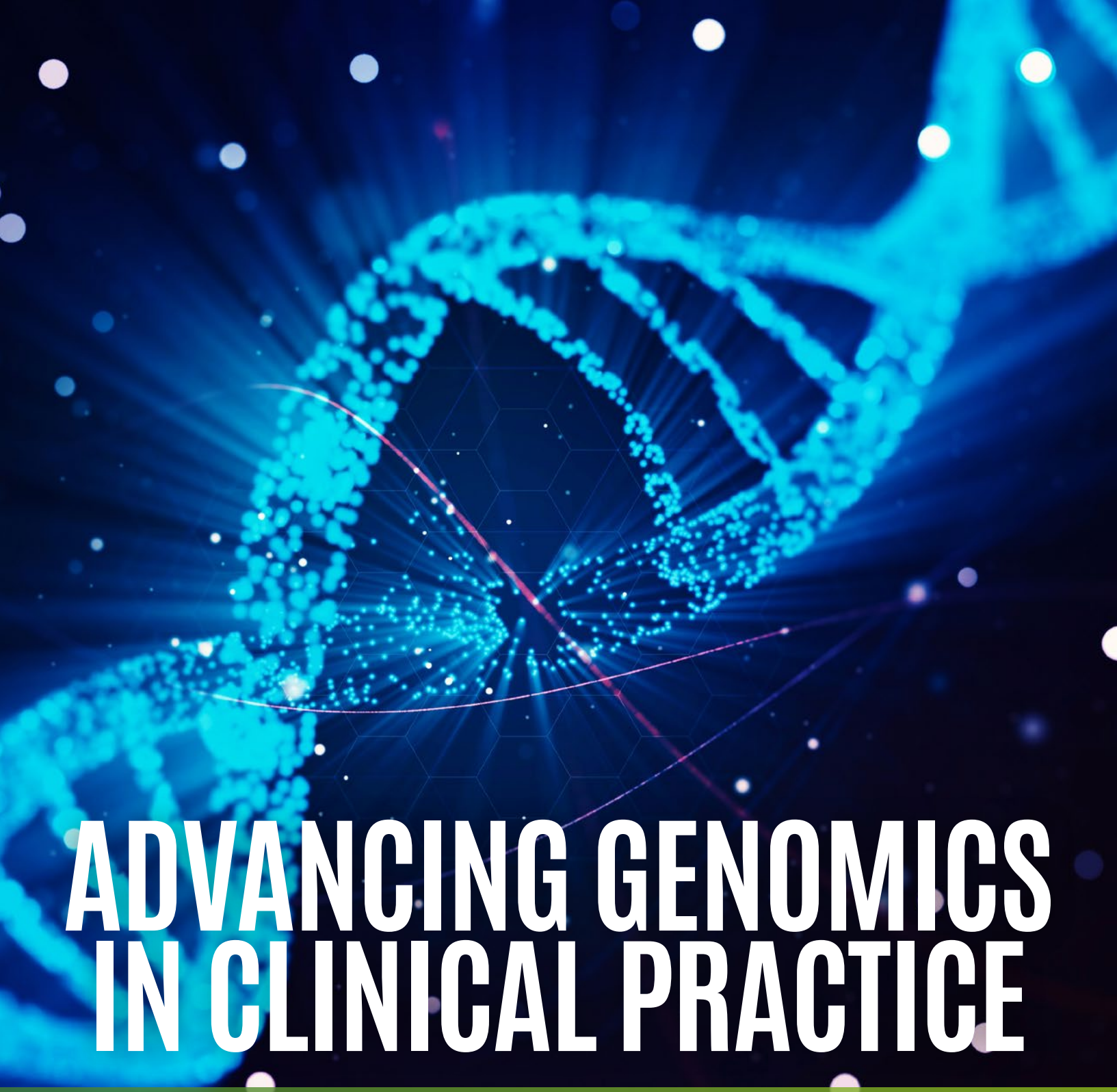

# ADVANCING GENOMICS IN CLINICAL PRACTICE

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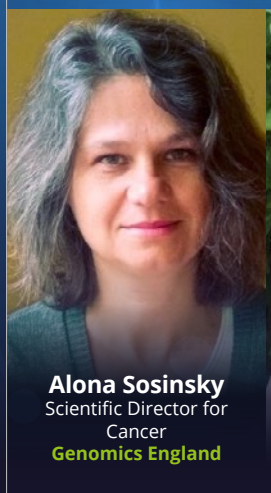

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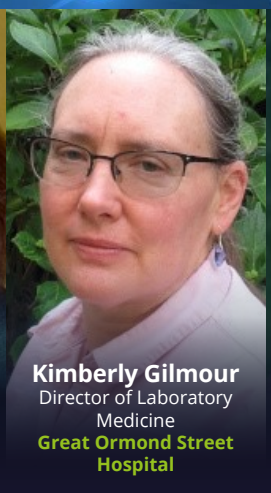

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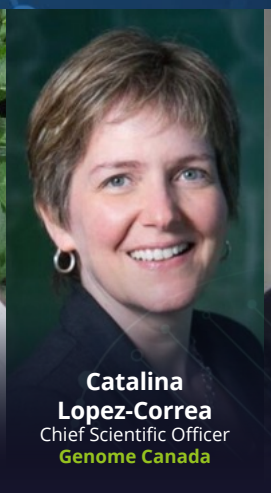

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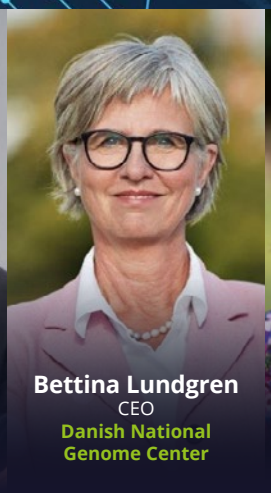

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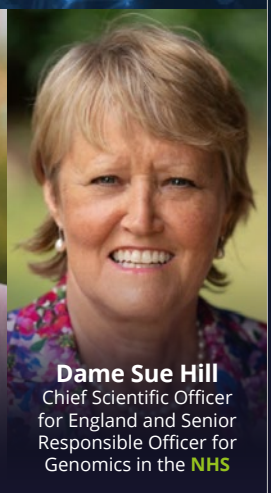

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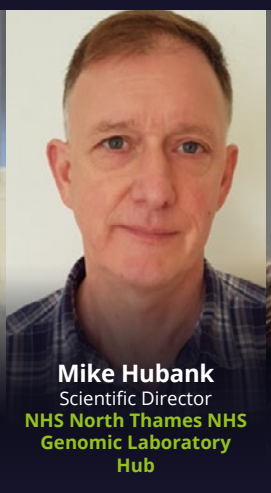

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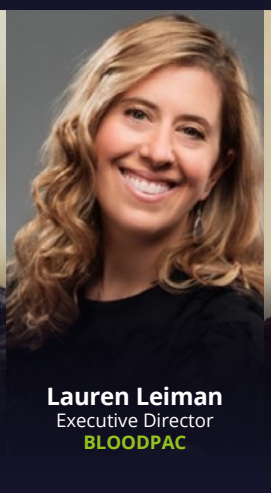

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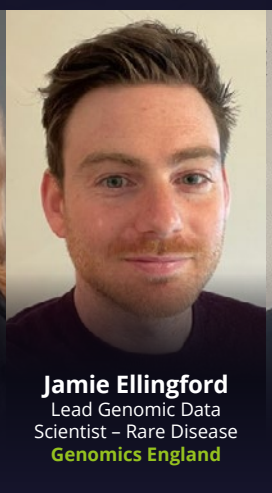

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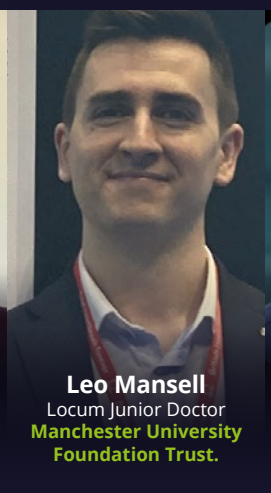

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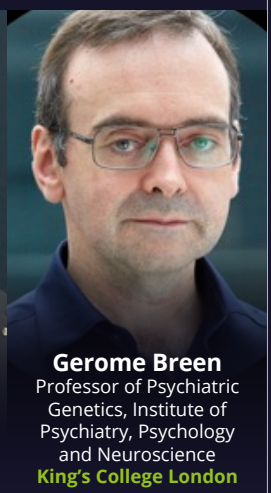

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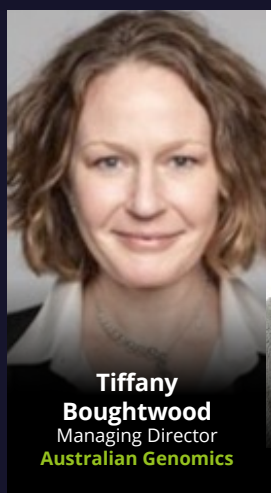

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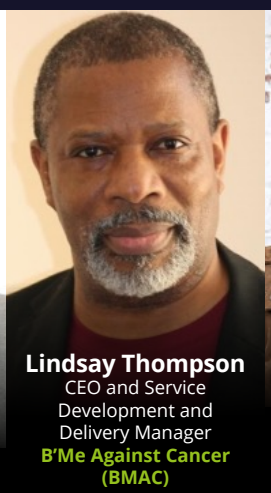

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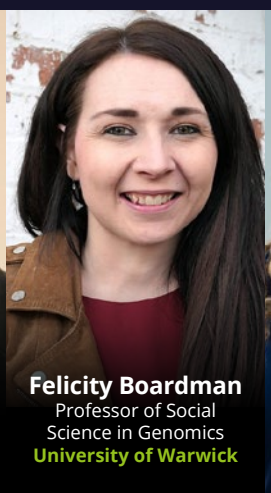

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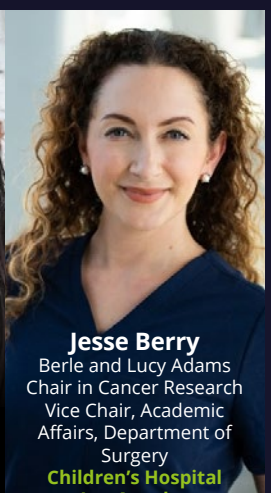

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In order of appearance

# FOREWORD

**DEVELOPMENTS IN SEQUENCING TECHNOLOGIES MEAN THAT THE HUMAN GENOME CAN NOW BE EXPLORED AT AN UNPRECEDENTED LEVEL. WE ARE ENTERING A GENOMICS REVOLUTION, WITH MANY EXPERTS AGREEING THAT IT IS THE MOST EXCITING TIME TO BE WORKING IN THE GENOMICS FIELD.**

Amongst all the hype, technological developments and ground-breaking research, one question remains: **How can all of this be translated to advance genomics in clinical practice?**

With that question in mind, we are introducing a new report – Advancing Genomics in Clinical Practice. The aim of this report is to explore the clinical aspects of genomics and how the genomics revolution can bring tangible benefits to patients.

Starting with the history of genomics and the impact on genomic medicine, we will then go on to look at current genomic services, ongoing projects and how to advance genomics in cancer and other diseases.

Next, chapters will cover how genomics can be advanced clinically to benefit everyone and the patient and public perspective of genomics. Finally, the report will conclude by exploring the next steps in advancing clinical genomics.

We would like to take this opportunity to thank all of our contributors for their time and insights when writing this report and the report sponsors Congenica, MGI and Saphetor.

As always, we hope that you find this report interesting and insightful.

**Liam Little**
Science Writer
**Front Line Genomics**

# CONTENTS


**5 CHAPTER 1:** A HISTORY OF GENOMICS

To introduce the report, the first chapter will go back in time and explore the history of genomics. The major developments in the field of genomics will be covered, along with what they meant for genomic medicine and how the past can be used going forward.

**10 CHAPTER 2:** CURRENT GENOMIC SERVICES AND PROJECTS

This chapter gives an overview of current genomic services and ongoing projects. Here, the NHS in the UK is used as the main example, with other countries from around the world also covered.

**17 CHAPTER 3:** ADVANCING GENOMICS IN CANCER

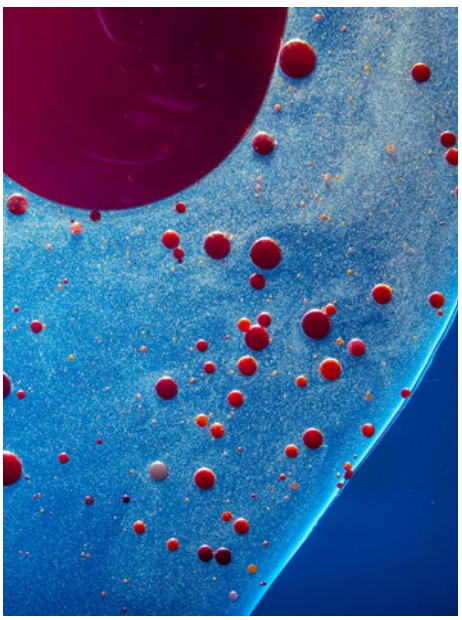
Cancer and genomics are intrinsically linked, and genomics has already been integrated into the clinical pathway. However, there is still more to be done. Chapter 3 illustrates how genomics has already impacted cancer and what more can be done in the future.

**23 CHAPTER 4:** ADVANCING GENOMICS CLINICALLY IN DISEASE

Genomics is also integral to the pathology, diagnosis and treatment of many different diseases and advancing genomics clinically in disease therefore remains a priority. Chapter 4 explores the use of clinical genomics in rare and infectious diseases, cardiology and mental health.

**29 CHAPTER 5:** ADVANCING GENOMICS FOR EVERYONE

Delivering equitable clinical genomics for as many people as possible is a huge undertaking that is constantly evolving, including many different factors. This chapter will explore some of the inequalities faced in clinical genomics, what is being done to tackle them and what more can be done in the future.


**32 CHAPTER 6:** THE PATIENT PERSPECTIVE OF GENOMICS

As genomics grows, more people will be offered genomic testing in the future. Chapter 6 will therefore explore genomics from the other side, to help those working in the field develop a better understanding of patient and public perspectives.

**37 CHAPTER 7:** ADVANCING GENOMICS IN CLINICAL PRACTICE – THE NEXT STEPS

Advancing genomics in clinical practice is a huge undertaking. As such, the final chapter of the report identifies some of the next steps. What are the main challenges? How can research be translated better? How can we ensure that the benefits are delivered to patients?

CHAPTER 1

# A HISTORY OF GENOMICS

LOOKING TO THE PAST IS A KEY FIRST STEP WHEN ASSESSING THE ADVANCEMENT OF GENOMICS IN CLINICAL PRACTICE.

Developments throughout the history of genomic medicine clearly illustrate the power of genomics and why the advancement of this field is so important for human health. This chapter will cover the history of genomics, how it has impacted genomic medicine and how clinical genomics can be advanced going forward.

## The foundations of genomics

The definition of genomics is the study of the complete set of DNA (including all of its genes) in a human or other organism[1]. As genomics brings together multiple elements of complex biology, the ability to study all of the genes in an organism did not happen overnight.

### EARLY DISCOVERIES

The early events that led to genomics as it is known today included the discovery of DNA, the identification of chromosome patterns and the detection of nucleotide bases (adenine, cytosine, guanine, thymine and uracil). Next, the concentrations of adenine and thymine, and cytosine and guanine, were always found in equal amounts in DNA, leading to the hypothesis that A always binds to T and C always binds to G. After that, the Hershey-Chase experiments demonstrated that DNA, rather than protein, was the molecule responsible for carrying genetic information[2].

