THE FUTURE OF CARE

2020 report

South West Academic Health Science Network

West of England Academic Health Science Network

Genomic science

Now and future

Contents

"Genomics and genetic testing enable clinicians to identify targeted, precision treatments and drug therapies for patients, and it is much better for patients to have that targeted treatment very early on in their disease pathway. I think that's transformative."

Natasha Swinscoe
Chief Executive
West of England AHSN

Executive summary

Genomic medicine has the potential to improve quality of care by targeting treatment, maximising its benefits and reducing side effects.

The science of genomics is opening up better diagnoses for patients, better and safer treatments, opportunities for screening and the possibilities for prevention.

Enormous progress has been made in the last two decades sequencing genomes quickly and cheaply. These advances open the door for more personalised medicine, bringing genomics into standard clinical practice, as well as discovering simple interventions that could help hundreds of thousands of people with a genetic disorder. But this developing technology also raises ethical questions and practical issues as we increase the demand for genomic testing and treatments.

Across the South West and West of England there is huge potential, but we must be prepared: there are significant training implications and the right policy framework and processes need to be in place.

An effective digital infrastructure to share data is also crucial. Here, the rapid progress of artificial intelligence (AI) or machine learning is a major contributor. Combined, genomics and AI present us with many exciting opportunities to transform healthcare.

To see how genomics can change lives, watch Emily's story: weahsn.net/emilys-story

Introduction

The West of England Academic Health Science Network's 'The Future of Care' events are exploring the new frontiers of science and innovation which are set to transform health and care in the future.

Bringing together experts from across the world to discuss the implications for the NHS and local healthcare systems like those in the South West and West of England, these events are exploring the latest breakthroughs in technology and ground-breaking medical research. This report captures the cutting-edge thinking and discussions from an event on genomics and how it will influence the future of care.

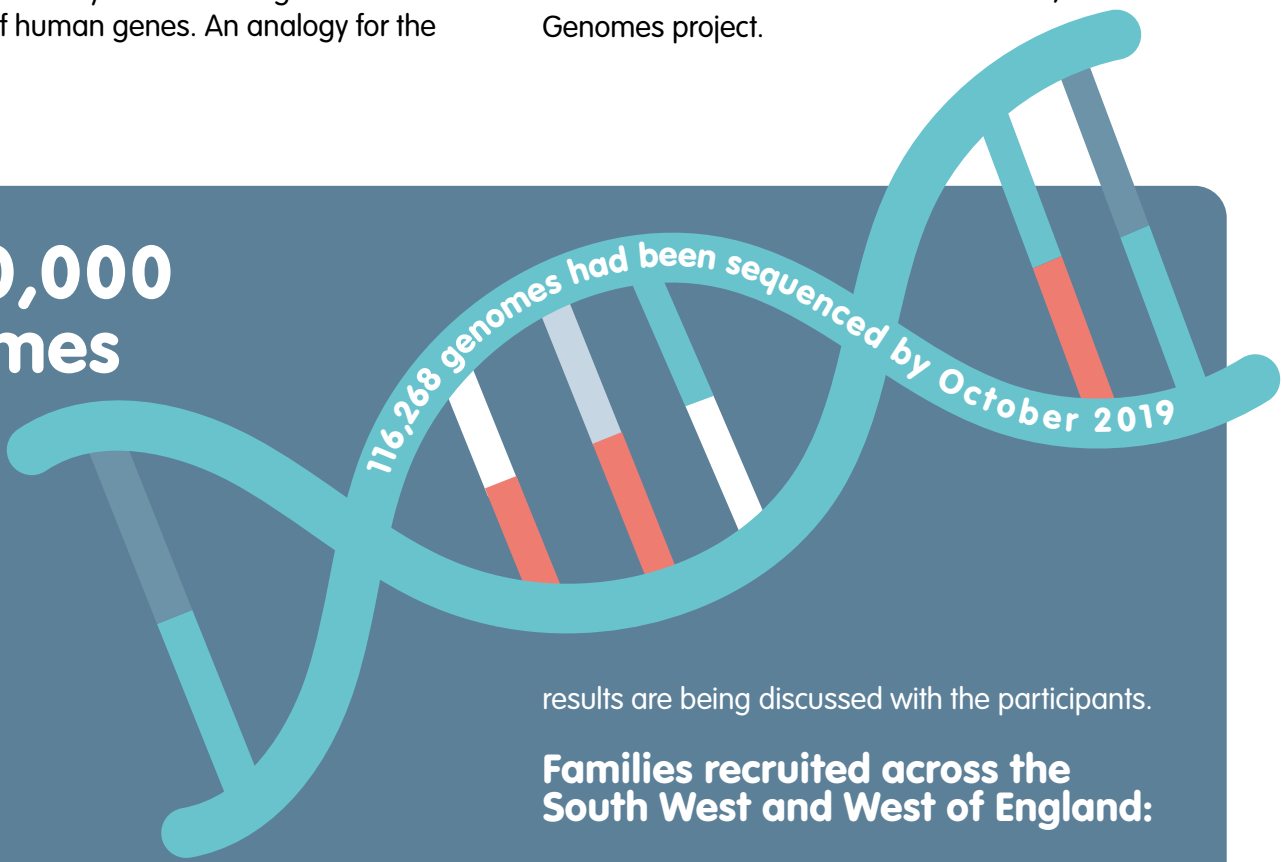
What is genomics?

