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The 100,000 Genomes project

Tim Hubbard

September 2018

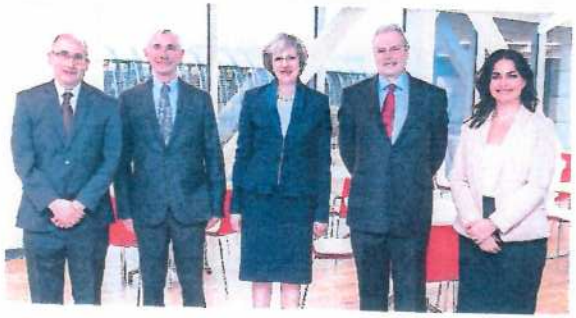
Outline

- Background
- Infrastructure for delivery
- Clinical interpretation and reports
- GeCIP and education and training

History

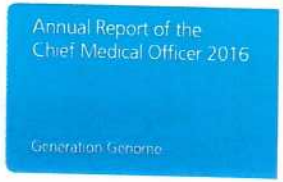
Announced by the former Prime Minister in December 2012
An Olympic Legacy

Announced by the former Prime Minister in December 2012
Genomics England announced by Secretary of State for Health in speech during NHS 65th Anniversary Celebrations, July 2013

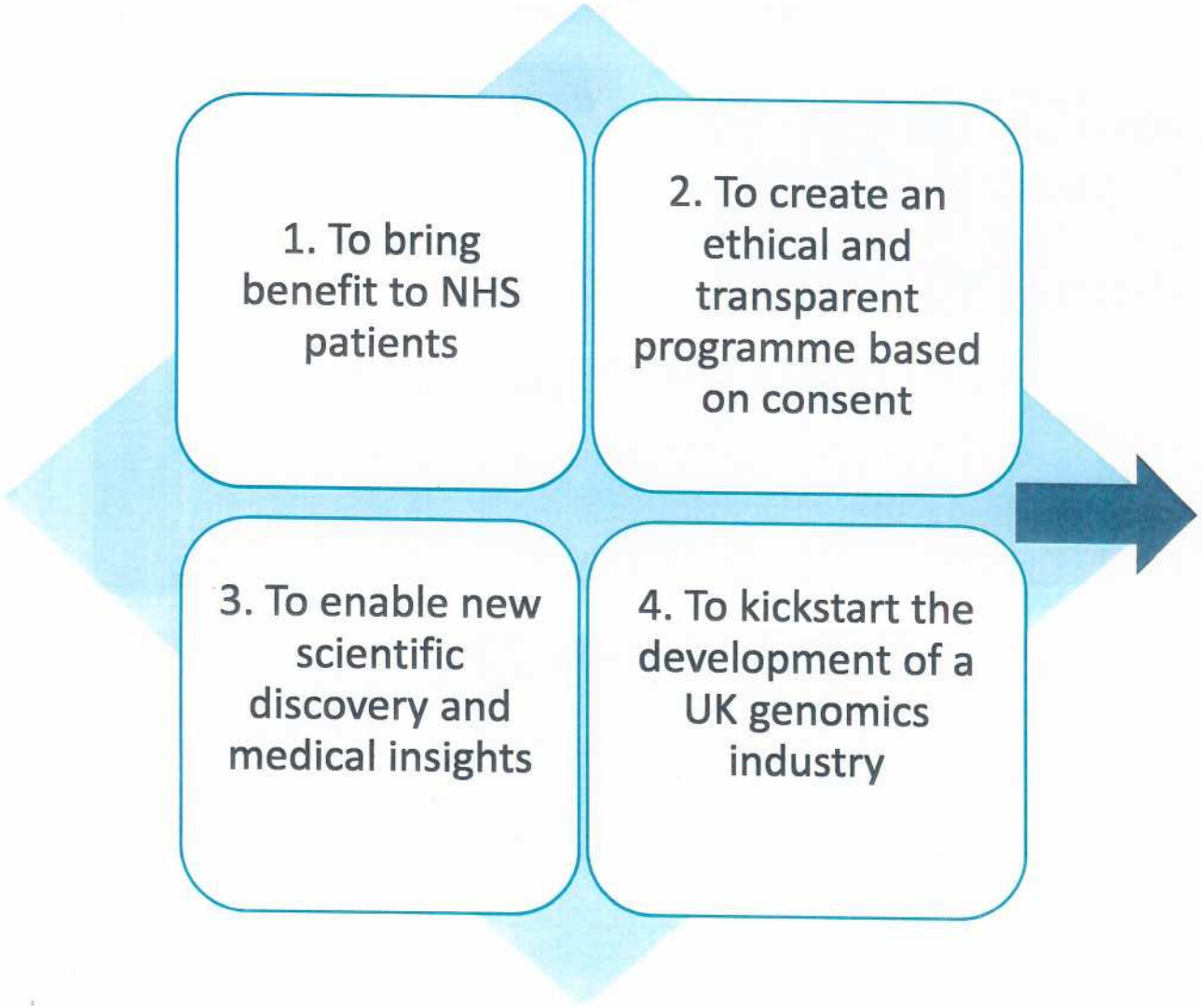


Opening of new Sequencing Centre in 2016

CMO's Generation Genome and the Life Sciences report in 2017



Four main aims



- Rare diseases
- Certain cancers
- Infections

A co-ordinated response across health and care

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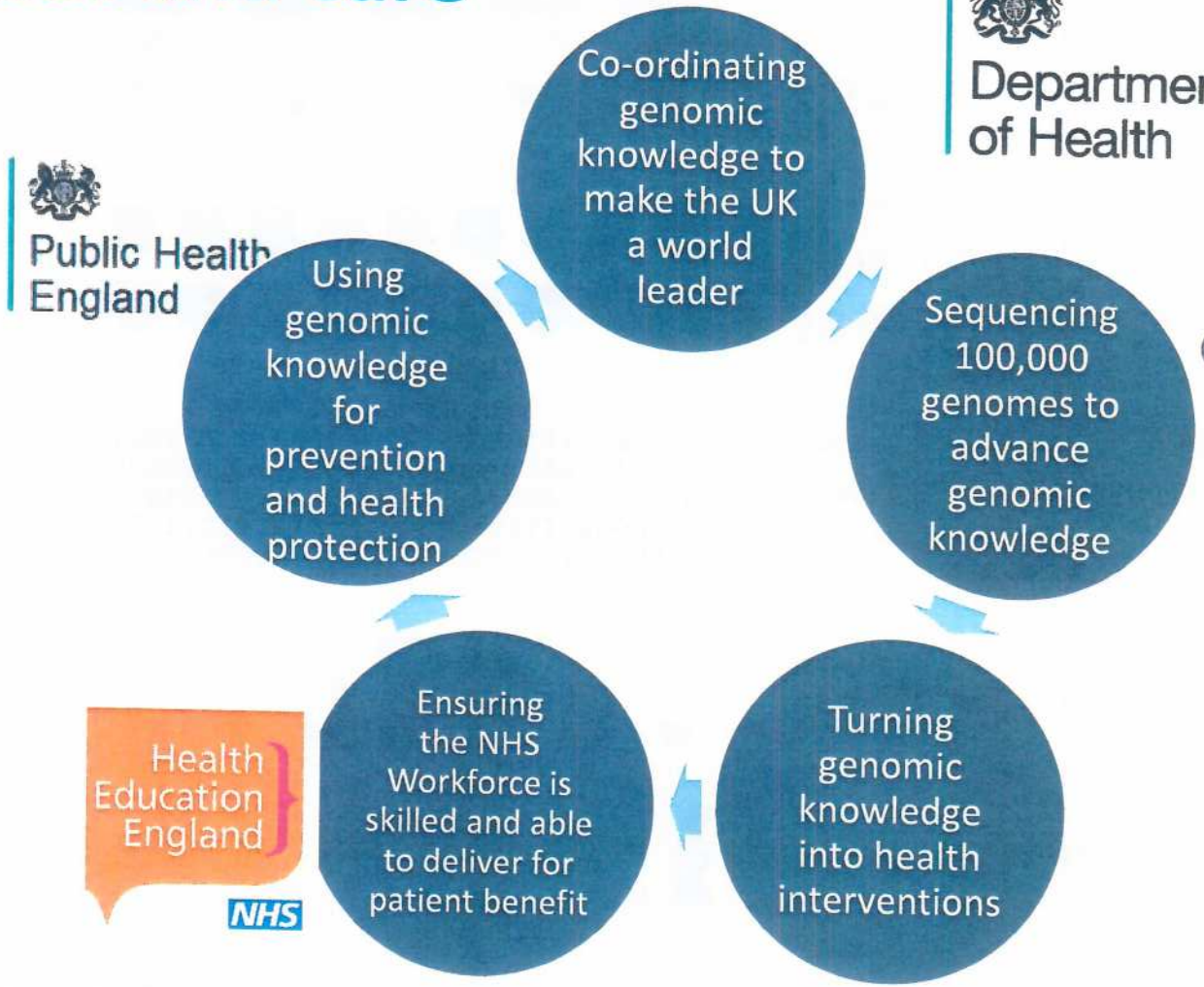
Department of Health

Public Health England



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Health Education England

NHS

NHS England

In numbers

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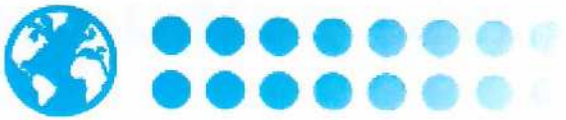
100,000 genomes