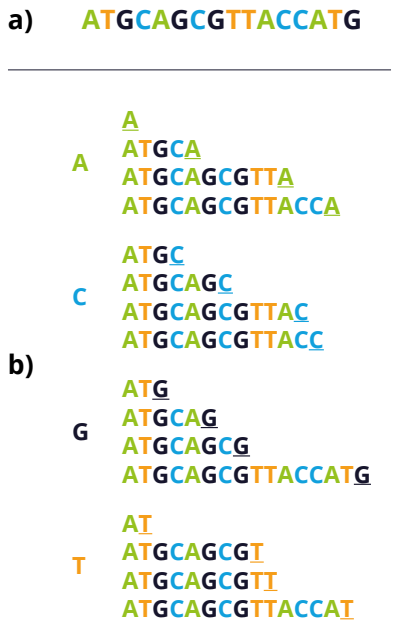
### THE DOUBLE HELIX AND MOLECULAR BIOLOGY

In the middle of the 20th century, the discovery of the double helix structure of DNA by James Watson and Francis Crick signified the beginning of modern molecular biology. However, this ground-breaking achievement is unfortunately marred with controversy. Watson and Crick used crystallographic evidence of the structure of DNA, generated by Rosalind Franklin, to inform their double-helix model, without Franklin's knowledge[3].

A further development was the identification of codons – the blocks of three DNA bases in which DNA is "read". Each codon encodes an amino acid, with multiple amino acids coming together to form a protein during synthesis. This discovery earned Marshall Nirenberg, Har Gobind Khorana and Robert Holley the 1968 Nobel Prize for Physiology and Medicine, along with Holley's research sequencing the first tRNA molecule[2].

**FIGURE 1: ILLUSTRATION OF SANGER SEQUENCING.**

*a) Example template DNA. b) Sanger chain-termination sequencing. Radio or fluorescently labelled ddNTPs (A, C, G and T) are included in DNA polymerase reactions at low concentrations and prevent further extension. The randomly generated sequence products can be visualised with gel electrophoresis and the nucleotide sequence of the DNA template inferred. Adapted from The sequence of sequencers: The history of sequencing DNA (Heather & Chain, 2016).*




## Sequencing and genomic medicine

In 1977, a major breakthrough from Frederick Sanger and team came in the form of the "chain-termination" technique for DNA sequencing. This technique involves the use of di-deoxynucleotides (ddNTPS) – analogues of deoxynucleotides (dNTPs) – with a mixture of radio-labelled ddNTPs and dNTPs used in a DNA extension reaction[4].

As ddNTPs are randomly incorporated during extension using Sanger sequencing, DNA strands of every possible length are produced (see Figure 1). Performing four reactions for each ddNTP and running the extension products on a polyacrylamide gel means that the nucleotide sequence of the original DNA can be inferred from the position of the bands on the gel[4].

### FROM SINGLE GENES TO THE GENOME

Moving forwards to the 1980s and 1990s, the genomics community was focused on mapping the genes of monogenic diseases and rare single-gene disorders. Sanger sequencing was instrumental in this, allowing the identification of disease-causing variations in genes. Approximately 1000 single-gene inherited diseases had been characterised by the year 2000. Key examples such as Huntington's disease and cystic fibrosis illustrated the clinical impact that this type of genomic analysis could have[5].

Other technical advances included the polymerase chain reaction (PCR), a technique that can be used to amplify DNA, and DNA profiling. In DNA profiling, a DNA profile is produced by counting the number of short repeating sequencing of DNA found at ten specific regions of the genome.

**ALONA SOSINSKY**
Scientific Director for Cancer
**Genomics England**

**Long reads make interpretation of complex rearrangements much easier because the patterns we see in the visual representation of sequencing data are much clearer. The other side is that LRS can elucidate the dark regions of the genome – the telomeric regions or centromeric regions. With SRS we can't get much information, hopefully by adding LRS into the WGS process at Genomics England we can begin to see into these dark matter regions.**

**One of the big advantages of the Oxford Nanopore Technology platform is that it is much more mobile. Machines can be brought closer to the patient, so we don't need to send samples to the central facilities – we can just bring the sequencing closer to the patients. This is one of the ways to improve turnaround times for WGS as well.**

In 1990, the Human Genome Project was launched, aiming to sequence the complete 3 billion base-pairs of the human genome in 15 years. The launch of the project marked a change of focus from individual genes to a genomics-based approach[2].

## Next generation sequencing

The Human Genome Project was completed in 2003 (2 years ahead of schedule) and confirmed that the human genome has 20,000-25,000 genes[2]. From the introduction of Sanger sequencing in 1977, to the completion of the Human Genome Project, significant technological advances were made. This led to widespread use of the technology and meant that large-scale projects (such as the Human Genome Project) could be completed.

Despite this, the sequencing, assembly and annotation of genomes using Sanger sequencing was still a significant and costly process that required specialised equipment, expertise and infrastructure[6]. The introduction of the first massively parallel DNA sequencing technology by Margulies et al., in 2005 changed this dramatically and informed the future of genomic medicine through next generation sequencing (NGS).

### NGS TECHNOLOGIES

NGS technologies share many of the fundamental principles of Sanger sequencing. The main difference is that NGS instruments perform the sequencing enzymology and data acquisition in a stepwise fashion, enabling thousands to billions of templates to be sequenced simultaneously[6].

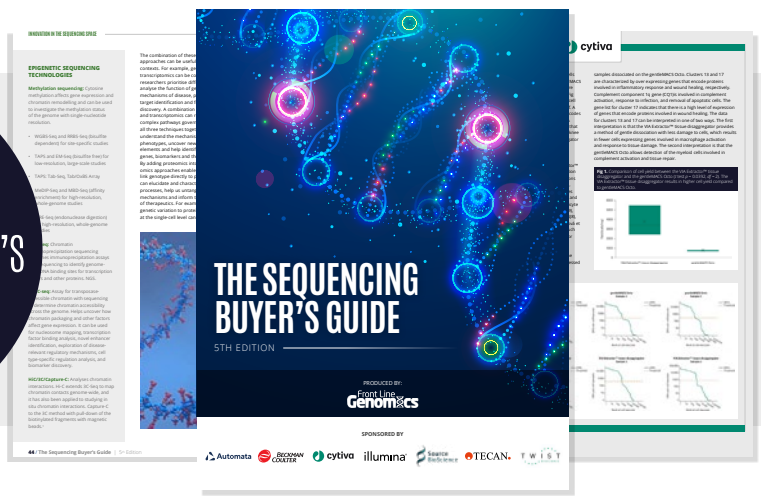
Several NGS technologies have been developed since the inception of the technique. These can be broadly categorised into short-read technologies and long-read technologies. With short-read technologies, sequencing is achieved by synthesis (using DNA polymerase) or ligation (using ligase enzymes). One of the strengths of short-read sequencing is the relatively high accuracy, which allows the identification of small genetic changes that can impact diseases like cancer. The short-read sequencing landscape is dominated by Illumina. Their range of instruments has led to the progression of NGS and facilitated implementation in clinical settings.

Compared to short-read sequencing, long-read sequencing allows for the analysis of much longer reads, greater than 10,000bp reads. "True" long-read sequencing technologies directly sequence single DNA molecules in real time, without the need for amplification. "Synthetic" approaches on the other hand use modified sampling and conventional short-read sequencing to reconstruct long reads from short read data. Commercially, Oxford Nanopore Technologies and PacBio are the key players in long-read sequencing.

### WHOLE GENOME SEQUENCING

NGS technologies have revolutionised genomics, progressing the field to a point where widespread use of whole genome sequencing (WGS) is possible. WGS allows for the detection of the full range of common and rare genetic variants across the entire genome, facilitating the discovery of clinically relevant disease-causing variants (single nucleotide polymorphisms, copy number variations, insertions/deletions and structural variants)[7].





**Alona Sosinsky**
Scientific Director for Cancer
**Genomics England**

*"The key benefit of WGS is that it is a one-stop-shop for your testing needs. Instead of doing multiple tests – each in a different lab with different material requirements – and trying to split your small biopsy between all these tests, you can instead perform a single test in a single location and produce a single report. With tests like FISH panels, for instance, you have to go through 400 cells to confirm a finding – a very laborious process that requires a lot of manpower. This doesn't mean other tests shouldn't be run in parallel to support WGS – if we combine their power, we can simply have higher confidence in our results."*

Over the past two decades, the cost of sequencing per human genome has decreased faster than Moore's Law (see Figure 2). If a technology is keeping up with Moore's Law, it is considered to be doing well. The trend showed by the cost of sequencing is therefore encouraging. The hope is that as the cost of NGS continues to decrease, WGS will become more feasible, more accessible and more widely used within genomic medicine.

## The impact of genomics in medicine

Since the completion of the Human Genome Project, advances in genomics have been broadly followed by advances in genomic medicine (see Figure 3).

**FIGURE 2: THE COST PER HUMAN GENOME.**
*Taken from DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP) (Wetterstand, 2021).*

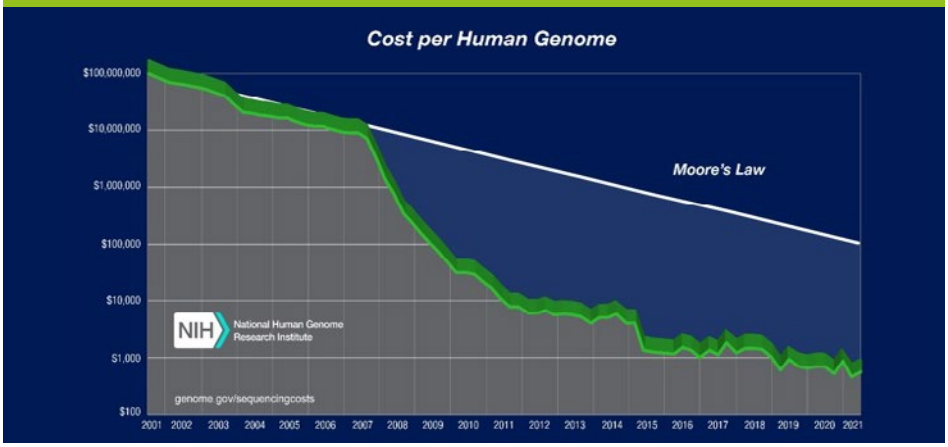
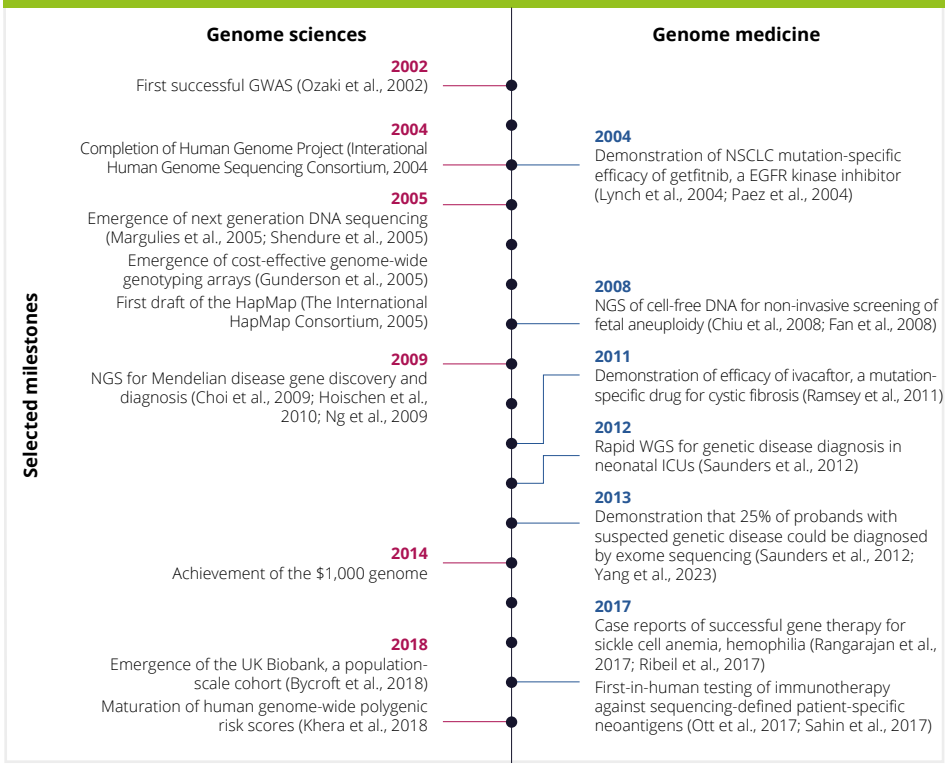



**FIGURE 3: PAST MILESTONES FOR GENOME SCIENCES AND GENOMIC MEDICINE**
*Taken from Genomic Medicine – Progress, Pitfalls and Promise (Shendure et al., 2019).*




## KIMBERLY GILMOUR

Director of Laboratory Medicine, **Great Ormond Street Hospital**

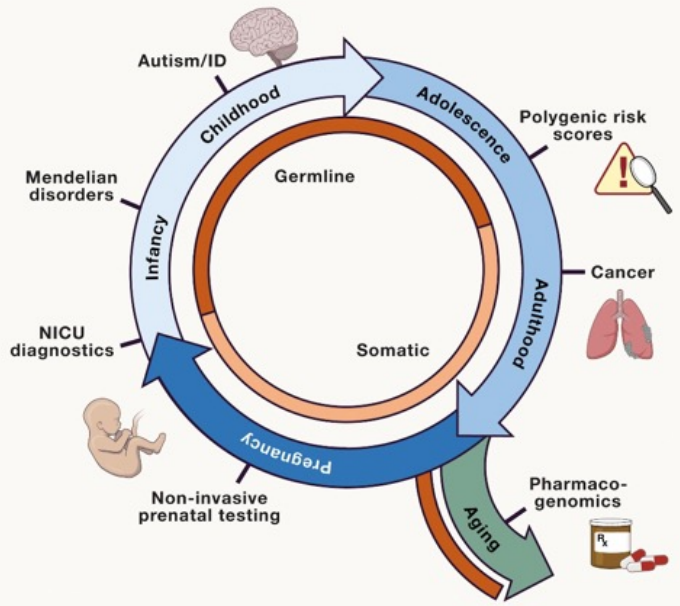
**The benefits and limitations of WGS are almost the same thing. The benefit is you get so much data. If you do whole genome sequencing, not only are you looking at the exons, the coding pieces of the gene, but you're looking at all the other areas that help control gene expression. You're looking at promoters, enhancers, and splicing machinery. You have a much higher chance of picking up disease-causing mutations – great for patients who may have been undiagnosed for many years – but you also pick up many more variants. These are even less likely for the computer programme to be able to model, because we're much better at modelling amino acid changes than we are for something sitting at a promoter site. So the benefit of WGS is that we find many more mutations and help diagnose patients who haven't been diagnosed before, but these are also the drawbacks, because we have these extra variants to functionally validate.**

Genomic medicine now has a far-reaching impact, employed in areas such as cancer, both common and rare diseases and reproductive health. The areas in which genomics has the potential to impact clinical care can be aligned with the life cycle of humans (see Figure 4).

For example, non-invasive prenatal testing can be performed during pregnancy. In childhood, germline variations can be linked to specific diseases. Later, polygenic risk scores can be used to assess an individual's risk of developing a particular disease and somatic mutations can be identified regarding cancer[8].

**FIGURE 4: GENOMIC MEDICINE THROUGHOUT THE HUMAN LIFE CYCLE.**

*The entry points for genomics to impact clinical care span the human life cycle from conception to death. Taken from Genomic Medicine – Progress, Pitfalls and Promise (Shendure et al., 2019).*




## The genomics revolution

2022 saw the expiration of some key technology patents in the sequencing landscape. This was predicted by many to lead to a new era in genomics – the genomics revolution. The numbers and growth in the sequencing marketplace certainly support this prediction.