Genomics is about the 'big picture'.

Genetics is the study of how changes in the DNA sequences that make up our genes cause disease. Sometimes these gene mutations are passed on to us by our parents, sometimes we acquire mutations during our lifetime.

But genetics is just the tip of the iceberg. Genomics by contrast is the study of our whole genome – the complete set of human genes. An analogy for the human genome is a library with 23 pairs of shelves (representing the chromosomes which contain our genes), holding 23,300 books or individual genes, present in every cell in our body.

Since Watson and Crick discovered the DNA double helix in 1953, technology has advanced rapidly. We can sequence and analyse DNA much more efficiently than before with 'next generation sequencing' (NGS) already improving diagnosis and research into new treatments, for example in tackling the recent Ebola outbreaks or malarial resistance. NGS was also used in the 100,000 Genomes project.



The 100,000 Genomes Project

In 2012, the government launched the 100,000 Genomes Project, mapping entire genomes to better understand rare diseases and cancer. 13 Genomic Medicine Centres were set up to deliver the project, including one in Exeter and one in Bristol.

The programme exceeded its target of recruiting 100,000 people and the sequencing has been completed; the analysis is underway and results are being discussed with the participants.

Families recruited across the South West and West of England:

Rare disease
5,446 people from 2,414 families enrolled

Cancer
1,515 people with cancer enrolled

You can find out more about 100,000 Genomes on the Genomics England website: www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project

One in 17 of us has a rare disease

Genomics can tell us about common diseases as well as rare diseases, and in any case one in 17 of us has a rare disease.

The beginning of clinical genomics is attributed to French paediatrician and geneticist Jérôme Lejeune, who in 1959 took DNA from children with Down syndrome and discovered the disorder was caused by an extra copy of chromosome 21.

Deletions and duplications are common types of genetic mutation. While the instances of disease may be rare, in fact we all have genetic mutations. Often they are harmless, but it's estimated that we all carry two recessive, faulty genes. If two people carry the same recessive gene, one in four of their children are affected. Cousins share one in eight of their genes, so the risk of recessive disease in the children of first cousins is one in 16.

People with a rare disease generally want genomics to help them answer four questions:

- What is wrong with me or my child?
- What will happen in the future?
- Is there a treatment or a cure?
- What are the implications for my children and my brothers and sisters?

Over the last 20 years, the biggest disorders have largely been discovered, but there are still many rare diseases that we don't yet know the causes for.

"For families that have had one child with a major illness, worried that it might happen again, we can answer that question."

Professor Sir John Burn
Professor of Clinical Genetics
Newcastle University

The rise of genomics

A story of exponential growth.

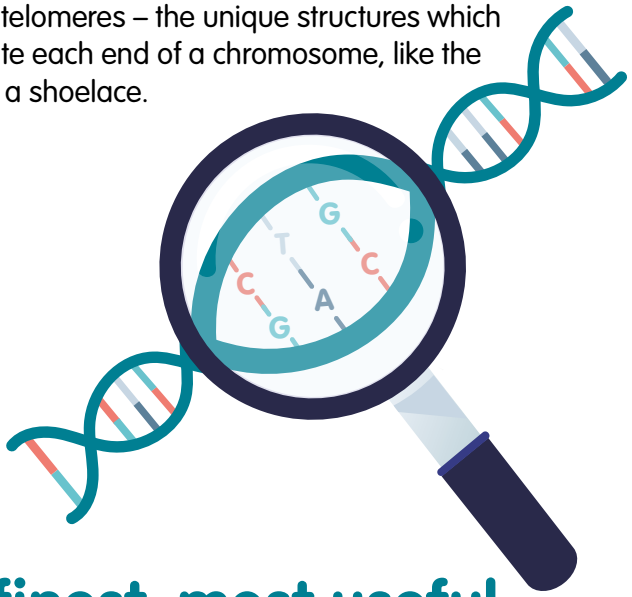
It took 14 years and three billion dollars to map the first whole genome sequence; it's now possible to complete them in a matter of hours.

Nationally, the Genomics Medicines Service (GMS) has been reorganised to be fit for this fast-changing future.