70,000 patients and family members

21 Petabytes of data.
1 Petabyte of music would take 2,000 years to play on an MP3 player.

13 Genomic Medicine Centres, and **85** NHS Trusts within them are involved in recruiting participants

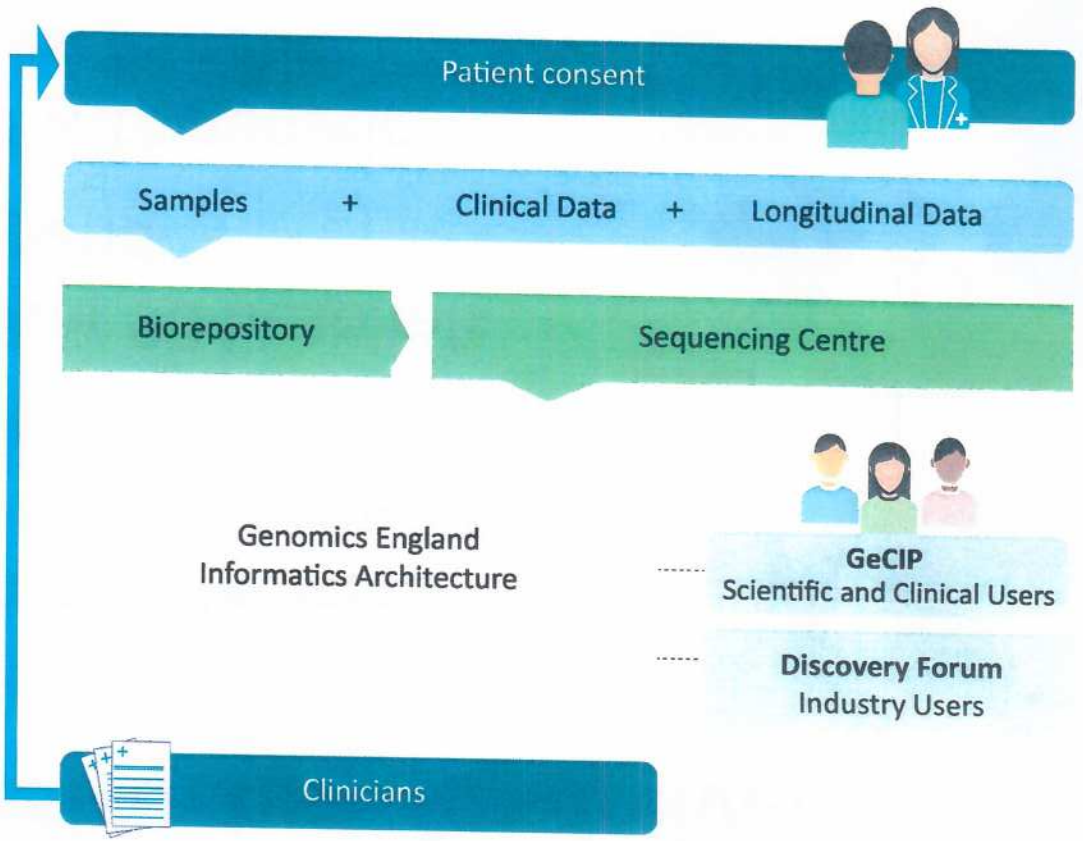
1,500 NHS staff
(doctors, nurses, pathologists, laboratory staff, genetic counsellors)