Between 2015 and 2020, the global NGS market exhibited double-digit growth. In 2020, the DNA sequencing market accounted for $8.41 billion. By 2030 it is projected to reach $40.64 billion. This huge growth is largely down to continued technological improvements and a reduction in costs, which has brought with it an upturn in the many potential applications of NGS.

What does this mean for the clinical application of genomics? Simply put - more sequencing power at a reduced cost. Ultima Genomics has claimed the first $100 genome and Illumina has announced its NovaSeq X Series, which promises to generate more than 20,000 whole genomes per year. As with previous technological advancements in genomics, these announcements and the genomic revolution will surely have a significant impact on the use of genomics in clinical practice.

**CATALINA LOPEZ-CORREA**

Chief Scientific Officer
**Genome Canada**

**I have been in this field for 20 or so years. And I think we're at the peak, we're at the most exciting time of genomics. Even being able to talk about global impact and global implementation, we could not talk about that 10 years ago. We have been talking about the genomic revolution. Well, this is the genomic revolution; having new companies coming to play, offering new equipment and really starting a healthy competition between those companies, and more offerings and more options for scientists who are now doing genomics.**

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CHAPTER 2

# CURRENT GENOMIC SERVICES AND PROJECTS

FROM THE INTRODUCTION OF THE FIRST GENETIC LABORATORY SERVICES IN THE 1960s TO THE GENOMIC SERVICES THAT ARE AVAILABLE TODAY, THE UK NATIONAL HEALTH SERVICE (NHS) HAS BEEN AT THE FOREFRONT OF INTEGRATING GENOMICS INTO HEALTHCARE.

Using the NHS as an example, and also looking at what other countries are doing, this chapter aims to give an overview of current genomic services and ongoing projects.

## The NHS Genomic Medicine Service

The NHS was formed in the UK in 1948 with the aim of providing healthcare services for all, for free at the point of delivery. This means that the NHS has seen the majority of the genomics developments detailed in Chapter 1.

The NHS Genomic Medicine Service (GMS) is designed to harness the power of genomic technology to improve the health of the population. Currently, genomic testing is provided in the NHS through a national testing network of genomic laboratory hubs[1].

### NHS GENOMIC LABORATORY HUBS

The NHS GMS is delivered using a network of seven genomic laboratory hubs, responsible for coordinating services across the country. The seven genomic laboratory hubs are:

- Central and South Genomic Laboratory Hub led by Birmingham Women's and Children NHS Foundation Trust
- East Genomic Laboratory Hub led by Cambridge University Hospitals NHS Foundation Trust
- North West Genomic Laboratory Hub led by Manchester University NHS Foundation Trust
- North Thames Genomic Laboratory Hub led by Great Ormond Street Hospital for Children NHS Foundation Trust
- South East Genomic Laboratory Hub led by Guy's and St Thomas' NHS Foundation Trust
- South West Genomic Laboratory Hub led by North Bristol NHS Trust
- North East and Yorkshire Genomic Laboratory Hub led by The Newcastle upon Tyne Hospitals NHS Foundation Trust

### THE NHS NATIONAL GENOMIC TEST DIRECTORY

Central to the NHS GMS is the National Genomic Test Directory. The test directory outlines the full range of genomic tests that are commissioned for the NHS in England and sets out which tests are available to patients that are eligible for a test. For both rare and inherited diseases, and cancer, detail is provided on the specific genomic tests available, the technology used for the tests and the patients eligible for access.

## Genomics England

Genomics England is a company wholly owned by the Department of Health and Social Care, formed to carry out the 100,000 Genomes Project. Genomics England continues to support the NHS with embedding genomics into routine healthcare, improving patient diagnostics and treatments, and powering research with their large genomic database[2]. Genomics England also have projects focused on COVID-19 and cancer (covered more in Chapter 3).

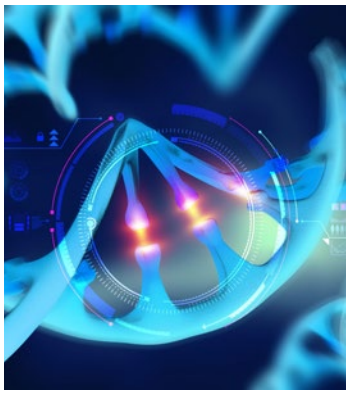
### 100,000 GENOMES PROJECT

The 100,000 Genomes Project was the very first initiative from Genomics England. Recruitment for the project was completed in 2018, with research and analysis of data still ongoing. The target of the project was to sequence 100,000 genomes (from around 85,000 NHS patients) to gain ground-breaking insights into rare diseases and cancer[3].

The project also aimed to integrate genomics into routine healthcare through whole genome sequencing (WGS). This approach also created the largest genomic healthcare data resource in the world, enhancing genomic research and uncovering answers for participants[3].

### NEWBORN GENOMES PROGRAMME

The Newborn Genomes Programme is being co-designed and carried out by Genomics England and the NHS. The study aims to explore the benefits, challenges and practicalities of newborn genome sequencing by analysing the genomes of over 100,000 newborns[4].



## MATT BROWN

Chief Scientific Officery
**Genomics England**

**Genomics England has a major diverse data programme, which will sequence between 15,000 and 25,000 largely disease-based groups over the next 2-3 years. This will explore the reasons in the genomic medical service as to why we don't do as well for non-European ancestries. For example, this includes differences in how we actually analyse the data, as well as learning more about genomic diversity in populations and individuals with diseases from different ancestral groups.**

The aim of the programme is to identify rare diseases in new born babies, as well as evaluating the feasibility and impact of offering WGS to all newborns on the NHS. In turn, this will also create a lifetime resource that can be used to explore the risks and benefits of storing an individual's genome over their lifetime[4].

### DIVERSE DATA INITIATIVE

The Diverse Data Initiative from Genomics England aims to reduce health inequalities and improve patient outcomes in genomic medicine for minoritized communities. The Diverse Data Initiative will deliver on its aims through four streams of activities:

***Research and discovery:***
***Understand the data gap***
Improve our understand of genomic diversity by reviewing, stimulating and conducting research into diversity and its impacts on scientific, clinical and health system outcomes.

***Community and engagement:***
***Close the gaps, together***
Convene and work with patient, genomic and data communities to design, develop and implement equity-enhancing strategies.

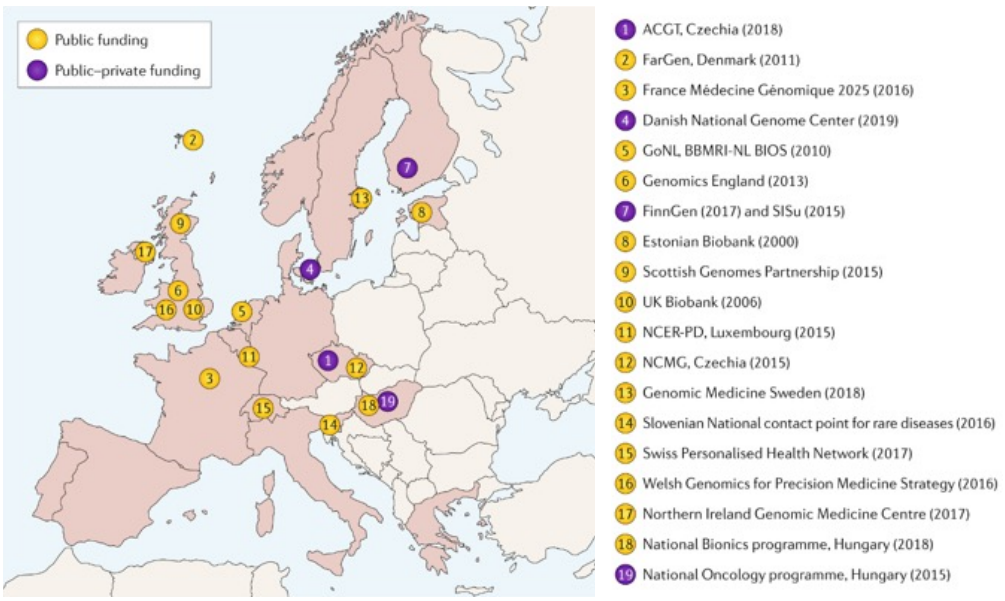
***Sequencing and data:***
***Fill the data gap***
Increase the volume and depth of genomic data available on individuals from under-represented groups by sequencing genomes and generating, linking and facilitating better access to data from diverse populations.

***Products, tools and behaviours:***
***Bridge the data gap***
Work with clinicians, analysts, researchers, patients and community groups to develop tools and processes to improve research, service-delivery practices, recruitment and care.

## Genomics in Europe

There are many countries in Europe that have national initiatives to generate genomic data (see Figure 1). Many of these are not specific to one disease, although disease areas include cancer, infectious diseases and rare diseases. In many European countries (e.g., Spain and Italy) genomics-based projects are linked to regional healthcare authorities[5].

**FIGURE 1: EXAMPLES OF CURRENT HEALTHCARE AND GENOMICS NATIONAL INITIATIVE PROJECTS ACROSS EUROPE.**
*Taken from Leveraging European infrastructures to access 1 million human genomes by 2022 (Saunders et al., 2019).*



### EUROPEAN 1+ MILLION GENOMES INITIATIVE

The European 1+ Million Genomes Initiative (1+MG) aims to enable secure access to genomics and clinical data through a collaboration across the EU and Europe. Since 2018, 24 EU countries (as well as the UK and Norway) have signed the Member States' declaration to create a European data infrastructure for genomic data and implementing common rules around data access[6].

***The objectives of the 1+MG are to:***

- Ensure that appropriate technical infrastructure is available across the EU, allowing for secure access to genomic data.
- Make sure that the ethical and legal implications of genomics are clear and taken into account.
- Ensure that the general public and policy makers in Member States and signatory countries are well informed about genomics – to ensure its uptake by healthcare systems and integration into personalised medicine.

The Beyond 1 Million Genomes (B1MG) project provides coordination and support to the 1+MG to create a network of genomic and clinical data across Europe. The B1MG goes "beyond" the 1+MG by creating long-term means to share data and enabling access to more than 1 million genomes[7].

## Genomics projects in the USA

The USA is home to multiple internationally renowned research and clinical centres, as well as many notable genomics projects. These include the first major genomics project, the Human Genome Project (HGP), and ENCODE. The HGP was a massive international effort, but work began in the USA and much of the funding came from American institutions[8]. The HGP paved the way for future projects, including ENCODE. ENCODE is a spin-off from the HGP, investigating the role of non-coding DNA and characterising different functional components of the human genome[9].

Also in the USA is the All of Us Research Program, an ongoing initiative across the country to create a diverse biobank for use in healthcare research and decisions. The project aims to recruit over one million people to provide DNA samples and build a resource to contribute to the development of precision medicine[10]. In December 2022, All of Us began returning personalised results to more than 150,000 participants with information including increased risk of specific health conditions.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# INSIGHTS INTO THE DANISH NATIONAL GENOME CENTER

THE DANISH NATIONAL GENOME CENTER IS A GOVERNMENT AGENCY IN DENMARK AND AN AUTHORITY WITHIN THE DANISH HEALTHCARE SYSTEM. THE AIM OF THE CENTER IS TO LAY THE FOUNDATION FOR THE DEVELOPMENT OF BETTER DIAGNOSTICS AND MORE TARGETED TREATMENTS FOR PATIENTS USING WHOLE-GENOME SEQUENCING.

THIS IS A SHORTENED AND EDITED VERSION OF AN INTERVIEW THAT WAS PUBLISHED ON FRONT LINE GENOMICS (29TH NOVEMBER 2022) WITH **BETTINA LUNDGREN,** CEO OF THE **DANISH NATIONAL GENOME CENTER.**

***What are the main goals of the work done at the Danish National Genome Center?***

**Bettina Lundgren:** The Danish National Genome Center was established in 2019, based on a strategy to deliver more personalised medicines for patients. In the strategy, all stakeholders – both the state and the hospital regions that run the hospital system in Denmark, as well as universities and other stakeholders – had a joint suggestion of building up technical infrastructure, which we are doing –and implementing genomes directly into healthcare for the benefit of patients today. But also benefiting future patients by using the genomes so we can develop more personalized medicine for future patients.

***What could the development of personalised medicine mean for patients? What could the direct benefits be for patients?***

**Bettina:** The initiative in Denmark is supported in the law. A law about establishing the Danish National Genome Center, and a law stating that whole genomes, or advanced genomes, made in a hospital setting should be reported into a centralised database. In that database, the patient's genomes can be viewed all over Denmark. If a patient is transferred, for example, from one place in Denmark to another place, the data can be reused and the data can be used for future patients. It was benefiting the patient directly, by giving them feedback in the form of a diagnosis, or better treatment, or maybe prevention if a patient had a hereditary disease, so they could use it for future pregnancies or other things. It's all about patients and it's about giving patients a better diagnosis. That's what the whole setup is all about. And this is also what my goal is – giving a better outcome for patients. Giving patients a better way of living their life.

***When the Danish National Genome Center first set out, what were attitudes like towards genetic analysis, particularly amongst patients? And in the last few years do you think these attitudes have changed?***

**Bettina:** In Denmark, we have a population that is very trustworthy towards the authorities and towards healthcare. When we first started, we did some investigations among citizens – some were scared that the data could be used in a way it should not be used. That's why in Denmark we have quite strict legislation about the way that genomes need to be kept in a safe infrastructure, and they cannot be used for purposes other than in healthcare and in research that has the goal of developing personalised medicine.

What we're finding at the moment, is that if you ask citizens, they don't know that much about what a whole genome or genome analysis is. If you explain to them, they will know more. For the regular citizen, around 65% support having it done – if you ask the patients if they will participate, most of them will say yes. I think we are on a journey, where the citizens and the patients are getting used to having their whole genomes sequenced in a setting of having better health care. We also have a population that supports research, so if you ask them if their data can be used for research, the majority of the patients say yes. We have a system where you can opt out if you don't want to have your data used for research.

The area is moving, but I think it's very important that you engage patients so that they participate. We also have them participating in our different networks where we discuss "How should we do that?" They are interacting and they know how the fields are developing. I think it's very, very important to engage patients about the work and how you proceed.

***Are there any recent developments that you're particularly excited about that you want to share?***

**Bettina:** I think in Denmark we have been aiming to change the healthcare system. If you introduce something new into healthcare and patient treatment, it's not only about building infrastructure and introducing diagnostics. You also have to ask: how will you actually interpret the data? How will you organize different departments, hospitals, regions and different workforces in the healthcare setting? You need more technology. You need different people coming in into the healthcare system to work with you.

At the moment, the focus is very much on implementation and a change of workflow. It is great to see how people all across Denmark and our experts are working together. This is being pushed into the healthcare system in an equal way, across all of Denmark. Patients with the same disease are getting the benefits of these advances. I think it's great that we can help to do that.

Of course, there are lots of good stories. Not long ago, we had a great story about a cancer patient. The treatment he had was not working anymore. He had his whole genome sequenced, and you could see there was an experimental treatment available. He was elected and transferred onto that. It could not save his life, but it could extend his life, so he could have more happy years with his family.

These stories come all the time. It's very important that we gather evidence to figure out exactly how to use genomics in patient care and how to use information about genes to develop more and more precise medicine. Maybe these things will also help us to organise the healthcare system in a different way in the future, so that people can get the right treatment. They don't want to have a one-size-fits-all treatment. They will have treatment that fits directly. For example, if I need to have blood pressure medicine one day, I don't have to try different medications out. I can figure out exactly which one will fit my body.