Next generation sequencing (NGS) was a step forward in speeding up genome sequencing. NGS works by cutting DNA into small fragments and amplifying it (copying it many times) to spot changes to a single letter of the genetic code. Now, long-read sequencing is allowing larger sections of DNA to be read in one go. This allows changes to be spotted where not just single letters but whole sections of DNA are missing, inserted or in the wrong place.

Another technique being developed uses handheld devices to read genes one letter at a time. DNA testing at the bedside is becoming a reality with simple, battery-operated point of care machines. However, these currently only test for specific conditions, using test cassettes designed to identify a single disorder.

It's important to remember that whole genome sequencing is still imperfect. There can be missing or erroneous data when trying to spot just one incorrect letter. Segments of genes, called exons, can assemble in different combinations and some genes may have thousands of variants – whole genome sequencing isn't yet able to distinguish between these variants. And it is still very hard to read telomeres – the unique structures which terminate each end of a chromosome, like the ends of a shoelace.



"Genomics will be one of the finest, most useful data layers for AI. We are already starting to see how we can segment which patients are going to benefit from screening in cancer, dementia or cardiovascular disease."

Dr Ignacio H. Medrano
Neurologist and founder of Savana Health and Mendelian

How artificial intelligence can boost genomics research

Artificial Intelligence + genomics is a powerful combination.

The last five to seven years has seen a shift in our approach to how we use computers. Instead of programming them to follow rules, data scientists started to explore what would happen if we taught them by example – much in the way humans learn. This is what we call machine learning or artificial intelligence (AI).

The rise of AI has been driven by greater access to data: computers (and humans) cannot learn if they don't have data. And in today's world, we now have immense amounts of data which modern computers are able to process very quickly. What is perhaps surprising is that making determinations according to statistical patterns often proves more effective than evidence-based approaches.

We can now create computers that mimic our intuition: black boxes that know nothing, but are incredibly accurate when they have enough past data to work with.

Consider Google Translate, which can accurately translate between languages without knowing what you are saying, or streaming music and video services which suggest new artists and programmes you might enjoy.

Computers are now overtaking humans in two areas: classification (diagnosis and screening) and prediction. Classification can be helpful, but prediction is much more powerful in improving prevention.

In healthcare, a tipping point was reached when researchers created a black box that could spot diabetic retinopathy with greater accuracy than ophthalmologists. This diagnostic tool has since been approved by the Food and Drug Administration (FDA) in America.

Because AI is not concerned with why correlations exist, it's possible to explore links that would not normally be considered in medicine. The same researchers investigated what else a retinal scan could tell them. They discovered in 2018 that AI can detect cardiovascular risk from a retinal scan with around 70 per cent accuracy.

The implications are clear: the increased use of AI in clinical practice will help predict and prevent more ill-health. The FDA has now approved around 20 data interventions since 2017 and this will only grow exponentially.

Genomics may be just another potential data layer, but it is one with enormous potential. If we continue to try and research genomic disorders by traditional methods alone, it will take a long time. Applying artificial intelligence in this field is vital if we want to speed up progress.

The promise of personalised care

Genomics is one part of the story of personalised medicine. As well as looking at the genome and DNA, personalised medicine can drill down to look at the RNA (ribonucleic acids), individual proteins and metabolites, and considers genome editing and stem cell therapies.

Surrounding these advances in personalised medicine are enabling technologies such as artificial intelligence, health data from wearable tech, and the rise in the 'internet of things' – devices that connect and exchange data with each other.

What's driving personalised medicine?

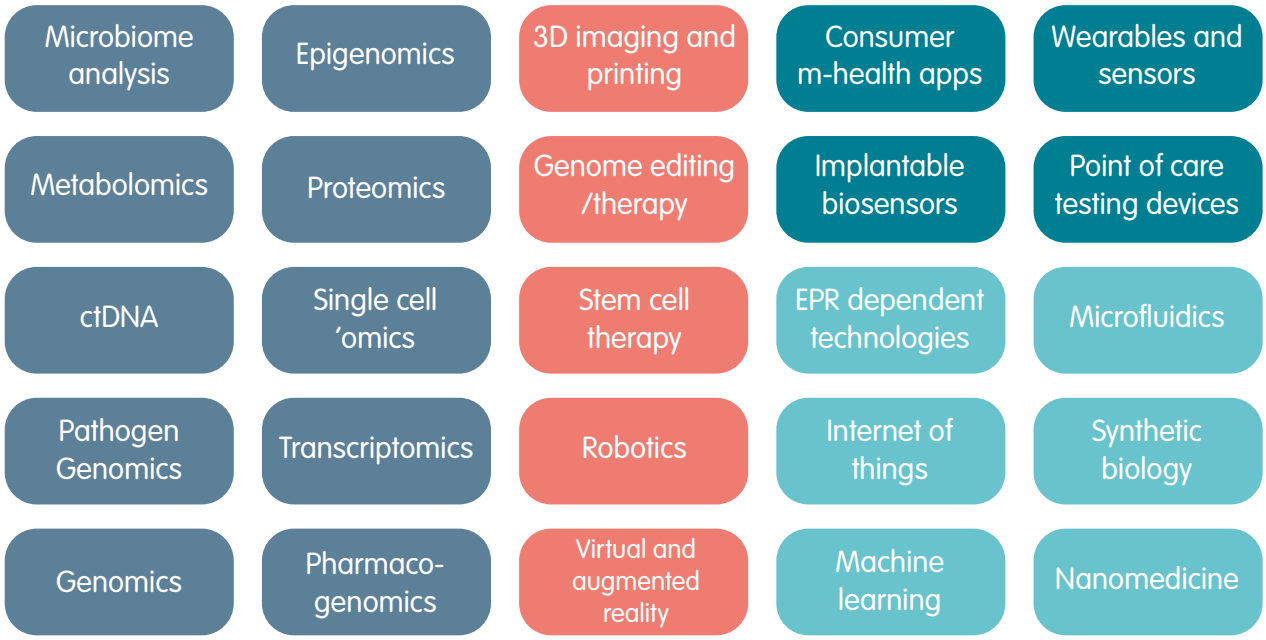
Developments in genomic sequencing technologies