2,500 researchers and trainees from around the world

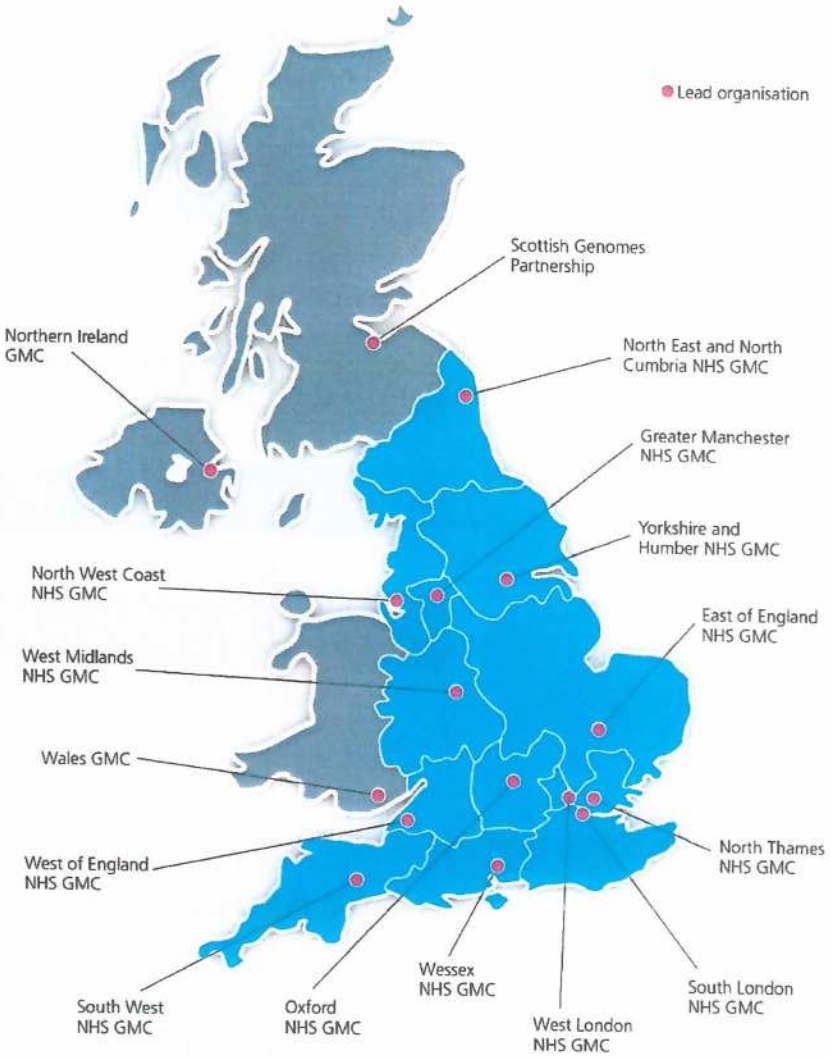
How the 100,000 Genomes Project works

- 13 NHS Genomic Medicine Centres covering England, over 90 hospitals
- Responsible for identifying and recruiting participants and for clinical care following results



The infrastructure for delivery

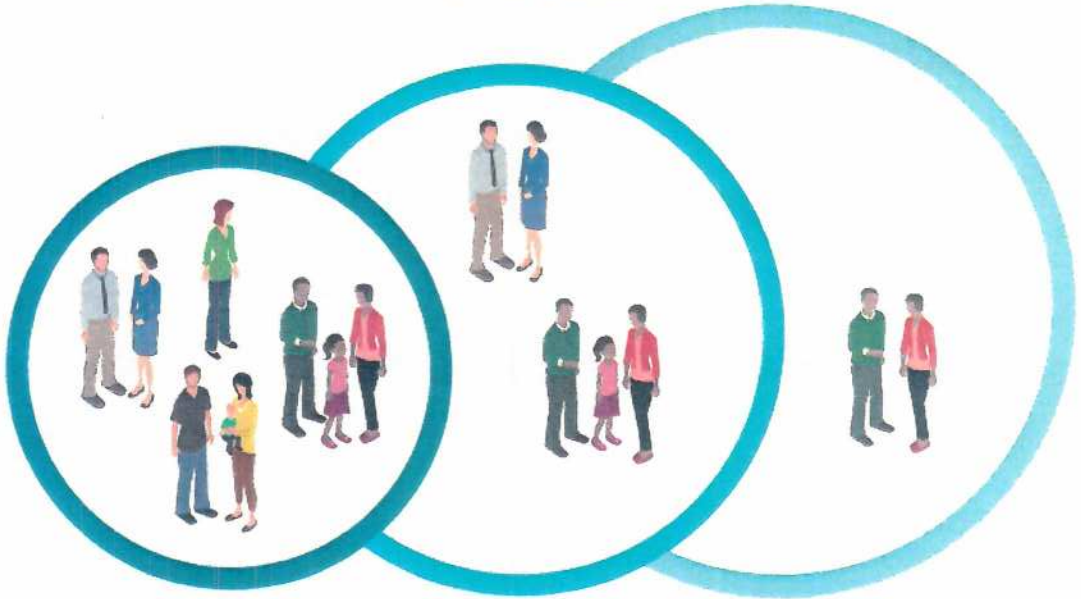
- Nationwide network of **13 NHS Genomic Medicine Centres** – each serving ~3-5 million population
- Includes over 90 hospitals across England
- Integrated with genetic laboratories, genetic services and local pathology laboratories
- Scotland, NI and Wales also now part of the Project



What are we telling participants?

- Information about a patient's main condition
- Information about additional 'serious and actionable' conditions (optional)
- Carrier status for non affected parents of children with rare disease (optional)

Types of potential feedback to participants



Main findings
All participants agree to receive results about the main condition for which they were referred

Additional findings
Participants can opt in to receive feedback on a selection of known genetic alterations of high clinical significance

Carrier status
Eligible adults can opt in to find out their carrier status for certain genetic diseases

Image courtesy of Health Education England

Additional findings offered in the 100,000 Genomes Project

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Bowel cancer predisposition:
MLH1 (adult only)
MSH2 (adult only)
MSH6 (adult only)
APC (adult and child)
MUTYH (adult only)

Breast and ovarian cancer predisposition:
BRCA1 (adult only)
BRCA2 (adult only)

Other cancer predisposition:
VHL (adult and child)
MEN1 (adult and child)
RET (adult and child)

Familial hypercholesterolaemia:
LDLR (adult and child)
APOB (adult and child)
PCSK9 (adult and child)

Autosomal recessive carrier status:
CFTR (Cystic fibrosis)

OPTIONAL!