"WHEN WE FIRST STARTED, WE DID SOME INVESTIGATIONS AMONG CITIZENS – SOME WERE SCARED THAT THE DATA COULD BE USED IN A WAY IT SHOULD NOT BE USED. THAT'S WHY IN DENMARK WE HAVE QUITE STRICT LEGISLATION ABOUT THE WAY THAT GENOMES NEED TO BE KEPT IN A SAFE INFRASTRUCTURE"

***Looking to the future, what do you hope will happen in personalised medicine?***

**Bettina:** I really hope that, together with our efforts across borders, we'll be able to figure out how we can use personalised medicine in a safe manner. I would like patients and citizens to trust that their data is not being misused, so that we can get legislation to make sure that we can use research data for patient treatment, because you're not allowed to do that in Denmark. Afer that, I hope that we can also get legislation to use other data, and use it directly to benefit patients now, and in the future. I hope that we can learn from each other and that we can move legislation across borders. I hope we can have technology to help us with using this data in a safe and wise way, in the context of providing a better life for all of us and for better treatment for patients.

# HOW IS THE NHS ACCELERATING GENOMIC MEDICINE?

**DAME SUE HILL,** CHIEF SCIENTIFIC OFFICER FOR ENGLAND AND SENIOR RESPONSIBLE OFFICER FOR GENOMICS IN THE **NHS**

In 2022, the NHS published Accelerating genomic medicine in the NHS. This document set out the strategy for embedding genomics in the NHS over the next five years, including four priority areas:

- Embedding genomics across the NHS, through a world leading innovative service model from primary and community care through to specialist and tertiary care.
- Delivering equitable genomic testing for improved outcomes in cancer, rare, inherited and common diseases and enabling precision medicine and reducing adverse drug reactions.
- Enabling genomics to be at the forefront of the data and digital revolution, ensuring genomic data can be interpreted and informed by other diagnostic and clinical data.
- Evolving the service through cutting-edge science, research and innovation to ensure that patients can benefit from rapid implementation of advances.

In the following sections, **Dame Sue Hill,** Chief Scientific Officer for England and Senior Responsible Officer for Genomics in the **NHS** gives an update on the progress made against the Accelerating genomic medicine in the NHS strategy.

## THE BENEFITS OF GENOMICS

**Sue Hill:** The benefits of genomics become clear when we look at our ability to use genomics in a preventative approach. Some of that has been shown in the expansion of our inherited cancer testing. The other side of that is linking genomics to much earlier diagnosis, again especially in cancer, through the use of circulating tumour DNA testing for example. The third aspect of this is our ability to provide a more comprehensive and accurate diagnosis up front. This is particularly important in some rare diseases that often take many years and multiple different specialists to get a genetic diagnosis.

The investment we have been able to get in genomics is linked to the awareness of what it can deliver to patients with rare diseases and in cancer – how genomics can change the clinical management of patients and precision treatments. Genomics is linked to the four P's of precision medicine. To be preventative; to give a more precise diagnosis; to enable more precision treatments (such as gene therapies); to be more proactive with patients and their families about the use of genomics.

Other benefits of genomics include the ability to cut down the number of other consultations that people need to have within the NHS. It enables us to move towards population-based health approaches. It also enables to use pharmacogenomics (which we are doing in a number of applications) to reduce adverse drug reactions and to deliver the benefits to patients and populations.

## DEFINING THE NHS GENOMICS STRATEGY

**Sue:** When defining the NHS genomics strategy, we had extensive stakeholder engagement and listing events around what people, patients and users of the service actually wanted to see. Bringing together all of the different themes that emerged, it was very clear that they fell into four main areas. The first was around, how do we make the infrastructure that we've created work better? This includes improving the service model, its governance, its partnerships – all so it can continue to be world leading. Secondly, we know that genetics and genomics are evolving at a rapid place. We need to have a service and elements around it that would be able to respond to those advances. Genomics also isn't just diagnostic tests, there was a lot of work to do on the digital data and informatics infrastructure. That was a straightforward one – to make sure data could flow across the system and shared when consent was given, to support research endeavours. Finally, we'd already supported the 100,000 Genomes Project. We wanted to make sure that we continued to align routine care with research and development for the greater good.

## EMBEDDING GENOMICS ACROSS THE NHS

**Sue:** We set out four main priority areas in the NHS strategy and in all of those there have been developments since we published. The first area is in embedding genomics in the NHS through a world leading innovative model. We are making progress on the integrated governance networks that bring all the elements of genomics together in each of our seven geographies. That means bringing clinical genomic services together with the genomic laboratory hubs and the Genomic Medicine Service alliances. There has been great progress on that.

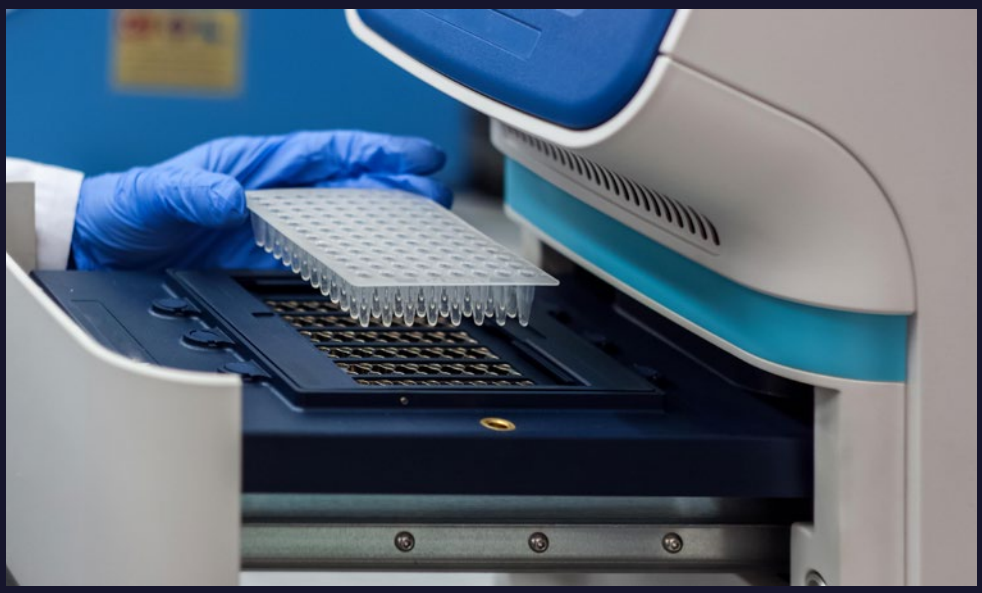
Secondly, we are making progress on the NHS genomic training academies. These academies are to support the education, training and development of our specialist workforce initially and then the broader workforce. We continue to work really closely with our people in communities forum and take different elements to them. Linking to that, we've progressed very well in the development of our equity, ethics and legal group. We've got a lot to do in workforce development, including workforce profiling. That's ongoing – we can benchmark the functions of different posts within the workforce and drive optimisation.

## DELIVERING EQUITABLE TESTING

**Sue:** Our second priority is about delivering equitable genomic testing. This is not just for the diagnosis and prevention of disease but also for precision medicine. We are continuously evolving the NHS Genomic Test Directory – there will be a significant number of amendments that will come out in April 2023. This progress is linked with our cancer panels, where we're aligning clinical trial targets with standard of care testing and continuing to roll out large gene panels for solid tumours and haematological malignancies. Both for cancer and rare diseases, we're also ensuring that we have a mechanism to understand the access of precision medicine associated with any given genomic marker.

## THE DATA AND DIGITAL REVOLUTION

**Sue:** Our whole genome sequencing services are going from strength to strength. Additional conditions have been added for eligibility and by the end of 2023, we will deliver around 30,000 whole genome analyses. It's important to remember that multiple tests are performed in rare diseases, and in cancer we test both blood and tissue. That means this number doesn't equate to 30,000 patients, it's actually around 12,000 patients in total. It is transforming care for those patients, as part of our commitment to embed the service at the forefront of the data and digital revolution. Part of the ongoing genomics implementation plan is to look at how we can expand the use of NHS generated genomic data to support research.



"ADDITIONAL CONDITIONS HAVE BEEN ADDED FOR ELIGIBILITY AND BY THE END OF 2023, WE WILL DELIVER AROUND 30,000 WHOLE GENOME ANALYSES."

## SCIENCE, RESEARCH AND INNOVATION

**Sue:** Our final priority is in research. In this priority area, we're about to publish expressions of interest for the establishment of NHS genomic networks of excellence. This is to work with life science partners, including academia and industry, to create evidence for the adoption of genomic technologies within the health service. We're working very closely with industry to develop a partnership framework. From that, we're evolving the first version of the NHS Genomic Medicine Service research collaboration, where we understand how to support research initiatives and projects through the NHS Genomic Medicine Service infrastructure.

# ADVANCING GENOMICS IN CANCER

CANCER CAN BE DEFINED AS A DISEASE OF THE GENOME. WITHIN CANCER DIAGNOSTICS, GENOMICS IS ALREADY A STANDARD AND INTEGRAL PART OF THE CLINICAL PATHWAY.

However, as both oncology and genomics are very broad areas, many cancer patients still fail to receive a genomic diagnosis. This chapter will therefore explore several key areas in which genomics is currently being used within cancer and how it can be advanced in the future.

## Identifying actionable mutations

Cancer is not just one disease – it is an umbrella term for a group of diseases that share the same characteristics but occur at different sites in the body. What fundamentally defines (and causes) cancer is the accumulation of genetic mutations. The characteristics that all cancers share are known as the Hallmarks of Cancer[1].

Mutations can be classified as germline (hereditary) or somatic (acquired). Over time, the accumulation of mutations in key tumour-suppressor genes (TSGs) and oncogenes lead to the fulfilment of the Hallmarks of Cancer and the development of malignancy. The link between genomics and cancer means that genomics is now a key tool in the study, diagnosis and treatment of the disease[2].

In particular, the identification of actionable genetic mutations – those mutations that have a clinical impact – is routinely performed using genomic technologies that may be considered rudimentary in today's landscape. The following two examples illustrate how this is achieved in both solid tumours and haematological malignancies.

### LUNG CANCER AND EGFR

Lung carcinoma is the number one cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) comprises of adenocarcinoma and squamous cell carcinoma and is the most common lung cancer subtype, accounting 80-90% of all cases[3].

Identifying mutations in the epidermal growth factor receptor (EGFR) gene has a clinical benefit within the treatment of NSCLC. Patients with EGFR-sensitising mutations, such as L858R mutations and exon 19 deletions, are eligible for treatment with tyrosine kinase inhibitors (TKIs). Since the introduction of TKIs, the survival of NSCLC patients with EGFR mutations has improved to the point where TKIs are recommended as the first-line treatment in this setting[3].

Clinically, somatic testing of biopsy-derived FFPE tissue can be performed using multi-target next-generation sequencing (NGS) panels to identify EGFR mutations. L858R and exon 19 deletions are the most common variants and account for 80-90% of EGFR mutations. Other variants include exon 20 insertions and G719X, S768I and L861Q mutations. Although some of the less common variants are less sensitive to TKIs, the presence of any sensitising EGFR mutation makes patients eligible for TKI treatment[4].

### BCR-ABL MONITORING IN CHRONIC MYELOID LEUKAEMIA

Treatment with TKIs has also revolutionised the clinical outcomes of patients with chronic myeloid leukaemia (CML). CML is a myeloproliferative neoplasm caused by a chromosomal translocation that produces a Philadelphia chromosome and the BCR::ABL fusion gene.

**CLARE TURNBULL**
Professor of Translational Cancer Genomics
**Institute of Cancer Research**

**It becomes challenging when we think about how to implement clinical sequencing of tumour material in cancer patients as a diagnostic test within routine care. This brings many challenges, such as how to obtain the right tumour samples and store them, what would be considered sufficient quality for a clinical sample, and how to get acceptable samples from biopsies. There are also logistical issues around tissue preparation and timing, since results are needed quickly if they are going to inform clinical management. Additionally, there is the challenge of distilling the complex genomic data into a report that would be meaningful for clinical management and provide relevant metrics around sensitivity, specificity, and other factors. I think this latter part is much more challenging in terms of implementing cancer genomics as a standard of care.**

This gene fusion aberrantly activates ABL1 kinase and leads to the overproduction of leukemic cells[5].

TKIs target the oncoprotein produced by the BCR::ABL fusion gene. From the early 2000's to the late 2010's the 5-year survival rate for CML patients has almost doubled, which can be attributed to the increased use of TKIs[5].

BCR::ABL monitoring is an essential part of the clinical management of CML patients. This can be used to determine an individual's response to TKI therapy and if they are beginning to show resistance. A common molecular monitoring method is reverse transcription-quantitative PCR (RT-qPCR), which estimates the number of copies of BCR::ABL1 mRNA relative to a reference gene[6]. This use of RT-qPCR is another example of how straightforward genomic techniques have revolutionised cancer genomics and translated into standard clinical care.

## What's next in cancer genomics?

Genomics has been firmly integrated into the clinical workflows for cancer diagnosis and precision medicine. However, the technologies used in the examples above could be considered outdated when compared to the innovations seen in the wider genomics industry and research.

Chapter 1 discussed the development of genomics technologies (including the ever-reducing cost of sequencing) and the subsequent benefits to genomic medicine. How can these technologies be applied clinically to advance cancer genomics?

### WHOLE GENOME SEQUENCING

Currently, the majority of genomic sequencing for cancer samples is performed using targeted NGS panels. The main limitation of these panels is that they are not able to detect mutations in genes that are not included in the panel design. Whole-genome sequencing (WGS), and whole-exome sequencing (WES), offer a solution to this problem and the ability to identify mutations across the entire genome[7].

Although the cost per genome is constantly decreasing, the true costs of implementing WGS clinically still limits its use for all cancer samples. Another obstacle is the amount of tumour material required for WGS. This is particularly relevant in certain cancer types, where only small biopsies are possible, yielding insufficient quantity, quality and purity for more advanced sequencing technologies[7].

### CANCER 2.0

Cancer 2.0 is an ongoing initiative from Genomics England, which is exploring long-read sequencing and multimodal data for the earlier and faster diagnosis of cancer. Long-read sequencing can analyse whole regions and large structural features of the genome that were previously not possible with traditional sequencing. Using machine learning methods, Cancer 2.0 is also combining data from genomics, pathology, radiology and clinical follow-up data from patients[8].

By bringing together long-read sequencing and multimodal data analysis, Cancer 2.0 aims to[8]:

- ***Support better patient outcomes*** by shortening the time it takes to receive accurate diagnostic results for more than 300,000 people diagnosed with cancer each year.
- ***Help clinicians deliver personalised treatments*** by exploring the potential of sequencing technologies to support with patient treatment decisions.
- ***Create a world-class research asset for the UK*** and make the country's genomic data richer by combining imaging, genomic and clinical data to generate new insights into cancer.

### DIGITAL TESTING WITH BRCA-DIRECT

The BRCA1, BRCA2 and PALB2 genes are associated with hereditary breast cancer. Germline genetic testing of these genes is a routine diagnostic service and identification of pathogenic variants has implications not just for the individual undergoing testing, but also their family[9].

BRCA-DIRECT is a study that aims to provide an easy way for patients to access genetic testing information through a digital pathway. In routine practice, information is usually provided face-to-face or through

## MIKE HUBANK

Scientific Director, **NHS North Thames NHS Genomic Laboratory Hub**

**There are issues with implementing whole genome sequencing for all cancer samples. These include the cost of tests, how fast sequencing can be performed and the requirement to also do germline testing. Sample availability, processing with FFPE and sample purity are other issues with whole genome sequencing. Another approach is to use large, comprehensive gene panels – that's how we deliver most of our genomic testing for cancer. Gene panels have a reasonably rapid turnaround time, we don't have germline requirements and we can do both DNA and RNA. They work with FFPE tissue and poorer quality samples. It doesn't cost as much, so we can sequence deeper and that gives us a higher sensitivity. We can cover all the known actionable variants. The only drawback is that we can't find mutations that are not part of the panel. That means we need to use good, flexible panels, that we keep up to date.**

telephone appointment. BRCA-DIRECT is examining the feasibility, safety and acceptability of a digital information model within breast cancer[9].