Leaps in computing

Scientific advances and innovations in biomedical and digital technologies

An evolving health innovation ecosystem

Technologies for personalisation



- Technologies for greater molecular level characteristics
- Technologies for personalised theraputic interventions
- Technologies for personalised disease and health monitoring
- Underpinning and enabling technologies

Adapted from: *The personalised medicine technology landscape* PHG Foundation report for NHS England, 2018

Case study

Circulating tumour DNA (ctDNA) testing

ctDNA testing detects and analyses fragments of tumour DNA in a person's circulation. The test is much more accessible and repeatable than a standard and invasive biopsy would be and evidence suggests it can be better at capturing tumour genetic variation.

The technology has been successfully used for lung cancer patients, where a biopsy is a particularly challenging procedure, and supports better prescription of targeted therapies.

Following a workshop by the PHG Foundation in 2017, the following recommendations were made to help the use of ctDNA testing spread:

- Greater engagement with the health system
- Clear guidelines for test use
- System support for testing provision and access to targeted therapies.

ctDNA testing is now available on the national genomics test directory as a core test accessible through the Genomics Medicine Service, and further companion diagnostic blood testing is being developed for colorectal and breast cancers.

Where next on the genomics journey?

Can we keep up with the pace and scale of change?

One of the most exciting aspects of genomics is the ability to find new ways to identify and treat disease at an early stage. For instance, identifying patients with familial hypercholesterolaemia and providing early treatment with statins can reduce the risk of them having a heart attack.

Another disease genomics can identify is haemochromatosis, the unwanted storage of iron in the liver and pancreas, which can lead to premature organ failure. One in ten people have this gene mutation and one in four hundred people will have significant haemochromatosis. However, those affected can reduce their risk simply by giving blood regularly, so a diagnosis is key.

Tests like these are helping change lives for patients who have an undiagnosed disease, but what about screening? Can we test more broadly on a 'just-in-case' basis to spot diseases people don't know they have? The field of polygenic risk scoring allows us to make predictive statements by looking at all of the markers across a range of common diseases. However, it is a test which is prone to errors. For example, tests can identify people with a three to four times greater risk of developing coronary heart disease. This could potentially identify 15 per cent of heart attacks, but as much as five per cent are false positives, so using this method as a screening test is flawed.

As genomics becomes more mainstreamed into general clinical practice, it raises a number of questions and concerns we need to plan for. One important consideration is that health determinants are not just about our genes. There are other factors involved such as our environment and lifestyle, which can make genomics an imperfect tool for general screening.

DNA testing will also increase demand, especially as over-the-counter tests become cheaper and more widely available, such as tests for prostate cancer. These anticipatory care tests could lead to an explosion in both demand for both testing and follow-up treatment.

Much of the ethical debate so far has focused on the ethics of germline engineering, the process by which the genome of an individual is edited: changes are made in the eggs, sperm or embryos to prevent severe genetic disease in babies yet to be born. We can now carry out whole genome sequencing in the womb. What are the ethics about how we carry out these tests and use the information and potential diagnostics?

Alongside germline engineering, breakthroughs have been made in genome editing that focuses on non-heritable diseases instead. Called somatic genome editing, clinical trials are underway for genome editing to avoid haemoglobinopathies and retinal disease. While an exciting technology, it faces similar ethical concerns and regulation will need to keep up.