Requirements:

- Reliably detected by genome sequencing
- Curated list of high confidence, high penetrance variants
- Treatable or preventable condition

Other conditions may be added if clinically appropriate and technically feasible

Scalable rare disease diagnostics

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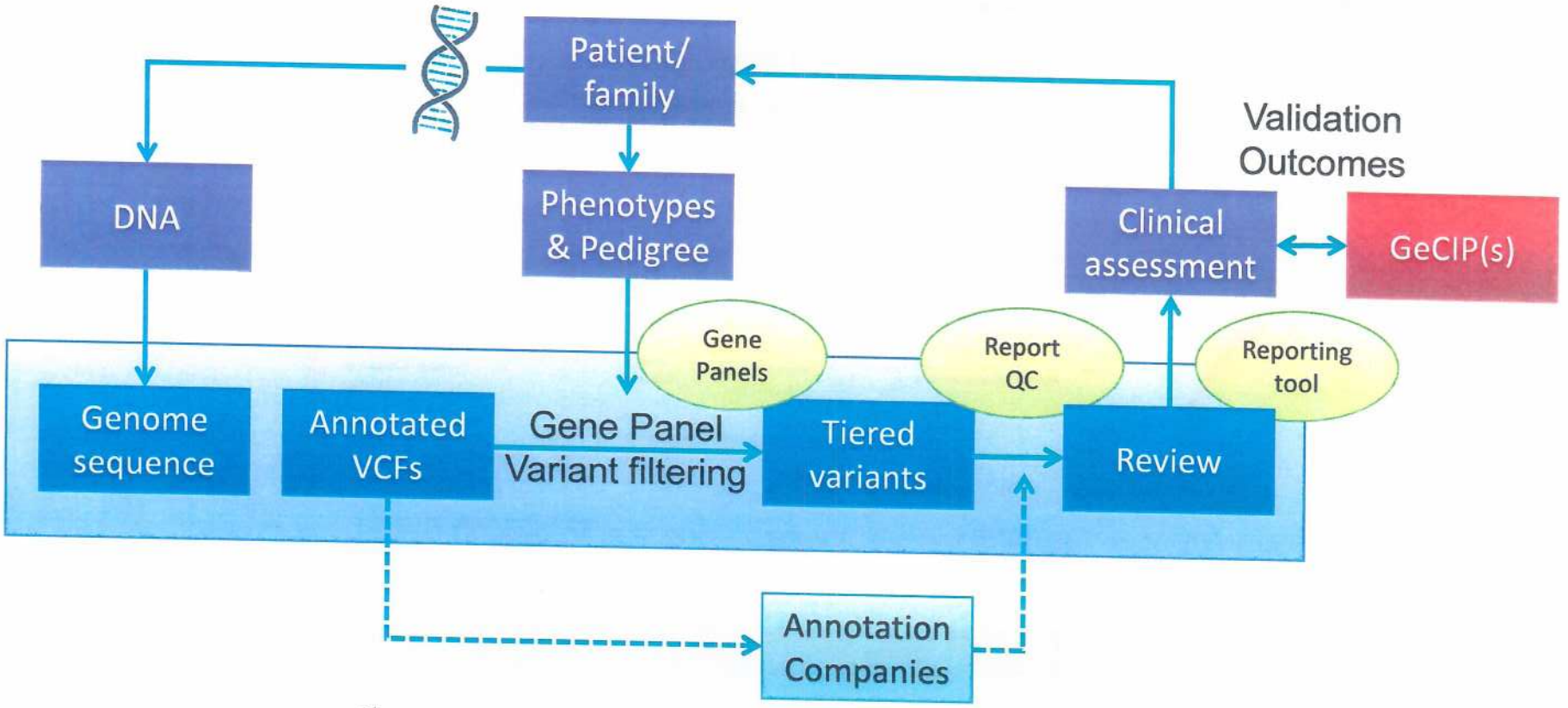