Recruitment for the study is now closed and initial findings were published in 2022. These showed that approximately 90% of participants that received test information digitally reported high levels of satisfaction and convenience. These figures are comparable to those who received information in the standard, non-digital way[10].

The initial results are encouraging, and it is hoped that if the digital pathway is successful, the concept can be expanded to other cancer types and hospitals[9].

**Clare Turnbull**
Professor of Translational Cancer Genomics
**Institute of Cancer Research**

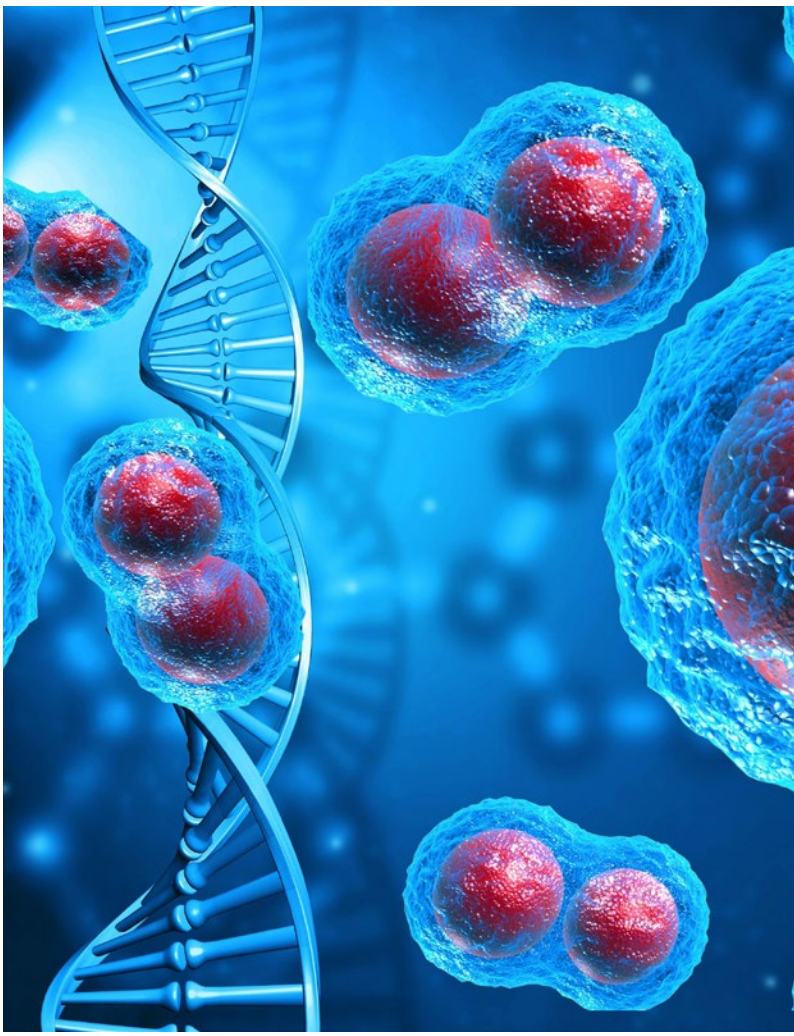
*"BRCA-DIRECT is a CRUK-funded initiative. The first phase of it was a randomised study. We wanted to look at a digital pathway for delivering BRCA testing. We randomised within this digital pathway whether patients get their pre-test information digitally via an online platform or whether they get it from a genetic counsellor.*

*Genetic tests aren't so expensive anymore for BRCA1 and BRCA2. Much of the cost, and where we lack capacity relates to the clinical workflow – genetic counselling, appointments etc. This means that the number of people we can offer a BRCA test to is restricted because we don't have sufficient clinical resources. We have historically developed very complex scoring systems around family and personal history to inform who is eligible for a test. This creates a paradox where we spend our limited clinical energy figuring out who can't have a BRCA test. With BRCA-DIRECT, we wanted to turn this on its head and determine whether we could take the generic elements of the clinical pathway and make them available digitally, with recourse to a genetic counsellor telephone helpline for specific enquiries. And in this way expand capacity."*

# Liquid biopsy

Liquid biopsy has seen increasing use in the molecular profiling of cancer samples. The ability to extract circulating tumour DNA (ctDNA) and circulating tumour cells (CTCs) from a minimally invasive blood sample offers a truly revolutionary approach to cancer diagnosis and monitoring[11].

Over the past decade, liquid biopsy has translated from a novel research area into a tool that is having a clinical impact in cancer genomics. In the following section, **Lauren Leiman,** Executive Director of the Blood Profiling Atlas in Cancer **(BLOODPAC)**, gives an update on how the organisation is accelerating the development, validation, and accessibility of liquid biopsy to improve the outcomes of patients with cancer.



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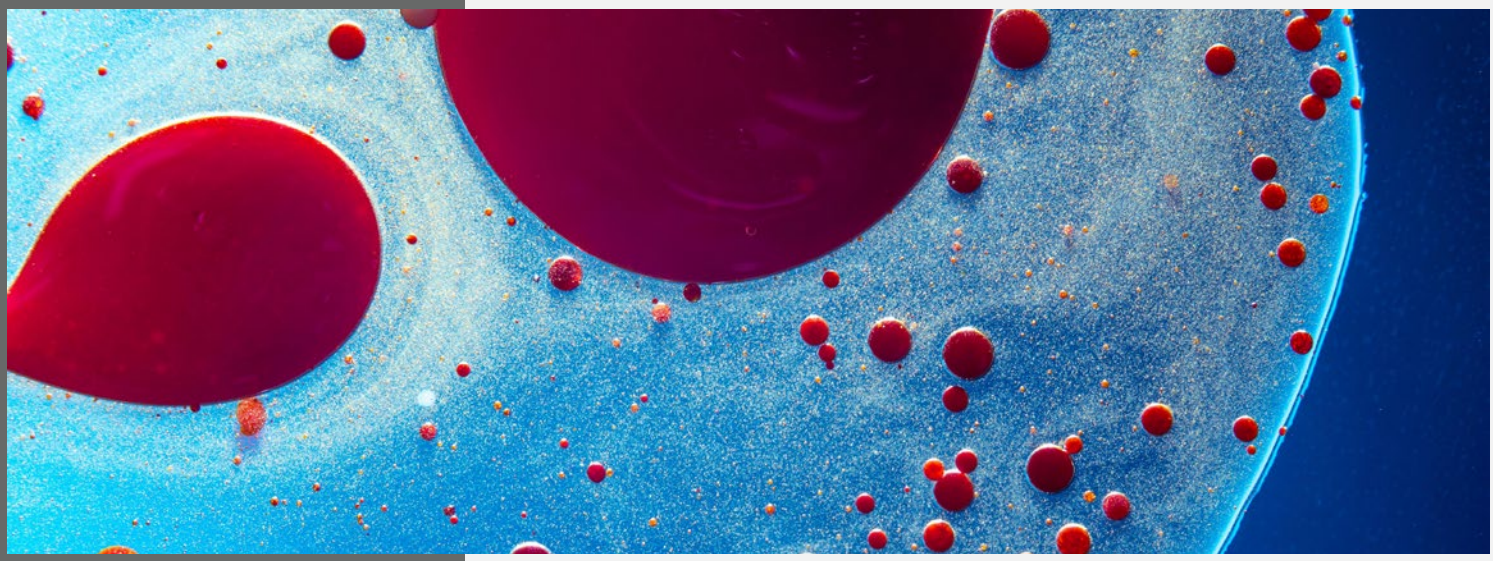
# DEVELOPMENT, VALIDATION AND ACCESSIBILITY WITH BLOODPAC




**LAUREN LEIMAN**
Executive Director
**BLOODPAC**


### AN UPDATE ON THE AIMS OF BLOODPAC

**Lauren Leiman:** The BLOODPAC consortium was created approximately six years ago with the mission of bringing the major stakeholders in the liquid biopsy field to the table in a collaborative, pre-competitive environment in order to accelerate liquid biopsy development, validation and clinical implementation. Our membership consists of over 60 regulatory, industry, academic, and nonprofit institutions, all of whom work together though our collaborative infrastructure to develop standards and protocols, organize and coordinate research studies, and operate the BLOODPAC Data Commons (BPDC) to support the exchange of raw and processed data generated by the global liquid biopsy community. In recent years, we've had more companies coming into BLOODPAC from outside the US, and the companies that we already work with are doing more business abroad. Consequently, we have recently started to expand our efforts globally as we develop standards, frameworks, and protocols: as you'd expect, regulatory considerations and issues of access and coverage can be quite diverse when you expand your focus outside of the US.

### LIQUID BIOPSY IN EARLY CANCER DETECTION AND SCREENING

**Lauren:** Around two years ago we started a cancer early detection and screening working group focused on single-cancer screening and multi-cancer early detection. There is huge potential for liquid biopsy in this area—if you can identify cancer early then you may be able to treat it better, faster and more effectively. Our working group consists of the major players in the field, from the commercial assay developers such as GRAIL, Exact Sciences, Adela, Delfi, and Guardant Health, to non-profit and regulatory institutions such as LUNGevity, Prevent Cancer Foundation, the US National Cancer Institute (NCI), and the US Food and Drug Administration (FDA).

The first project we worked on together was to identify the challenges in early cancer detection and screening, which culminated in a publication that came out in late 2022. In that work, we also discussed the opportunities and potential positive impact that earlier detection technology would have on patients and the community as a whole in the future.

We concluded that the technology's potential benefits far outweigh the challenges and it is essential that we continue to support the growing field.

The working group's follow up deliverable includes the establishment of a field-specific lexicon to ensure that different organizations apply consistent definitions to key terms in the field. A BLOODPAC early detection and screening lexicon has recently been completed and will be submitted for publication by Q2 2023.

### ADDRESSING MINIMAL RESIDUAL DISEASE (MRD)

**Lauren:** A subsequent deliverable on our agenda this year is to create a list of preanalytical recommended data elements (RDEs), both for MRD as well as early detection technologies. The purpose of these is to provide guidance for any study being conducted in these areas on what types of data to collect—we recommend collecting those key variables with the potential to change the results of an assay, and which outside researchers would need in order to replicate a study. We're basing these application-specific RDEs on our original 11 preanalytical data element recommendations available here. Our working groups have been discussing what aspects are similar and what are different when performing screening and early detections liquid biopsies versus MRD assays, to guide us to the data elements that would affect the outcome of each type of test.

"THE LIQUID BIOPSY FIELD IS INNOVATING AT A RAPID PACE. TO ENSURE THESE PROTOCOLS REMAIN RELEVANT AS TECHNOLOGY EVOLVES, BLOODPAC IS INITIATING AN OPEN FEEDBACK PERIOD TO ASK THE COMMUNITY HOW IT USES THE PROTOCOLS AND WHETHER ANY UPDATES ARE WARRANTED. "

I'd also like to touch on our work around liquid biopsy accessibility. From our inception, BLOODPAC has always remained cognizant of the fact that there are people who don't have access to a medical institution that they can visit regularly and easily. In the US and around the world, there are people that don't have access to physicians all the time and that prohibits them from having the best care possible.

We know that liquid biopsy opens up a world of opportunity in this space. If you can have your blood drawn to find out if you need further testing, rather than undergoing a surgical procedure for a traditional biopsy, or expensive imaging in a specialized facility, that would make a world of difference for a large proportion of the population. BLOODPAC is working hard to identify places where we can make this promise of greater accessibility to care a reality as liquid biopsy becomes part of the standard-of-care, and companies come out with new early detection and MRD assays. We know that having these tests available is going to be a huge game changer for patients everywhere. This is just the beginning.

### CONTINUING TO IMPROVE ANALYTICAL VALIDATION OF CTDNA-BASED ASSAYS

**Lauren:** BLOODPAC works iteratively and always looks for constant feedback from the broader community. One of our biggest achievements early on was the publication of our generic protocols for analytical validation of ctDNA-based assays, in partnership with the FDA. The analytical validation of ctDNA is particularly challenging because these tests are often looking for a needle in a haystack: very few tumor-derived DNA molecules may be present in circulation relative to the amount of non-tumor-derived cell-free DNA. Consequently, ctDNA-based assays need to be exquisitely sensitive and specific in order to minimize false negatives, and a lot of thought needs to go into the methods required to demonstrate these characteristics. Our goal for these validation protocols was to increase the speed and efficiency of liquid biopsy development and dialogue with the FDA, and to set a benchmark for best practices in assay validation.

The liquid biopsy field is innovating at a rapid pace. To ensure these protocols remain relevant as technology evolves, BLOODPAC is initiating an open feedback period to ask the community how it uses the protocols and whether any updates are warranted. The feedback form is available on the front page of our website and will be available until the 18th of July 2023.

We encourage anyone who has read or uses the validation protocols to share their thoughts through the feedback form below, so we can continue to serve the field. The updated validation protocols will be revised and published after consideration of the public comments and further subject matter expert discussion.

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CHAPTER 4

# ADVANCING GENOMICS CLINICALLY IN DISEASE

THE NATURAL LINK BETWEEN GENOMICS AND CANCER CAN MEAN THAT THE ATTENTION OF THE GENOMICS COMMUNITY IS OFTEN FOCUSED ON CANCER. HOWEVER, GENOMICS IS ALSO INTEGRAL TO THE PATHOLOGY, DIAGNOSIS AND TREATMENT OF MANY OTHER DISEASES.

Advancing genomics clinically in disease therefore remains a priority. This chapter aims to give an overview of what's happening currently and what more can be done.

## Which diseases can benefit from genomics?

There is a lot to cover when looking at genomics in disease, as a genetic component can nearly always be found when studying disease pathology. As covered in Chapter 1, rare diseases were some of the first diseases in which (mono)genetic components were identified. Genomic analysis is still integral to rare disease diagnosis and treatment. For example, whole genome sequencing (WGS) of rare diseases was widely performed in the 100,000 Genomes Project[1].

Other key disease areas covered in this chapter include infectious diseases, cardiology and mental health. How genomics is applied in cardiology presents a solid case for the use of genomics in disease. Mental health represents an area of disease that is less well understood. Here, genomics is revealing some of the causes of mental health disorders, genes that may increase susceptibility, and potential new treatments.

### INFECTIOUS DISEASES

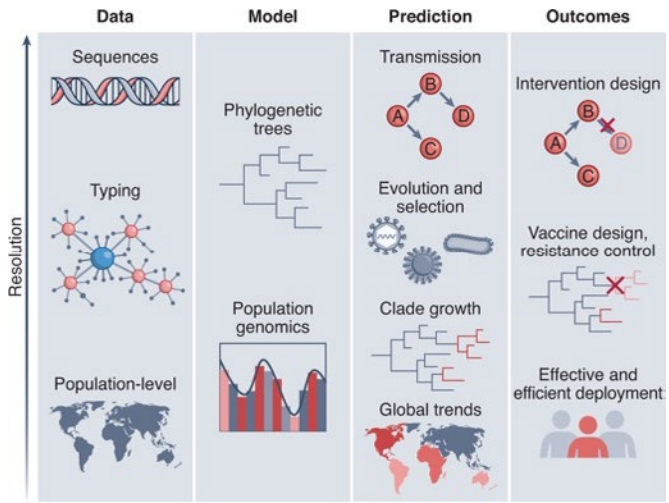
The clinical application of genomics often focuses on the analysis of the human genome – identifying variants in genes that may be acted upon clinically. The use of genomics in infectious diseases adopts a different approach.

Genomic technologies have enabled a deeper understanding of how pathogens function, evolve and interact. Pathogen diversity can be measured with precision and resolution and models can be generated that forecast the emergence and size of infectious disease outbreaks. This was exemplified throughout the COVID-19 pandemic[2].