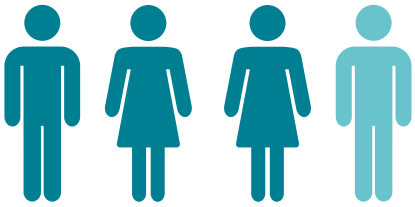
Case study
Lynch syndrome

Lynch syndrome is an inherited disorder that increases the risk of many types of cancer, particularly colorectal cancer. It's caused by mutations in the genes that repair errors in DNA during the process of cell division.

A new test has been developed for Lynch Syndrome by spotting microsatellite instability (MSI), the signature feature caused by defects in the proteins that repair these DNA mismatches. More accurate testing for micro-satellite instability is now very fast and cheap. It helps distinguish cancers that are hereditary from those which are caused during a person's lifetime.

In 1999, researchers started recruiting people with Lynch Syndrome to trial whether taking aspirin would reduce the risk of developing cancer. They found that people who take doses of 600mg aspirin a day for two years halved their cancer rate at five years.

Even twenty years on, the difference between those who had aspirin and those who had a placebo is still being observed. NICE have now recommended this as an intervention for people with Lynch Syndrome.



3 in 4 people

with Lynch Syndrome will develop cancer between 18 and 75

The challenges ahead

Implications for the healthcare system in the South West region.

Here are some of the key points delegates raised at the Future of Care event:

Strategic planning

AI and genomics are moving very fast. As we create the changes required, we need to get the processes and policy framework right, and involve patients. Data governance and ethical consent are key issues.

There is clearly lots of potential with genomics, but little knowledge of how to prepare both nationally and locally. What new delivery models are needed? How will this be funded and commissioned? How should we evidence the return on investment (ROI) for illnesses that are prevented rather than treated?

Changes need to be made without swamping existing services, but we also need to recognise the opportunity to move more healthcare away from acute to primary care and pharmacy. Within Trusts, we need to plan for more unified systems that cut across specialities. We need to support equity of access and care that is not class dependent or based on clinicians' free time to bring it into practice.

Training

The implications for training are huge and there will need to be both localised and tailored training for acute and primary care. We need to start with the culture of the workplace and find the people who can take this complex information and present it in ways that can be applied to care.

Face-to-face training was thought to be better than e-learning, as genomics is a complex topic. Medical schools should also be involved in updating their curriculum to take account of genomics. A wider public education programme was also needed, involving public health, schools and non-clinicians to manage demand and expectations. There is little patient information available for healthcare professionals to use.

Data infrastructure

The importance of data and the right digital infrastructure to share it most effectively was a key concern. Being clear about what clinicians and others need from the IT was important in design, as well as sharing data as widely as possible, ideally nationally. The continued integration of IT systems is critical.

At a personal level, patients will want to be assured that their personal data is being held securely and that it is being used appropriately for research and diagnosis.

Risks and issues

Delegates recognised the unintentional consequences of increased testing – including private testing that people fund themselves, for instance over-the-counter tests available on the high street – and the limitations of genomic medicine for screening.

Updating the process around consent was welcomed. Patient involvement in navigating how we use genomics in future is extremely important. We need more, informed discussions with patients as we start to signal health risks to people at an earlier stage and plan for their screening and treatment.

It was felt the ethical debate is struggling to keep up and as genomics is also a political objective, there could be issues of patient trust, commercial conflicts of interest, and a risk of creating a two-tier healthcare system between those who have easy and early access to sequencing and those who don't. This could also create potential legal challenges where sequencing may have led to better healthcare outcomes.

A sketch note from the Future of Care event held in Bristol in December 2019.
Credit: Jenny Leonard

"It's everybody's responsibility. The health system, professional groups, policy makers and government to support the health system to do this. The emphasis here is collaboration."

Dr Laura Blackburn
Head of Science
PHG Foundation

Genomics in the South West

How genomics services are organised in the region.

In England, the NHS Genomic Medicine Service is working to mainstream genetic medicine into standard care, and provide consistent and equitable genomic-driven care for the whole population.

This will include:

- Setting common national standards and protocols
- Creating a single national testing directory
- Local partnerships to support delivery.

Genomic tests currently available on the NHS can test for

3,000

rare disease indications

The South West Genomics Hub serves five million people

Genetic laboratory services are organised into seven hubs nationally, with the hub for the South West region of England located in North Bristol. It covers a population of more than five million people and works across 30 hospitals in nine acute hospital trusts. There are two genetics laboratories, based in Royal Devon & Exeter NHS Foundation Trust and North Bristol NHS Trust.

Every hub provides testing for rare diseases and cancer to its local population and they also provide a national service for different specialties. In the South West region, these are tests for cardiac, renal, endocrine and neurological disorders.

The National Genomics Test Directory lists the genomic tests currently available within the NHS and which patients will be eligible for each test. It has 22 test technologies available, which include 3,000 indications for rare diseases and 180 indications for cancer.

