding its UK manufacturing facilities as demand for its technology increases. The company raised £100 million in March 2018 from global investors, bringing its total funding since inception to over £450 million.

Genomics is already changing medicine, making it more personalised, and ultimately more effective. **NewGene**, in Newcastle, provides molecular diagnostic services to NHS hospitals and other healthcare providers, using high throughput genome sequencing and genetic profile analysis. These diagnostics help clinicians identify the most appropriate treatment for specific patients. The group, set up as a partnership between the Newcastle-upon-Tyne Hospitals NHS Foundation Trust and Newcastle University, also works with pharmaceutical companies and the NHS to validate novel biomarkers and to develop new diagnostic tests that can further guide treatment choices.

Cambridge Cancer Genomics is using artificial intelligence and smart genomics to develop new, smarter blood tests that can rapidly signal whether, and how well, a patient's cancer treatment is working. Liquid biopsies test the blood for cancer cells or cancer cell DNA that may be circulating in the blood. Besides being relatively quick and simple, liquid biopsies could help pick up cancer at an earlier stage than other kinds of tests. They may one day be able to better predict the most appropriate therapy for patients before treatment has even started.

Cambridge Epigenetix is building diagnostics and therapies based on their understanding of the multiple epigenetic influences on disease. The epigenome is the set of chemicals and processes that make up our genetic "control panel", regulating which genes are turned on or off, when, and for how long. Multiple external factors – our environment, lifestyle, diet, age, stress levels and more – can affect the structure of our epigenome, and with that, our risk of disease. Indeed, mutations within epigenetic regulators are among the most prevalent across all cancers. Cambridge Epigenetix's range of technologies enable the identification of sensitive, disease-specific epigenetic markers from samples of blood and tissue. Such epigenetic markers may enable earlier detection of certain complex diseases like cancer. The company is developing diagnostics – including minimally-invasive liquid biopsies – for various important diseases and offers a biomarker discovery service. Privately-owned Cambridge Epigenetix was spun out of the University of Cambridge in 2012; its backers include Google Ventures and Syncona.

What next?

The UK is clearly a world-leader in terms of genomic science, with the potential to create genomic "unicorns", companies with >$1B market capitalisation. However, before the UK can unleash this potential the challenge is transforming this academic excellence into an industry that can compete internationally. The UK genomics market is currently characterised by smaller companies, many of which have 10 or fewer employees and are at pre-revenue or spin-out stage. Genomic companies therefore struggle with many of the challenges common to start-ups and scale-ups across the biotech sector, most notably access to long-term finance. The implementation of the Patient Capital Review, a government initiative exploring how to increase the supply of capital to grow innovative firms, and measures set out in the Industrial Strategy will address some of these issues. Nonetheless, the UK genomics industry will continue to face several challenges that are specific to the field.

Using genomics to predict, cure disease and improve disease management."

Compared to other areas of bioscience, genomics is still in its infancy and is, by its very nature, inherently uncertain. As whole genomes are sequenced, a large number of variants will be identified in an individual, and yet their significance will be largely unknown. Using genomics to predict, cure disease and improve disease management involves understanding interactions between multiple genes and the impacts of environmental factors. This requires extremely large data-sets and significant clinical investment, well beyond what can be achieved solely in the UK. International collaboration will therefore be a crucial part of furthering our understanding of genomics and how to apply it and ultimately growing a domestic genomics industry.

The UK is already at the forefront of many of these international collaborations, including the Global Alliance for Genomics and Health (GA4GH). The Alliance brings together over 500 organisations working in healthcare, research, patient advocacy, life science, and information technology worldwide to create frameworks and standards to enable the responsible, voluntary, and secure sharing of genomic and health-related data. Initiatives such as this, which ensure the interoperability of data globally, will become increasingly important as the sector grows, and sequencing technologies become cheaper and more readily available. Plans to increase and improve the use of patient data in the UK, such as the Digital Innovation Hubs, must take internationally agreed standards and frameworks into account if they wish to contribute to the broader genomic effort and position the UK as a world-leader.

Conversations around consent and how best to store patient data in a way that is secure but allows access for research will also be key to unlocking the potential of genomics. These conversations must include discussions around the commercial use of patient data to ensure that the UK genomics industry is not stifled by a lack of access to appropriate datasets. Recent polling conducted by Ipsos MORI on behalf of The Health Foundation shows that the public are generally happy to share their data with professionals involved in their care but few support commercial organisations accessing health data to undertake research.[2] Genomic companies should work alongside the NHS, patient organisations and charities to explain the value of research conducted by commercial organisations and its role in the broader biomedical process.

As part of the social contract around sharing patient data, the UK should invest in the bioinformatic and software development skills required to analyse and interpret genomic information in order to develop new treatments and diagnostics. In 2015, Deloitte predicted

2 www.nuffieldtrust.org.uk/files/2018-06/1530028974_the-nhs-at-70-what-will-new-technology-mean-for-the-nhs-and-its-patients.pdf

that the NHS faced a shortage of 24,000 informatics professionals, when compared with the US health system. To support the delivery of the 100,000 Genome Project, Health Education England developed a Genomics Education Programme to upskill NHS staff however, genomic expertise will be needed across the ecosystem, including in industry. There are a number of initiatives already in place to address the shortage of bioinformaticians as part of the UK government's efforts to address the broader STEM skills shortage. In addition, the government should ensure that a post-Brexit immigration system does not make it unduly burdensome for UK genomic SMEs to bring people with the skills they need in to the UK.

The overarching aim of genomic science is to improve healthcare by developing new diagnostics and treatments that can be personalised for each patient, but this requires significant buy-in and investment by the NHS. In June 2018, the government announced that the NHS would receive a £20.5bn increase in real-terms funding by 2023/24. As part of the announcement, the Prime Minster highlighted *"the opportunity to lead in the use of data and technology to prevent illness, not just treat; to diagnose conditions before symptoms occur, and to deliver personalised treatment informed not just by general understanding of disease but by your own data including your genetic make-up."* However, achieving this ambition will require more than just money. The NHS will need to develop a culture that embraces change to support the adoption of this level of innovation. If this can be done, the NHS, as a single national purchaser and provider of healthcare with access to large datasets, will become a significant 'pull' factor for genomic companies deciding where to locate and invest.

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