Genomic data of pathogens can be used to model genotypes, which can then be used to predict disease trends and inform outcomes (e.g., intervention and vaccine design)[2] (see Figure 1).

**FIGURE 1: DATA, MODELS, PREDICTIONS AND OUTCOMES IN INFECTIOUS DISEASE GENOMICS.**

*These may cover multiple levels of resolution and many combinations that can be used to optimise the actions required at each step. Taken from The potential of genomics for infectious disease forecasting (Stockdale et al., 2022).*




## Rare diseases

Although the incidence of each individual disease is rare, the approximately 10,000 disorders that are classified as rare diseases affect 6% of the Western population. Rare diseases are often debilitating and difficult to manage. Unfortunately, one in three children diagnosed with a rare disease will die before their fifth birthday[1].

More than 80% of these diseases have a genetic component. Although the progression of next-generation sequencing (NGS) over the past decade has improved diagnosis rates, many patients with a rare disease still go without a molecular diagnosis after standard testing[1].

A study assessing the effects of WGS of rare diseases in the NHS found a substantial increase in the yield of genomic diagnoses with a WGS approach.

## JAMIE ELLINGFORD

Lead Genomic Data Scientist – Rare Disease
**Genomics England**

**The non-coding genome is 98% of 3 billion nucleotides that make up the genome. It has had a lot of different names through the years, including "junk DNA". One thing that is now clear is that there are regions of the non-coding genome that are essential to ensure that genes are switched on in the right place, at the right time. What controls that process can differ from cell to cell – there's a complexity there. Within a single gene, there may be different parts of the non-coding genome (enhancers, repressors) controlling the expression. These may be thousands of nucleotides away from the coding part of the gene. There may be different enhancers in the brain or the heart, for example, despite the same gene being expressed. Different enhancers can also control expression in the same tissue but at different times of development – early-stage development vs maintenance in that that cell type.**

In a quarter of those who received a genetic diagnosis, immediate clinical interventions were available. The findings from the study support the case for WGS in rare diseases as part of the National Genomic Medicine Service[1].

### UTILISING THE NON-CODING GENOME IN RARE DISEASES

The majority of clinical genomics focuses on the protein-coding regions of the genome. Sequencing of genes is usually only performed on those with a confirmed role in disease pathology. Despite the widespread use of this approach, it is not without its disadvantages. Adopting this approach in rare diseases means that, even with a suspected genetic cause, many patients will not receive a genetic diagnosis[3].

An alternative approach in individuals that could not receive a genetic diagnosis with gene panels or exome sequencing, is to perform WGS. WGS allows for the analysis of a previously overlooked part of the genome – the non-coding genome. The importance of non-coding genome variants in rare disease is being increasingly demonstrated, fuelled by an increased adoption of WGS[4].

Until a paper published in Genome Medicine in 2022 by Ellingford et al., there was a lack of guidance on how guidelines designed for protein-coding variants should be adapted for variants in the non-coding genome.

In 2015, the American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG/ AMP) released a set of guidelines for the interpretation of pathogenic of short sequence variants (single-nucleotide variants (SNVs) and indels <50 bps). In the 2022 paper, guidance was provided on how to apply these standards to variants identified in the non-coding genome[4].

**Jamie Ellingford**
Lead Genomic Data Scientist – Rare Disease
**Genomics England**

*"The aim was to expand some of the standardised, worldwide adopted guidelines for how we interpret a genomic variant. This is a five-point scale which ranges from benign to pathogenic. Variants which are likely pathogenic and pathogenic are in most cases the variants that would underpin a genetic diagnosis. What didn't exist previously was a standardised way to do this for the non-coding genome. We tried to provide guidance on lots of different aspects. Firstly, how to decide whether a particular part of the non-coding genome should be analysed clinically for variants. Having done that, whether you can provide an evidence base to classify it on this five-point scale. We re-used and re-developed some of the evidence base that was already in use for protein-coding variants but tailored it just to the non-coding parts of the genome."*

## Genomics in cardiology

*This section was compiled with the support of **Leo Mansell,** Locum Junior Doctor primarily based at **Manchester University Foundation Trust.** Leo is pursuing a career in cardiology and has a particular interest in inherited cardiac disease.*

Genomics, particularly genetic testing, has become a cornerstone in cardiology clinical practice. Specifically, genomics is routinely used in the diagnosis, investigation and management of a subgroup of cardiology patients – those with inherited cardiac conditions (ICCs).

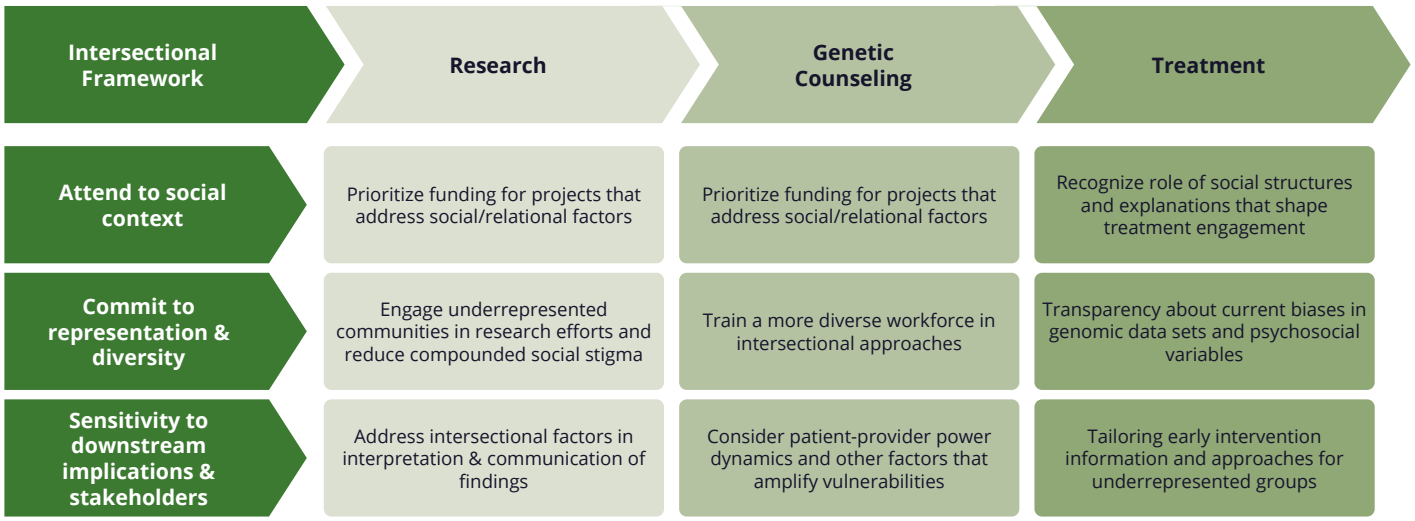
ICCs encompass a broad range of heart conditions. In the context of genomics, they can be broadly categorised into those involving the heart's muscle (cardiomyopathies) or it's electrical conduction system (primary inherited arrhythmias or channelopathies). Both of these conditions can predispose patients to sudden cardiac death (SCD).

### CARDIOMYOPATHIES

Hypertrophic cardiomyopathy (HCM) is one form of cardiomyopathy and provides an excellent illustration of the clinical application of genomics in cardiology. HCM patients have an exaggerated and pathological thickening of their heart muscle (hypertrophy). This is primarily in the wall of the left ventricle, which can lead to early heart failure and also cause life-threatening arrhythmias leading to SCD.

Early observations indicated that there was a hereditary form of HCM in a proportion of patients. Variations in genes coding for large, chain-like proteins in the sarcomere (the contractile unit of heart muscle) were confirmed to cause the majority of hereditary HCM cases. At present, up to 30% of all HCM patients will have a pathogenic gene variant and 60% of those will have a family history. The remaining 40% are likely to have a variant that has yet to be discovered.

**FIGURE 2: THE INTERSECTIONAL FRAMEWORK FOR PSYCHIATRIC GENOMICS.**
*Taken from Psychiatric genomics, mental health equity, and intersectionality: A framework for research and practice (Brown et al., 2022).*




The most common "sarcomeric" gene variants are in the genes MYH7, MYBPC3, TNNT2 and TNNI3 and are inherited in an autosomal dominant fashion. The variations lead to dysfunctional proteins causing exaggerated contraction as well as thickening and disarray within the architecture of heart muscle. As mentioned previously, this can eventually lead to heart failure and lethal arrhythmias.

If an individual manifests with HCM clinically, they are offered genetic testing targeting the pathogenic variants. If a variant is found, genetic testing can then be offered to other family members. Family members found with an inherited pathogenic variant can then be kept under regular surveillance (even without clinical manifestation), offering earlier intervention if the disease develops.

### OTHER CONDITIONS

Cascade genetic testing is also performed in primary inherited arrhythmia disorders (often termed channelopathies as they are caused by a fault in cell membrane ion channels). Looking at Long QT Syndrome (LQT), three primary genotypes exist: LQT1, LQT2 and LQT3. Each of these is caused by a different mutation in the potassium ion channel of the myocyte. Each genotype also displays a slightly different clinical phenotype and potential severity. Genetic testing can therefore be used to inform slightly different disease management approaches.

Research is ongoing and increasing in all fields of cardiology. A particular interest is shown in the inheritance and genetic predisposition to coronary artery disease and lipid disorders, meaning that the future of cardiology and genomics is very exciting.

## The genomics of mental health

Unlike some other diseases, the causes of psychiatric illness cannot easily be narrowed down and quantified for diagnosis and treatment. Mental health is multi-factorial. Disorders can also be defined in different ways – from diagnostic conditions, structural conditions, the person diagnosed and that person's social ties[5].

A paper published in 2022 presents an intersectional framework to be used in psychiatric genomics as the field expands (see Figure 2). The aim of the framework is to better incorporate issues of social context, racial and cultural diversity and downstream ethical considerations into the work performed by professional in psychiatric genomics[5].

The framework can support psychiatric genomics across three key areas: genomic research practices; genetic counselling for patients and families; enhancing biomedical models of psychiatric care[5].

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# INTERVIEW: GENETICS AND MENTAL HEALTH

THIS IS A SHORTENED AND EDITED VERSION OF AN INTERVIEW THAT WAS PUBLISHED ON FRONT LINE GENOMICS (3RD JANUARY 2023) WITH **GEROME BREEN,** PROFESSOR OF PSYCHIATRIC GENETICS AT THE INSTITUTE OF PSYCHIATRY, PSYCHOLOGY AND NEUROSCIENCE AT **KING'S COLLEGE LONDON.**

***Could you talk us through the Genetic Links to Anxiety and Depression study and explain what the main goals of the study are?***

**Gerome Breen:** GLAD or the Genetic Links to Anxiety and Depression Study is a research project where we aim to recruit 40,000 or more people who have experienced anxiety or depression during their lifetime. The goal is to recruit these individuals into an NIHR BioResource supported framework that will allow us to gather questionnaire information about their mental health, link to their medical records, and to collect DNA samples for genome-wide association studies and potentially whole genome sequencing of the dataset. In addition to genetics, we also focus on social and environmental risk factors. Our goal is to recruit a very large sample not just for the discovery of specific risk factors, but also to make the study participants available for follow-up studies based on their genetics, polygenic risk scores, clinical features, and response to treatments. By creating the study, we aim to make translational research in depression and anxiety more affordable and provide the largest contactable resource for depression and anxiety research in the world.

***Is the GLAD study helping to understand the comorbidity of psychiatric disorders better?***

**Gerome:** Yes – GLAD is broadly addressing common mental health disorders. We designed the GLAD questionnaire to assess different types of depression and anxiety disorders. Depression and anxiety are often comorbid, but more research has been done on depression. In GLAD, we administer a detailed questionnaire that asks about symptoms of both depression and each different anxiety disorder. This has allowed us to build a unique dataset on anxiety and depression comorbidity, which is valuable and interesting to clinicians. We also asked about physical health and found that a high BMI is linked to depression in our dataset.

"WE'RE TRYING TO RECRUIT 10,000 PEOPLE WITH EXPERIENCE OF ANY EATING DISORDER. WE LAUNCHED THE PROJECT ONE WEEK BEFORE THE PANDEMIC STARTED, AND DESPITE VARIOUS PROBLEMS RELATED TO THAT, WE'RE NOW AT AROUND 4400 CASES AND HOPE TO KEEP RECRUITING TO MEET OUR TARGET."

In other studies, such as in East Asia, lower BMI is associated with higher depression risk. Although this (higher or lower BMI) could be thought of as a comorbidity, it may reflect the social environment that predisposes people to depression in different parts of the world.

***The GLAD study is currently only in the UK. Do you think it's important to carry out studies like these on a global scale?***

**Gerome:** Yes, we think it's very important to carry out studies on a global scale. The environment affects our genetic results, and this is often overlooked. For example, we find that 15-20% of the genetic variants associated with depression in European samples are related to BMI. However, studies in East Asia have revealed that these genetic associations are probably mediated by the environment.

To take that further, if we gather large samples from different populations around the globe, we can develop a good understanding of the core biology of depression. Social and environmental risk factors vary across different countries, and to understand the core biology of depression, we need samples from different ethnicities, populations, and countries at a very large scale. This is even before considering global equity in research and addressing the fact that almost no studies have been done on depression genetics in African populations.

Along with investigators in Edinburgh and Cardiff, we have initiated a project called Depression Genetics in Africa (Dec. Gen. Africa) in collaboration with investigators in Ethiopia, Malawi, Nigeria and South Africa, with funding from the Wellcome Trust. Our goal is to recruit 10,000 people from these countries with severe depression to carry out the first large-scale depression genetics study in Africa. The project will also train African investigators in psychiatric genetics and set up the local infrastructure to allow larger studies to take place.

***There is a huge need for better therapeutics in this area. Do you think personalised medicine could exist given the genetic background of psychiatric disorders?***

**Gerome:** I do. There are only one or two mechanisms of action for current medications for depression, for example. This means that if a person fails to respond to one antidepressant, they have a reduced probability of responding to a second one. Thankfully, many people do respond to different antidepressants, but it would be better if someone who failed to respond to a common type of antidepressant like a serotonin reuptake inhibitor (SSRI) could be tried on a drug with a totally different mechanism of action. This is similar to what people do with pain medication, where they switch the mechanism targeted to address the pain. I think genetics could give us a diversity of mechanisms to target; it could be great to have 10-12 different mechanisms that can be targeted by medications as if a patient doesn't respond to SSRIs, they could potentially respond to another mechanism. By broadening the spectrum of therapeutics, more patients will have access to a therapeutic that works for them.

***How can genomics improve the clinical trial approaches that are currently used in mental health?***

**Gerome:** I think one of the key areas that interests us is the ability to recruit participants based on their genetic makeup. For example, we could recruit people with high or low polygenic risk scores and use different trial designs that focus on genetic selection (of participants) rather than phenotypic clinical variables. Another example would be if a drug company is developing a therapeutic, and they know that a specific genetic variant is important for the drug's target or response, they could recruit participants based on that genetic variation.

***Do you think by studying the genetics of mental health, one day we can have the predictive power to assess certain people that might be more susceptible to psychiatric disorders?***

**Gerome:** No, I don't think that we can do that accurately. Mental health disorders like depression and anxiety are simply too complex for that kind of prediction. However, what we might be able to do better is assess a person's genetic risk for certain disorders when they present at a clinic. For example, if someone presents with severe depression, we might be able to determine their risk for developing bipolar disorder (manic depression). We might also be able to develop a profile for that person that indicates potential side effects, likely comorbidities, and their likelihood of responding to certain medications. But I think this would be more useful once someone has already presented with symptoms and is being referred to a clinic. Otherwise, the risk of false positive predictions at a population level would be too high.