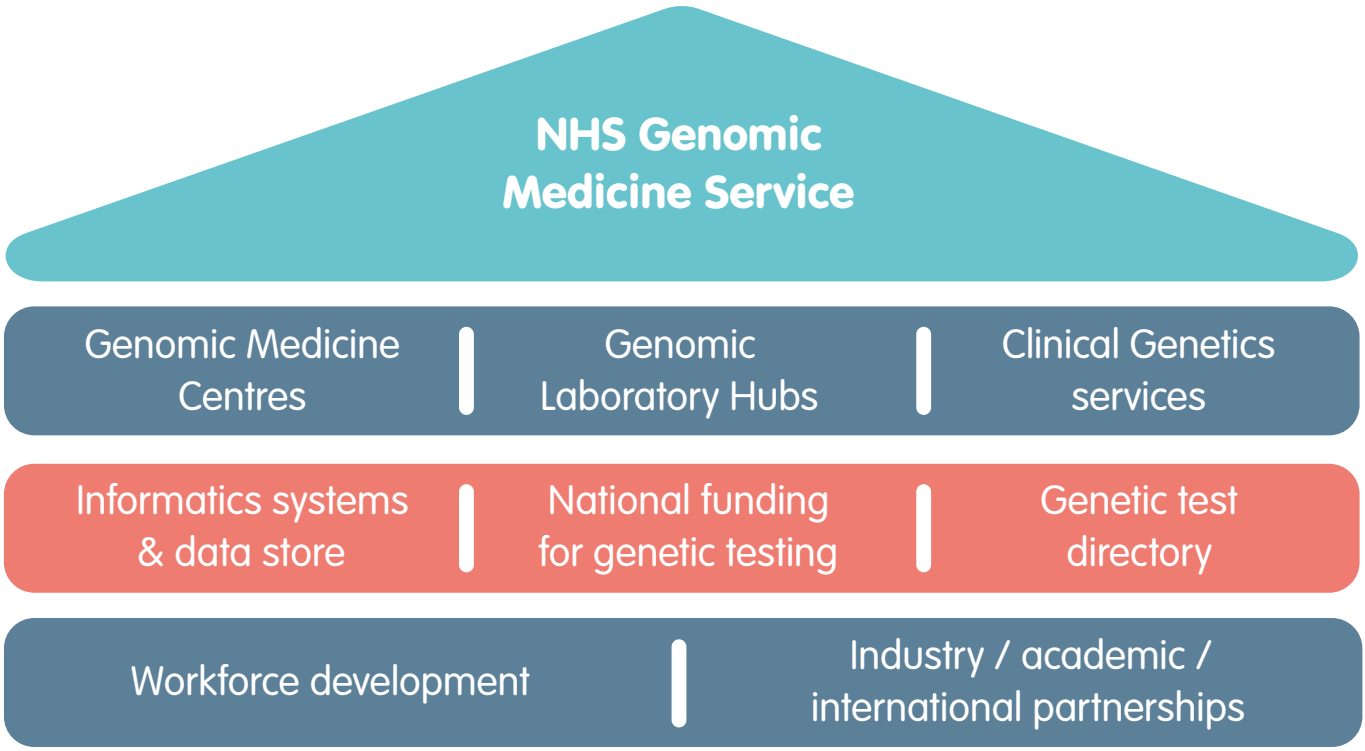
Rapid exome sequencing in Exeter

Usually, the presentation of a specific disease leads to a request for a specific test, but sometimes there is a need to test more broadly for a possible genetic disorder, for instance in acutely unwell babies and children. One option is whole exome sequencing.

Exons are the parts of the genes responsible for making protein, and most genetic disorders are caused by faults within these exons. Collectively, all 180,000 exons in the genome are called the exome. They contain around 30 million pieces of genetic information, for which only one or two may be at fault.

This presents a substantial challenge to laboratory expertise, particularly carrying out these tests at speed. The Exeter laboratory is the national centre for rapid exome sequencing. They are able to turn around tests in just nine days and since the service launched in October 2019, have been able to confirm a genetic diagnosis in an incredible 40 per cent of cases.

One example in the north of England led to a successful diagnosis for a premature baby, born at 26 weeks with a severe illness and who had spent 14 months on a neonatal intensive care unit. Suspecting a Rasopathy disorder, rapid whole exome sequencing identified an ultra-rare disorder called Costello syndrome. This diagnosis highlighted potential future medical problems that needed to be managed, including monitoring for the risk of cancer and heart problems.



Adapted from an NHS England diagram showing the scope of the NHS Genomic Medicine Service.