FABRIC GENOMICS™ CONGENICA WuXiNextCODE

Reporting back to the NHS

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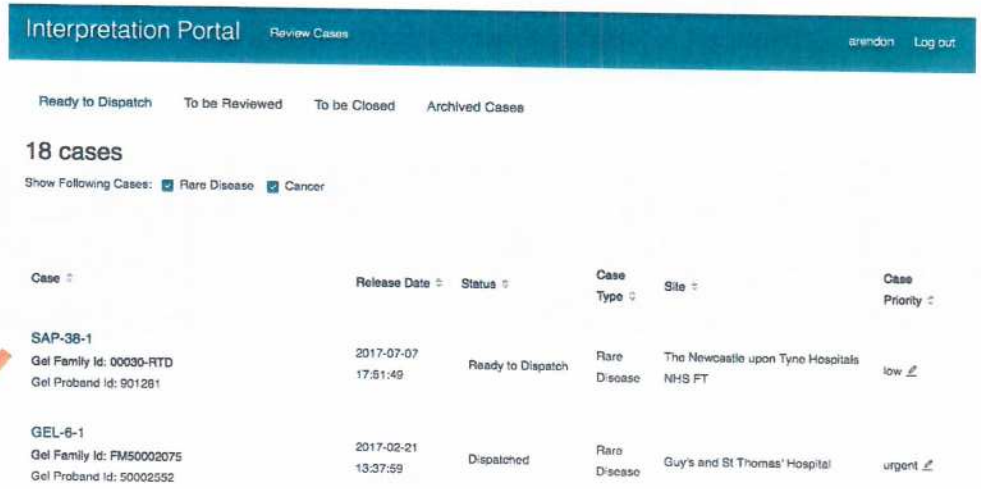
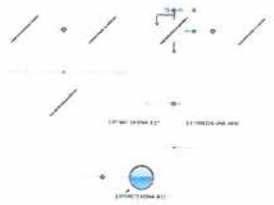


1. View family pedigree

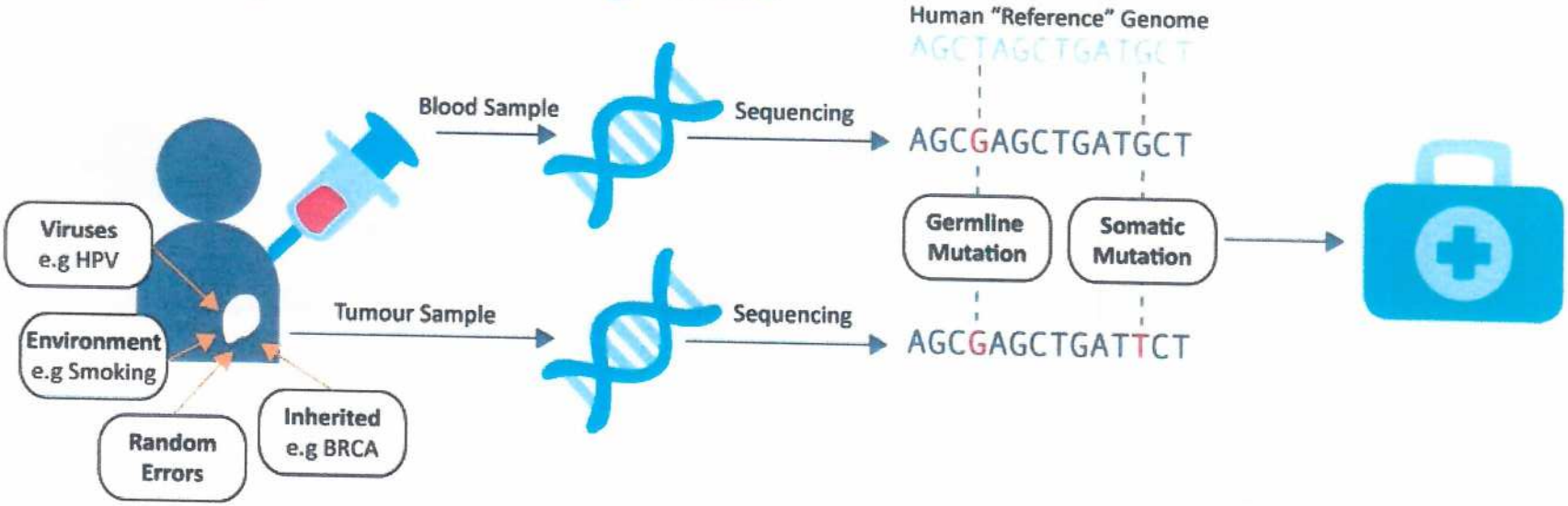


2. Review variants and close case

3. Download the report

Cancer

Genomics England Cancer Programme



Common cancers included initially:

- Lung, Breast, Ovarian, Prostate, Colorectal

Now included:

Renal, sarcoma, childhood cancer, Adult Brain Tumours, Endometrial, Melanoma, Upper gastrointestinal (GI) tumours, Testicular, Head and Neck, Cancer of Unknown Primary, Haematological Malignancies

Molecular pathology

Complex NHS transformation underway

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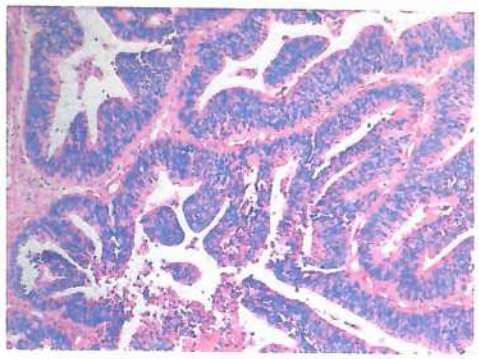
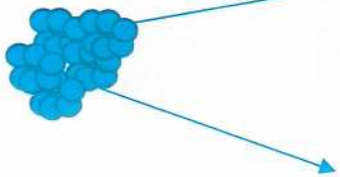
Tumour samples are traditionally preserved in formalin then fixed in paraffin (FFPE) to preserve cellular architecture for diagnosis under the microscope