***You also do some work with eating disorders, are there certain disorders that have a stronger genetic link?***

**Gerome:** Yes, when we look at psychiatric disorders as a whole, they can be grouped into three categories based on the strength of their genetic effects. Disorders like schizophrenia, bipolar disorder, autism and ADHD have heritability rates of between 65% and 90%. Eating disorders have heritability rates of between 45% and 70%. And disorders like anxiety and depression have heritability rates of 30% to 40%. Heritability refers to the proportion of the risk of developing a disorder that can be attributed to genetic factors. So, while there is a substantial genetic component to depression and anxiety, it is a minority, while the majority of the risk for eating disorders can be attributed to genetics.

***How have you been studying them? Have you been working on a program similar to GLAD?***

**Gerome:** Yes, we have a sister project to GLAD called EDGI-UK, which stands for the Eating Disorders Genetics Initiative in the UK. We're trying to recruit 10,000 people with experience of any eating disorder. We launched the project one week before the pandemic started, and despite various problems related to that, we're now at around 4400 cases and hope to keep recruiting to meet our target.

***What are you looking forward to in the future?***

**Gerome:** I think what's really interesting about genetics is that every two years represents at least one decade of scientific advancement in other fields. What's really interesting to me about genomics is seeing all the new things people are doing across various disorders, and all the new resources and technologies that are coming out.

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CHAPTER 5

# ADVANCING GENOMICS FOR *EVERYONE*

GENOMICS HAS THE POTENTIAL TO BENEFIT THE LIVES OF EVERYONE ON THE PLANET. UNFORTUNATELY, SOME PEOPLE HAVE SEEN LESS OF THAT BENEFIT THAN OTHERS. ENSURING EQUITABLE CLINICAL GENOMICS FOR AS MANY PEOPLE AS POSSIBLE IS A HUGE UNDERTAKING THAT IS CONSTANTLY EVOLVING, INVOLVING MANY DIFFERENT FACTORS.

This chapter will therefore explore some areas in which genomics can be advanced clinically to benefit everyone.

## Increasing accessibility in genomics

The translation of genomics into routine clinical care has a number of challenges. These include the validation of tests and the development of infrastructure required to perform them. However, the biggest factor involved with the clinical translation of genomic technologies is cost. The purchase of (often very expensive) instruments, training staff on a new technology and running new workflows can all add up to a prohibitive cost in many cases. The following section will review what is being done globally to improve access to genomics in developing countries.

### IMPROVING GENOMIC ACCESS GLOBALLY

The cost of implementing genomics is felt hardest in developing countries. Even though the price of sequencing an entire genome has reduced dramatically since the completion of the Human Genome Project in 2003, the reality of maintaining even a single sequencing facility, let alone a sufficient number to support an entire population, exceeds the available funds in a lot of developing countries.

In 2022, the WHO Science Council (set up by the Director General Dr Tedros Adhanom Ghebreyesus) produced a report that included the impact of genomics during the COVID-19 pandemic. In the report the authors stated that "a long lag time between the availability of genomic technologies in rich countries and their availability in less-resourced countries is neither ethically nor scientifically justifiable."

### CLOSING THE GENOMIC GAP

To promote the adoption or expanded use of genomics, the WHO Science Council has made four recommendations:

- ***Advocacy for genomics*** to persuade governments and other organisations of the clinical and economic benefits of genomics.
- ***Overcoming obstacles*** by implementing local planning, financing, training and the low-cost provision of instruments and infrastructure.
- ***Collaboration*** between governments, funding organisations, academia and industry to establish genomics and expand capacity.
- ***Effective oversight,*** including national and international standards, to promote ethical, legal and equitable sharing of methods and information.

High-income countries can also play a role in advancing genomics for everyone. International collaborations between developed and developing countries will lead to a substantial increase in genomic capabilities. Funding, equipment and training can help to support the establishment of sequencing facilities in developing nations. More open-access literature must also be encouraged as the access to subscription-only journals is another prohibiting factor in genomic research.

### TIFFANY BOUGHTWOOD

Managing Director, **Australian Genomics**

**One of the issues and problems with sequencing, is that it causes huge discrepancies in healthcare, between the ability to have these advanced technologies, and not. This is not only in the context of ethnicity and representation of genomic data sets, but also in terms of equity of access and affordability. If it's not covered by the public purse, then these technologies are just not accessible to most. Not only do we need to facilitate and foster new sequencing technologies emerging from foundational research, but we need to enable their translation into the healthcare system. This requires working with governments so that they are aware of what technology is coming through the pipeline. Subsequently, this will allow them to budget accordingly, address legal or regulatory barriers, and consider the overall social impact to ensure that the healthcare system is prepared and aware of how these latest technologies can be most beneficial to patients.**

# The lack of diversity in genomics

Despite the increasing interest in genomics and a considerable increase in data being generated, the lack of diversity in genomics still raises issues. The overwhelming majority of genomic data available today comes from individuals of European ancestry[1].

As well as this, racially and ethnically minoritized groups are less likely to participate in research, meaning that clinical trial data is not reflective of true population demographics. The result of this lack of diversity can lead to biased interpretation of results. Clinically, this can cause genetic misdiagnosis from testing that is not suitable for the needs of diverse populations.

### INCREASING DIVERSITY

There are multiple large-scale projects dedicated to tackling the diversity problem within genomics. The All of Us Research Program in the USA and the Diverse Data Initiative from Genomics England are examples that were covered in more detail in Chapter 2.

Considerable effort is being put into addressing the imbalance between the genomic resources across Africa and the genomic data available from individuals in the continent. The Human Health and Heredity in Africa Initiative (The H3Africa Consortium) consists of a network of NIH and Wellcome Trust funded research sites across Africa, empowering African researchers to be competitive in genomics.


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## KAROLINE KUCHENBAECKER

Professor of Genetic Epidemiologyr
**University College London**

**Currently, genomic studies are not very diverse. Around 80% or so of published studies use data from people who have European ancestry – so the vast majority. If you compare that to the proportions of the world's population, obviously, 80% of the world population are not white. There are other major ancestry groups and there's a big imbalance. For example, the second largest group is people of East Asian ancestry and some groups like this are severely underrepresented. The thing that really surprised me was when we looked at these numbers is that over time it hasn't really changed. So, things haven't improved in the past few years, despite repeated calls for action, and despite a lot more awareness.**

# CASE STUDY: TACKLING PROSTATE CANCER IN BLACK MEN

THE FOLLOWING CASE STUDY WAS COMPILED WITH THE HELP OF **LINDSAY THOMPSON,** CEO AND SERVICE AND SERVICE DEVELOPMENT AND DELIVERY MANAGER AT **B'ME AGAINST CANCER (BMAC).**

Health inequalities exist in the diagnosis and treatment of black men with prostate cancer (PCa). 1 in 8 white men will develop PCa throughout their lifetime. In the African-Caribbean population, that risk is dramatically increased, with 1 in 4 men developing the disease over the course of their life. As well as this increased risk, African-Caribbean men diagnosed with PCa are twice as likely to die from the disease[2].

## THE PERCEPTIONS OF SCREENING

A recent body of research has emerged examining the perceptions of PCa screening in black men, both in the UK and the USA. Multi-factorial socioeconomic factors may explain the disparities seen in the healthcare of black men with PCa. The history of segregation and mistreatment in healthcare systems contributes to this, leading to poor communication, a lack of information and a fear of PCa diagnosis[3].

All of this leads to a decreased uptake in PCa screening, which has been suggested to contribute to the worse outcomes experienced. However, this does not fully explain why black men don't respond to treatment as well and are still twice as likely to die from PCa than white men.

## THE GENOMICS OF PROSTATE CANCER

Recent studies have suggested that genomics may help with understanding the health inequalities in PCa. Genomic and transcriptomic analysis performed in African American men revealed unique PCa tumour biology connected to ancestry. Specifically, significant upregulation was observed in genes related to DNA mismatch repair, hypoxic conditions (including reactive oxygen species) and pathways related to immune response and apoptosis[4].

These genes and their related pathways are commonly associated with many different cancer types and the hallmarks of cancer. The analysis of these genes and genetic changes could therefore not only provide a method of earlier diagnosis, but also potential targets in the treatment of black men with PCa.

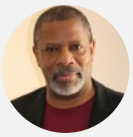
## GENOMICS IN THE COMMUNITY

Despite the promising results, there is a major lack of genomic data from men of African descent with PCa. This could be down to a lack of diversity in genomics studies in general. However, a more complex issue has also been raised, which links back to the perceptions of screening in black communities.

In the past, black people have been mistreated within research and represented negatively in results published in scientific journals. Examples such as historic clinical experimentation without consent have further decreased the trust between black communities and scientists. This translates to an underrepresentation of black people in clinical data or enrolled onto clinical trials, adding to the lack of results about black men with PCa[3].

Adopting an alternative, community-driven, approach has shown positive results in the numbers of African-Caribbean men undergoing PCa screening in the UK[2]. An example of this is the United Against Prostate Cancer project ran by the NHS in the East of England and BMAC. Central to the approach is community engagement and involvement (including a dominoes tournament) alongside information and awareness sessions on PCa.

The little genomic data that is available indicates that black men have a genetic profile that may explain the increased risk of PCa, providing avenues for early detection and therapeutic intervention in the future. It is clear that more genomic data needs to be collected on black men. However, the way clinical trials have been performed so far have failed to address this problem. Moving forward, a community-driven approach (as evidenced by the increased screening rates) also needs to be adopted here in order to increase genomic data from black men and tackle the health inequalities in PCa.



**Lindsay Thompson**
CEO and Service and Service Development and Delivery Manager
**B'Me Against Cancer (BMAC)**

*"In our 14-year history and experience as an organisation, we have found that community engagement and involvement are crucial factors to secure positive outcomes. However, for statutory bodies and commissioners of services, this element has been an afterthought in almost every single case. Due to the historical and cultural landscape relating to the lack of participation in research and clinical trials, there is an unfounded pre-supposition that black people are not interested in taking part in genomic medicine research. However, according to research findings,* this is not actually the case. *Furthermore, the application of some elements of ethics relating to research and clinical trial participation are also major barriers."*

CHAPTER 6

# THE PUBLIC AND PATIENT PERSPECTIVE OF GENOMICS

TO THOSE FAMILIAR WITH GENOMICS, THE BENEFITS ARE CLEAR. AS THE FIELD GROWS, MORE PEOPLE ARE LIKELY TO BE OFFERED GENOMIC TESTING IN THE FUTURE.

However, much of the public do not have a detailed knowledge of genomics. This chapter will therefore explore genomics from the other side, to help those working in the field develop a better understanding of the perspectives of the most important stakeholders – patients and the general public.

## Whole genome sequencing for genomic testing

Genomic testing has shown to be of benefit in the diagnosis and management of cancer, rare diseases and many other disease areas. Technological developments, increased accessibility and reduced sequencing cost are driving the use of whole genome sequencing (WGS) in these disease areas. Increased translation into clinical practice means that routine WGS will be rolled out to the wider public in the future[1]. Although this is an exciting prospect, there are many considerations from the patient side that it is important to be aware of.

### CONSIDERATIONS FOR GENOMIC TESTING

The increased use of WGS comes with unique issues that can raise both ethical and practical concerns. These include the identification of incidental findings (IFs) and variants of unknown significance (VUSs). IFs are genetic variants found during WGS that are unrelated to the condition being investigated. VUSs are genetic variants with unknown pathogenicity[1].

In specific cases (in rare diseases, for example) the identification of these variants may provide some explanation for disease pathology or even offer a target for therapy. However, when performing WGS in an asymptomatic population, the identification of such variants may cause unnecessary anxiety[1]. For example, it has been found that individuals undergoing WGS are less likely to want to know about VUSs compared to IFs, due to the non-actionable nature of VUSs[2].

Aside from these concerns, there are many other advantages to assessing the public's view of genomics. These include improved quality of research and ensuring that studies are designed to be relevant to all communities. Social acceptance of genomic testing can also be increased, facilitating its safe implementation into routine healthcare[1].

### ANALYSING GENOMICS USING THE NASSS FRAMEWORK

The non-adoption, abandonment, scale-up, spread and sustainability (NASSS) framework developed by Greenhalgh et al., can be used to examine technology-based health interventions[3]. In 2022, the NASSS framework was used to assess how public perceptions can inform implementation of genomic testing more broadly[1].

It was found that public perceptions of genomics could be applied to several NASSS domains, including technology, value proposition, the adopter system and the wider context. The identification of the NASSS domains translate as key areas in genomics that can be influenced by the public perception[1].

**TABLE 1: DEFINITIONS OF ENGAGEMENT FROM RESEARCH PROGRAMS THAT PRESENTED IT.**
*Taken from Promoting patient engagement in cancer genomics research programs: An environmental scan (Schuster et al., 2023).*

| Research program | Definition of engagement |
|---|---|
| **Cancer Moonshot Biobank** | "The establishment of an ongoing trusting and mutually vested relationship between study participants, healthcare providers and the Biobank" |
| **PE-CGS Network RFA** | "An ongoing, bi-directional and mutually beneficial interaction between participants, their communities, and researchers, where participants are included as an integral part of all phases of the research process: including the identification of research priorities and the design, conduct, and uptake of the research" |
| **All of Us** | "The concept of engagement in the [All of Us Research Program] is about partnering with different stakeholders for the purposes of making potential participants aware of the [All of Us Research Program], enrolling them to participate, and retaining them within the program" |
| **eMERGE Network** | "A process of inclusive participation that supports mutual respect of values, strategies, and actions for authentic partnership of people affiliated with or self-identified by geographic proximity, special interest, or similar situations to address issues affecting the well- being of the community of focus" |

Furthermore, it was found that the public have far-reaching and insightful concerns about genomics, including data storage and management, privacy, cost of testing, genetic engineering and more[1].

# Patient engagement in cancer genomics

Cancer is one of the main disease areas that has benefitted the most from the application of genomics. However, multiple different cancer types still lack suitable genomic classification and many patient populations have not been adequately represented in clinical research. Recently, patient engagement has seen increasing attention as it has the potential to democratise research into cancer genomics and increase the clinical impact[4].

## PATIENT ENGAGEMENT AND EQUITABLE GENOMICS

Promoting patient engagement is a priority within cancer genomics research. The concept of patient engagement directly relates to increasing genomics in diverse and traditionally under-studied populations[4].

Patient engagement has the ability to transform individuals from "passive" study participants to "active" participants involved in all aspects of the research. Including a greater diversity of study participants ensures that research and clinical trials benefit people from all communities[4]. Several active research programs have presented their definitions of patient engagement (see Table 1).

Three needs have been identified aimed at advancing the use of patient engagement in cancer research in the future:

1. ***Reach an agreement*** on the meaning of patient engagement.
2. ***Develop a clear taxonomy of measures*** to be able to assess the quality and comparative effectiveness of engagement strategies.
3. ***Identify the comparative effectiveness*** of engagement strategies.

By addressing these three needs, patient engagement in cancer genomics would be increased, along with a better understanding of how to tailor different engagement strategies to different groups[4].

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# INTERVIEW: THE SOCIAL AND ETHICAL IMPLICATIONS OF GENETIC SCREENING

THIS IS A SHORTENED AND EDITED VERSION OF AN INTERVIEW THAT WAS PUBLISHED ON FRONT LINE GENOMICS (1ST DECEMBER 2022) WITH **FELICITY BOARDMAN,** PROFESSOR OF SOCIAL SCIENCE IN GENOMICS AT THE **UNIVERSITY OF WARWICK**. IN THE INTERVIEW, FELICITY DISCUSSES HER RESEARCH INTO THE SOCIAL AND ETHICAL IMPLICATIONS OF REPRODUCTIVE GENETIC TECHNOLOGIES USED IN PRENATAL, PRECONCEPTION AND NEWBORN SCREENING.