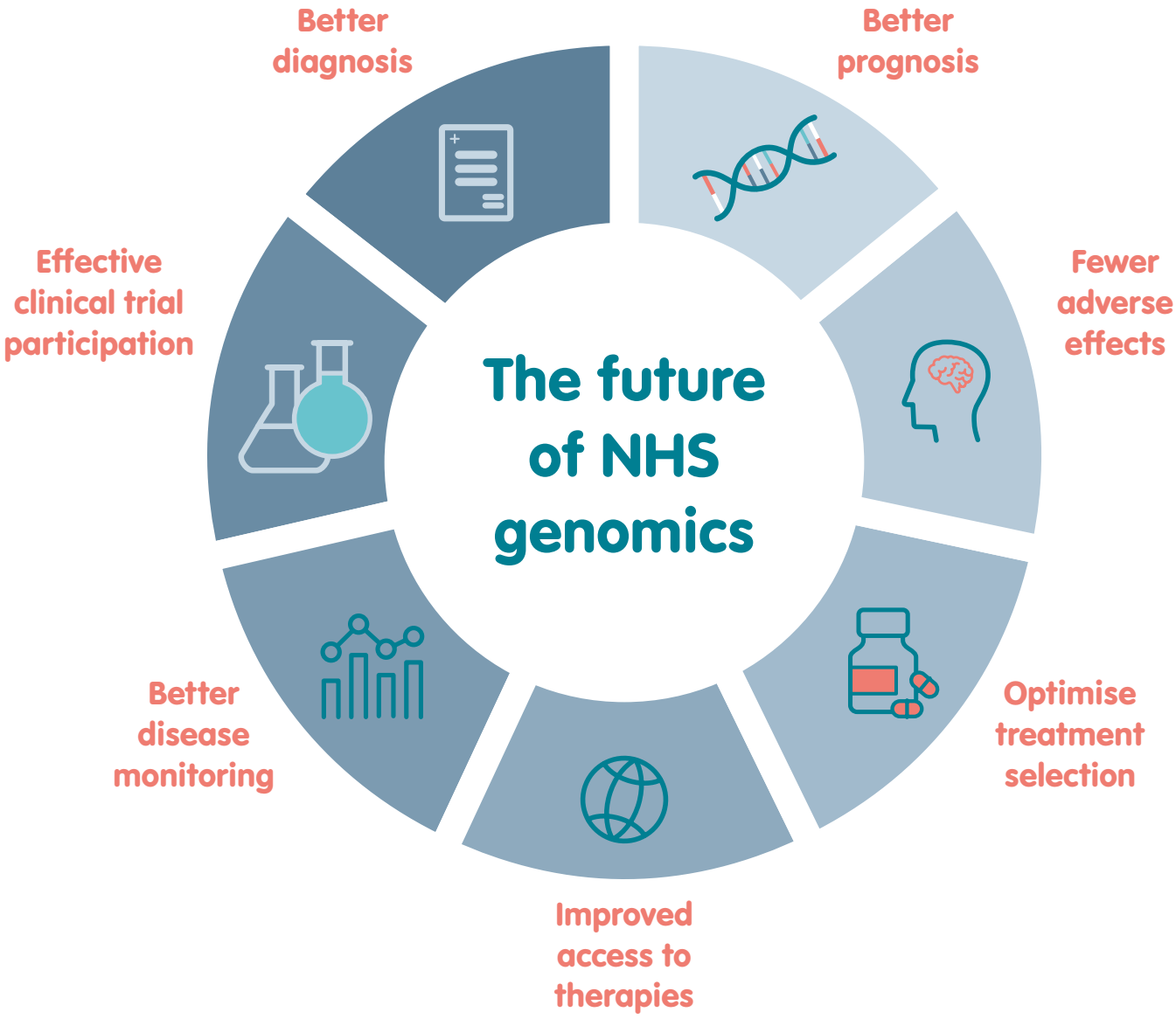


Diagram adapted from original by NHS England

A new standard for consent

The NHS Genomic Medicine Service will set consistent national protocols for all hubs to follow. This will include a new genomics informatics system for clinicians to see which tests are offered by each hub, requesting tests and viewing results.

Patient experts have helped devise a new way of getting permission from patients and their families to undergo genetic testing.

Rather than a simple consent process, patients will have a series of discussions, often over a number of sittings, to ensure they fully understand the implications of the diagnostic procedure. They will also be asked whether their data may be added to a new genomics research library, to inform future research and innovation.

Conclusion

As our understanding of genomics has grown exponentially, so has our understanding of the potential. Such is the pace of change, that we are bound to struggle to keep up with these exciting new possibilities. However, we need to stay mindful that we manage this growth in a sustainable, ethical and safe manner.

Artificial intelligence will help speed up progress and amplify the potential of genomics as more data becomes available. The future will see more point of care testing and genomics becoming more embedded as part of everyday clinical practice.

There will be many challenges to overcome to make sure staff have the necessary capability and capacity, that systems work together in ways that make best use of the technology and are affordable, and that we listen to patients' expectations and concerns. But there is no doubt that the impact of genomics is going to shape a very different healthcare service in future.