DNA extracted from samples treated like this is damaged and broken



Use part of the sample for FFPE and histology

Freeze part of the sample for genetic tests

- Need to make sure the sample contains mainly tumour cells

This new pathway requires very significant changes in sample handling, affecting surgeons, interventional radiologists, pathologists and oncologists

Cancer whole genome analysis report

Preliminary analysis report:

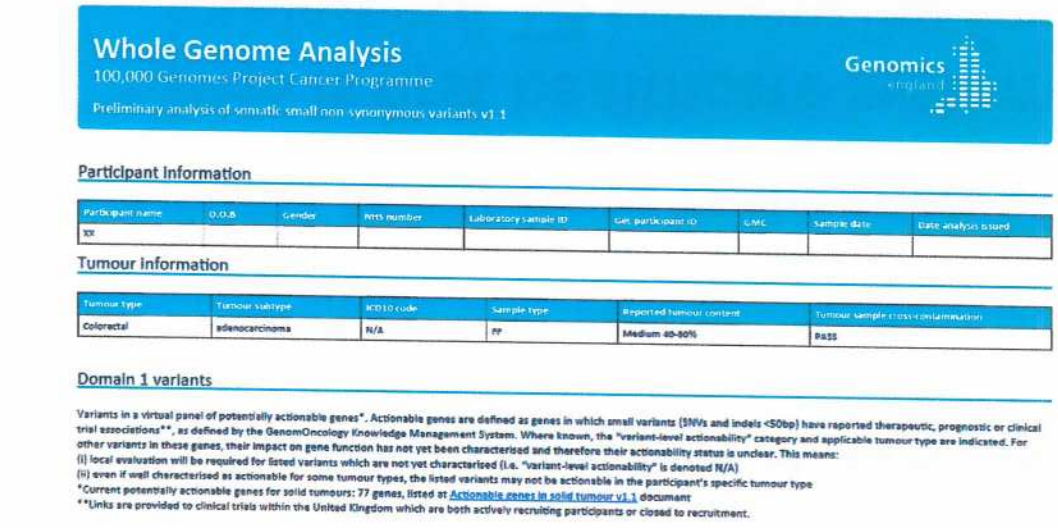
- Domain 1 variants - directly relevant to cancer treatment
- Domain 2 variants – other cancer related genes

Supplementary analysis report

- Domain 3 variants & other relevant information

Links to **Clinical Trials**

- Remainder of results are mostly of research interest for now, but in future may assist:
  - Drug development
  - Targeted treatment selection
  - Prediction of prognosis
  - Monitoring of disease progression



Whole Genome Analysis
100,000 Genomes Project Cancer Programme
Preliminary analysis of somatic small non synonymous variants v1.1

Participant Information

Participant name	D.O.B	Gender	NHS number	Laboratory sample ID	GeL participant ID	GMC	Sample date	Date analysis issued
XX								

Tumour Information

Tumour type	Tumour subtype	ICD10 code	Sample type	Reported tumour content	Tumour sample cross-contamination
Colorectal	adenocarcinoma	N/A	FF	Medium 40-80%	PASS

Domain 1 variants

Variants in a virtual panel of potentially actionable genes*. Actionable genes are defined as genes in which small variants (SNVs and indels <50bp) have reported therapeutic, prognostic or clinical trial associations**, as defined by the GenomOncology Knowledge Management System. Where known, the "variant-level actionability" category and applicable tumour type are indicated. For other variants in these genes, their impact on gene function has not yet been characterised and therefore their actionability status is unclear. This means:
(i) local evaluation will be required for listed variants which are not yet characterised (i.e. "variant-level actionability" is denoted N/A)
(ii) even if well characterised as actionable for some tumour types, the listed variants may not be actionable in the participant's specific tumour type
*Current potentially actionable genes for solid tumours: 77 genes, listed at Actionable genes in solid tumour v1.1 document
**Links are provided to clinical trials within the United Kingdom which are both actively recruiting participants or closed to recruitment.

Infections and Pathogens

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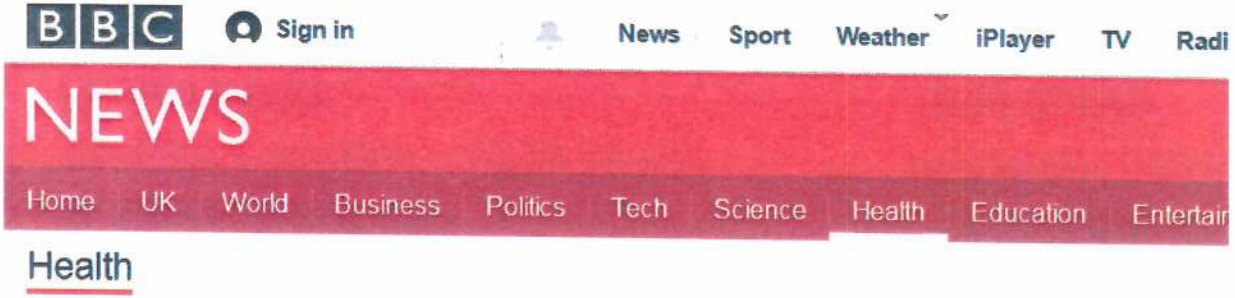
- 3000 Multi-drug resistance TB strains
- NHS is first healthcare system in the world to implement TB sequencing for diagnosis
- Global registry of TB resistance