***FLG: Felicity, could you introduce yourself and give us an overview of your work?***

**Felicity Boardman:** My name is Felicity Boardman and I am a Professor of Social Science and Genomics. I'm also a person with a genetic condition myself. I have generalised dystonia; I am a wheelchair user and I have children myself. That is partly where my interest in reproductive genomic medicine stemmed from, as I had to face some of the decisions around the use of genetic technologies in reproduction myself. I've come across some of the debates and social and ethical concerns about how genomics technologies should be used. My research has tried to highlight the perspectives of people who have this lived experience – trying to understand that lived experience and how it can be useful in helping us untangle some of the social and ethical difficulties around the use of these technologies.

***FLG: Can you give us some background on the current regulations surrounding genetic screening in the UK?***

**Felicity:** At the moment, all screening programs are looked at by the UK National Screening Committee. This is an advisory group that makes recommendations to the government on which screening programs should be introduced. They do this through a process of evidence review, with a set number of criteria that the conditions are measured against. It is very much a condition-by-condition approach to screening.

I think in some ways, genomics is challenging that way of looking at screening programs. This idea of being able to get a lot out of data all at once through one test is very different than the way in which the current approach to assessing screening programs has been set up. It has been set up on a case-by-case basis and there are very strict criteria that a condition has to meet before it can be approved or recommended for a screening program. Importantly, within those criteria is the need for treatment. This is something that is also changing with genomics. We are seeing the introduction of gene therapies. So, in many ways, I feel like recent advancements in genomics are challenging the way that we approach screening, as well as treatment.

***FLG: What are the ethical concerns of genetic screening? Can you give some examples?***

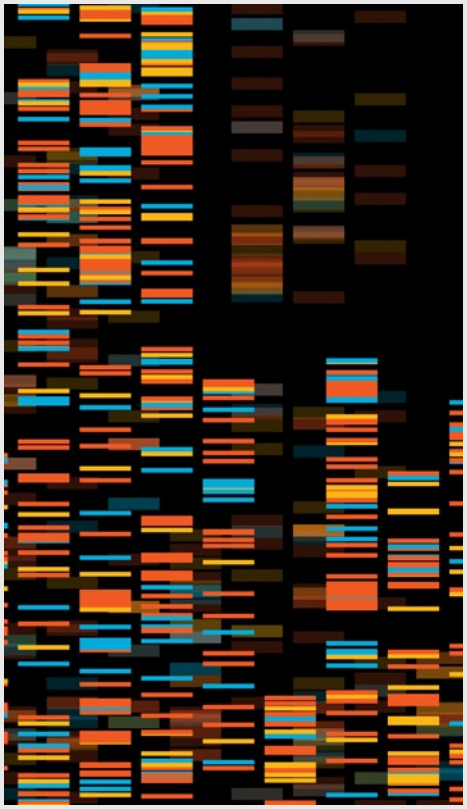
**Felicity:** Well, the ethical concerns are very different depending on the type of screening. In the context of reproductive genetic screening, ethical concerns can vary depending on when the screening is done. If it is done pre-conception, before a couple of has conceived the child, there are concerns about which conditions should be included the screening program. Moreover, when you are screening a couple before conception, it has the potential to influence the way in which people approach relationships. There is this potential for people to want to check out each other's genetic profile before deciding whether or not they would want to have children with that person.

In some of the interviews that I have done, where couples have had children affected by genetic conditions, that sort of question about, "Are we compatible?" came up. So, I do not think it is a leap to say that in the future, if we all know about the conditions that we are carriers for, could that influence who we enter into long term relationships with, and who we end up having children with? This is something that we need to consider because there are there are arguments that genomics, particularly in this context, can be used in a eugenic way.

There is a history that needs to be considered when thinking about the use of pre-conception genetic screening and prenatal genetic screening. So, screening in pregnancy has a unique set of ethical and social issues around it, because it's associated with pregnancy termination. It's about identifying a potential condition in that foetus, and then making a decision about whether or not to continue that pregnancy. It is also challenging, because at that moment when screening is being performed, there is no phenotypic information. It is based solely on the genotype and there might not necessarily be a good correlation between the two. It is hard to predict, particularly for conditions where there is a high degree of variability, what that child's life is going to be like based on their genotype. From my research, I could see the ways in which different social factors were important especially when considering how some of these families live their lives as well as the clinical factors.

Some of the ethics around prenatal genetic screening focus on ensuring that there is balanced information about life with the condition identified, but also making sure that screening does not become too routine to the point that it jeopardises consent. There is no argument that pregnant women go through scans and screening because it's something that you just do in pregnancy. It's the expectation that you will go to your 20-week scan and have a nice opportunity to see the baby, but not necessarily thinking about that as a foetal anomaly scan. There are also ethical concerns around making sure that people really understand what could come back from some of these tests.

"I THINK IN SOME WAYS, GENOMICS IS CHALLENGING THAT WAY OF LOOKING AT SCREENING PROGRAMS. THIS IDEA OF BEING ABLE TO GET A LOT OUT OF DATA ALL AT ONCE THROUGH ONE TEST IS VERY DIFFERENT THAN THE WAY IN WHICH THE CURRENT APPROACH TO ASSESSING SCREENING PROGRAMS HAS BEEN SET UP."



Finally, there is newborn screening. The newborn genomes program is something that's very much at the forefront of many people's minds – how genetic screening could work for newborns. Again, the question about what to look for is important. There is a question about whether parents will want to know about late-onset conditions or conditions for which there are no treatments, and even defining what we mean by "treatment". Is it surveillance or intervention? Is that enough grounds to want to tell a family about a potential future condition? How much uncertainty might there be? Even with examples like cystic fibrosis newborn screening, there can be uncertain results. For cystic fibrosis, we have these designations – positive, inconclusive diagnosis, or CF speed – which means the children usually remain healthy but could develop cystic fibrosis at some point in the future.

Another concern around genomic screening at birth is that there could be more uncertain results and we need to consider the potential harm that could cause families. That is something that needs to be thought about – what the reality of living with a designation could look like. This is the same for conditions that are early onset but not immediate – there is a concern that parents can lose that "golden time" with their child, where they do not realise there is anything wrong with their child. In the interviews that I did with families who had children with fragile X syndrome, some of them said they wish they had known earlier. They felt like they were not being believed when they were telling doctors that something was going on with their child and that they kept being sent away. Others were saying how they got those few years of "golden time" before realising and if they had undergone newborn screening that time would have been taken away.

There is an argument about protecting that latent period before the condition, as screening can be seen as almost extending the illness. With the condition being identifying earlier, that baby suddenly becomes a child with a condition. Another concern with newborn screening is related to genomic sequencing. There is the issue of what is done with the data afterwards.

Whether that data is stored, whether it is linked, whether it is dipped into over time. All of this comes with ethical concerns about consent, about who has access, when recontacting is okay or not. Is it okay to for someone to get a phone call out of the blue to say, "Oh, by the way, we now understand what one of your variants means and this is what it's going to mean for your life"? Is it possible for people to give advanced consent for that and how often would you have to take consent from someone for recontacting? That is just skimming the surface of the ethical and social concerns about genetic screening – there is a lot to think about.

***FLG: Could you tell us about how you are exploring attitudes towards pre-conception carrier screening and the Imagining Futures Project?***

**Felicity:** I did a series of surveys and interviews – quantitative surveys and in-depth interviews. The families involved were living with one of five genetic conditions: thalassemia, hemophilia, fragile X syndrome, spinal muscular atrophy or cystic fibrosis. They are very different conditions, and they present very differently. I picked these genetic conditions because I wanted to look at a range of different experiences – but even within each condition, there is a high degree of variability.

What I found was that families were broadly very supportive of introducing pre-conception genetic screening. There was a lot more concern about a prenatal genetic screening program being introduced, but newborn screening and pre-conception screening were much less controversial. What I found interesting was how people's attitudes towards genetic screening were linked to their lived experiences. Those who had much more negative experiences dealing with these conditions were the people who were much more likely to be supportive of genetic screening in all its forms. Those who had more positive experiences were more likely to be sceptical about the value of genetic screening programs.

Interestingly, I also found that having a negative experience with your condition had very little to do with the severity of the condition. There are a range of factors that make living with a genetic condition either a negative or positive experience, not just clinical severity. That is important to think about when considering which conditions we should be screening for. I don't think you can "read out" what someone's lived experience is going to be based on the projected clinical severity of that condition.

Those who had early onset and clinically speaking, more severe conditions, were much more likely to be positive about their lives and to be ambivalent about genetic screening than those who had milder presentations of the condition that were later onset. I think it has a lot to do with the fact that when you have a late-onset condition you've lived your life a certain way. Then there's this period where you have to renegotiate your identity, your role, your lifestyle. People were reporting things like losing their jobs or their marriages breaking down, because they're having to adjust to big changes in their abilities. That process of deterioration was almost viewed more negatively than the resulting level of disability. I think uncoupling between severity and the patient's lived experience is a key finding that has come out of my research and how that contributes to some of the debates around which conditions should or should not be screened for.

***FLG: Do you think attitudes may change in the future? Perhaps if there is a better understanding of these conditions or better ways of teaching patients how to live with them?***

**Felicity:** We are going to see people become much more familiar and comfortable with the idea of genomics. It is increasingly being integrated within the NHS, not just in terms of screening, but in terms of diagnostics and treatments as well. However, we are seeing a rise in people wanting to talk about the realities of their conditions and to challenge screening programs if they feel that they do not value or don't recognise their lived experience. We have seen that recently in relation to Down's syndrome as expressed by Heidi Crowter. Heidi Crowter is a person with Down's syndrome; she spoke out about the existence of screening programs and how they were devaluing her life and the lives of other people with Down's syndrome.

You are also going to see people who advocate for genetic screening and celebrate the increased accessibility of genomic medicine to more and more people through genetic screening. It is opening it up at population level. Even people who do not have a history of genetic conditions, could have access to these technologies. There is also a huge potential there as well because I think that many of the families are supportive of the idea of choice. However, they are concerned that any choice that comes with technology needs to be an informed choice. This is why they would focus on balanced information, while at the same time supporting genomic technologies.

***FLG: In the future, when genomic technologies become more common, will people have a better understanding of the implications involved and therefore be able to make more of an informed choice?***

**Felicity:** It is really important that to have access to that lived experience. That is one of the things I have tried to do through the Imagining Futures research program – to bring some of that lived experience into the debate. We are not just talking about whether the general population wants to be screened, but we're also looking at what these conditions mean for the people who live with them.

Alongside the Imagining Futures research program, I also collaborated with a company called STAMP and we developed an art installation that was built directly out of the research findings. There was a double helix centrepiece, surrounding it was a word soundscape and videos played as well. It took the words directly from people involved in my research and projected them into this space. You could go in and see this denaturing double helix and hear the stories of people living the different types of genetic conditions and their experiences.

We toured this exhibition in different venues over a couple of years and got some interesting feedback. Many people spoke about how they had never heard of some of these conditions, never met anyone with them. They found it really enlightening to have those stories brought to them in a creative way. We need more of these projects, which make the lived experience of people living with genetic conditions accessible to the general population.

CHAPTER 7

# ADVANCING GENOMICS IN CLINICAL PRACTICE - THE NEXT STEPS

THE FINAL CHAPTER OF THE REPORT FOCUSES ON THE NEXT STEPS FOR CLINICAL GENOMICS. ADVANCING CLINICAL GENOMICS IS A MASSIVE UNDERTAKING.

An understanding of the main challenges is required, along with co-ordination with research to optimise clinical translation. As not everything can be covered in this report, the final chapter aims to explore some of the next steps for advancing genomics in clinical practice.

## Challenges in clinical genomics

**Bettina Lundgren**
CEO
**Danish National Genome Center**

*"Time is a significant factor when it comes to implementing new ways of working in healthcare systems. It requires specialised expertise to correctly interpret and analyse data. It can therefore be a challenge if health professionals do not have the necessary training or resources to handle complex data. Lack of standardisation also poses a challenge in working with data. There is still a lack of standardised guidelines and protocols for the use of genetic health data in clinical practice and in research, respectively. We also cannot forget the ethical and legal dilemmas that arise as people want to drive the development of personalised medicine. Ethical and legal issues associated with the use of genetic data in clinical practice as well as research will always be something to consider. Therefore, it is also important to develop guidelines and policies to protect patients' rights while promoting the use of personalised medicine. These are just some of the challenges in the development of personalised medicine."*

### IMPLEMENTING PRECISION ONCOLOGY

The increased use of genomic profiling for the diagnosis and monitoring of cancer has the ability to reshape therapy in many different tumour types. The desired outcome for the advancement of genomics in cancer is the implementation of precision oncology[1].

The major challenges in the implementation of precision oncology include equal access to genomic tests, increasing the robustness of clinical studies for new drugs and technologies, enabling the better interpretation of genomics data and empowering patients towards shared decision making[1].

### RARE DISEASES

As mentioned in Chapter 4, more than 80% of rare diseases have a genetic component. Despite the progression of genomics and sequencing techniques, many patients with a rare disease still fail to get a genetic diagnosis[2].

**Matt Brown**
Chief Scientific Officer
**Genomics England**

*"Looking specifically at rare monogenic diseases – there are two major challenges here. (a) Why do only around 25% of rare disease families get a diagnosis after short-read whole genome screening? (b) What are the effective therapeutics after diagnosis?*

## Translating genomics research

There is a large amount of cutting-edge genomic research being published. However, as discussed in previous chapters, the gap between research and what is actually implemented clinically can be quite wide. In this section, we asked some of our expert contributors: What can be done to ensure that research is translated to achieve the most clinical impact?

**Matt Brown**
Chief Scientific Officer
**Genomics England**

*"Try to focus on disease areas where there is a major unmet need and look beyond the 'usual suspect' conditions. These are not always the ones where there is the biggest need."*

**Jesse Berry**
Berle and Lucy Adams Chair in Cancer Research
Vice Chair, Academic Affairs, Department of Surgery
**Children's Hospital Los Angeles**

*"Using the NCI precision medicine website, it is important to understand if the alteration you have reported has a companion therapy. These can be hard for patients to interpret, so consulting with other genetic professionals (e.g., genetic counsellors) can also be helpful, especially for germline variants."*

**Bettina Lundgren**
CEO
**Danish National Genome Center**

*"Good collaboration across the application and development of personalised medicine is important. There is great potential in multidisciplinary collaborations and teams, where different professional groups collaborate to diagnose, develop and implement new methods and tools. In addition, it is advantageous to focus on relevant, specific diseases where the clinical effect is potentially greatest, and identify the clinical areas where there is the greatest need. The healthcare system and other relevant factors must also be geared to the data universe that must be worked in when we talk about genomic medicine. The right skills must be present, so that the right tools and solutions can be developed, put into use and benefit the patients. Last but not least, it is also important that the development has the right legal conditions and that you have a strategy for the way forward."*

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## Delivering the benefits to patients

The scope of clinical genomics (and this report) is vast. However, at the heart of this is delivering the benefits of genomics to the people that need them, the patients, in order to improve their lives.

**Matt Brown**
Chief Scientific Officer
**Genomics England**

*"There needs to be an increased delivery of proper genomic profiling for cancer patients as the uptake has been very patchy in England. There also needs to be more comprehensive linkage between genomic profiling in the NHS and clinical trials for new cancer therapies. Other big areas that require much more attention are pharmacogenomics and common disease profiling to assist in early diagnosis."*

**Bettina Lundgren**
CEO
**Danish National Genome Center**

*"With a new ambitious strategy for personalised medicine, we must ensure a balanced approach to the implementation in clinical practice and continue to involve relevant stakeholders in national collaborations and promote the multidisciplinary collaborations that already exist. Over time, research will support patient treatment to a greater extent, and conversely, patient treatment will support research."*