Delivering on the promise

- Innovation and merging of different technologies are widening the options available for more personalised prevention, diagnosis, monitoring and treatment.
- A coordinated approach to implementation will be key to successful transformation.
- There is a great opportunity to build on existing expertise and infrastructure, being established as part of the National Genomic Medicine Service.

"Genomics is genuinely all of life and all of healthcare. As it becomes technically more accessible, it will start to colour every aspect of our healthcare."

Professor Sir John Burn
Professor of Clinical Genetics
Newcastle University

Acknowledgements

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Professor Sir John Burn
Professor of Clinical Genetics
Newcastle University and Chair at
Newcastle Hospitals

Dr Laura Blackburn
Head of Science
PHG Foundation

Dr Ignacio H. Medrano
Neurologist and founder of
Savana Health and Mendelian

Professor Andrew Mumford
Professor of Haematology and
Medical Director
South West Genomic Laboratory Hub

Professor Sarah Smithson
Clinical Director
West of England Genomic
Medicine Centre

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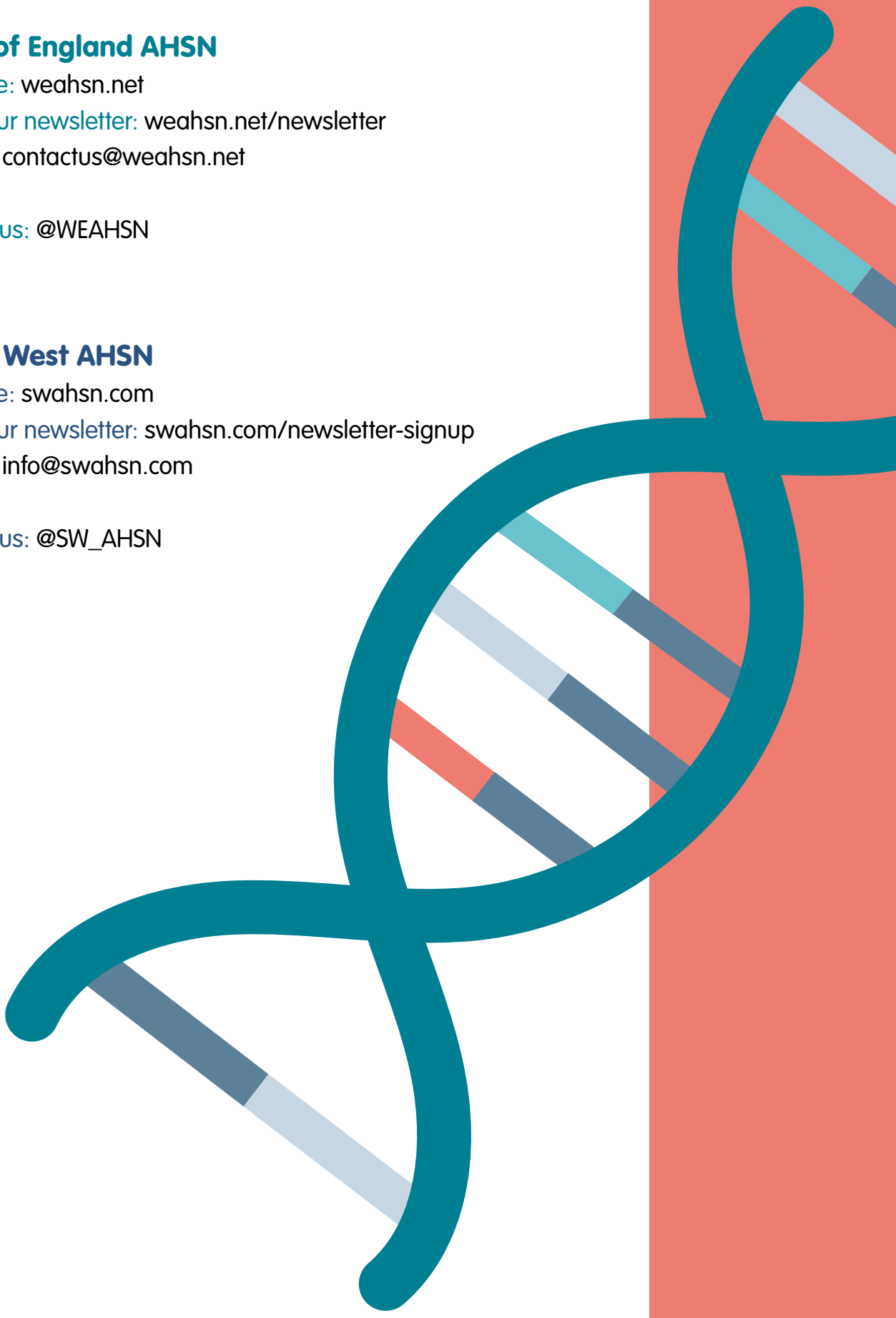

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