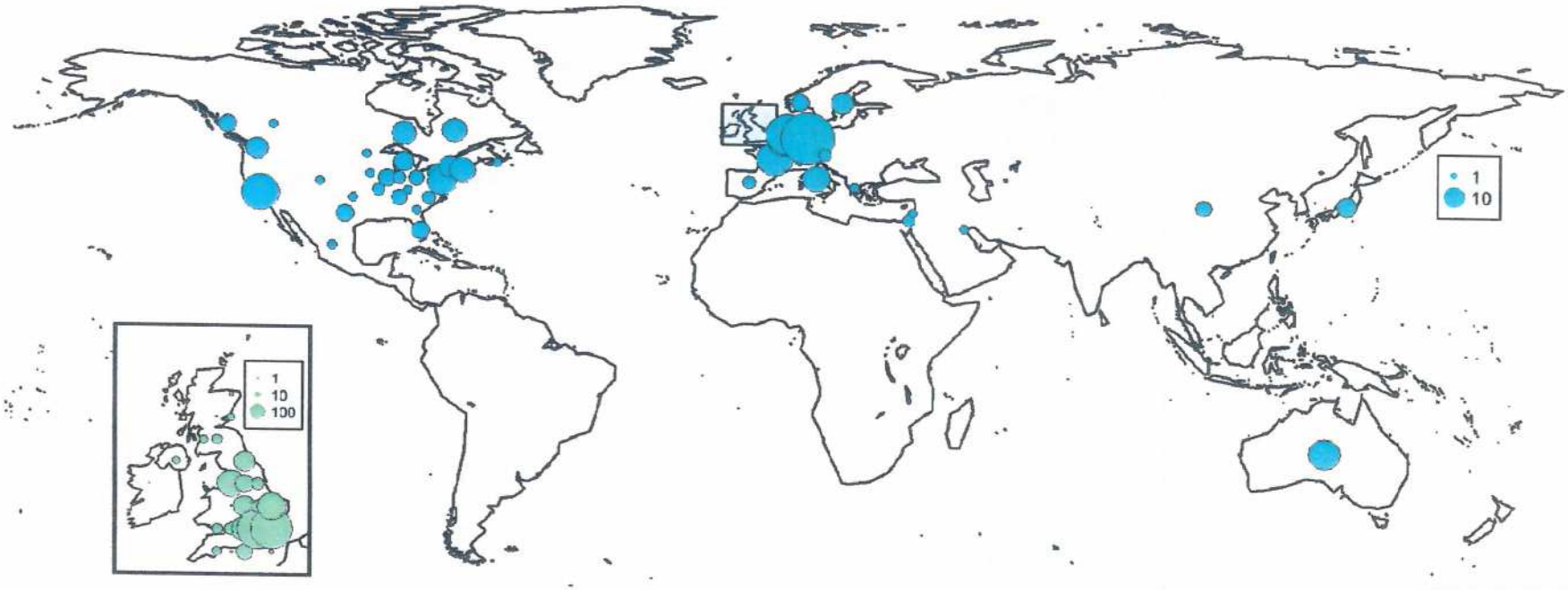
Public Health England

Genomics England Clinical Interpretation Partnership (GeCIP)

- A research consortium
- Partnership between over 2,500 researchers from academia and the NHS, trainees, plus international collaborators
- Designed to accelerate academic/industry partnership and development of diagnostics and therapies
- Over 35 topics (domains) of research and most domains cover a single disease or group of diseases and some are wider e.g. epigenomics, health economics and technology
- All data generated contributes to the Genomics England Dataset

GeCIP Members

From 300 institutions and 24 countries



Institution	Count
UK Academic	1744
NHS Trust	634
International Academic	198
Other	333

Genomics England Research Environment at a glance

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Data and documentation

Genomes (BAM and VCF) in Isilon share

Clinical data in LabKey

Confluence

- data release notes
- user guides
- airlock
- live issues

Tools and analysis

Virtual desktop interface provides GUI and security

LibreOffice for document editing

R and Rstudio for data analysis

Internet browser: access to whitelisted sites

Command-line tools and HPC cluster for large-scale analysis

Collaboration

Domain-specific and shared storage for files

Social media platform for communication

Research registry:

- promote collaboration
- enforce publication moratorium

Data in our Research Environment

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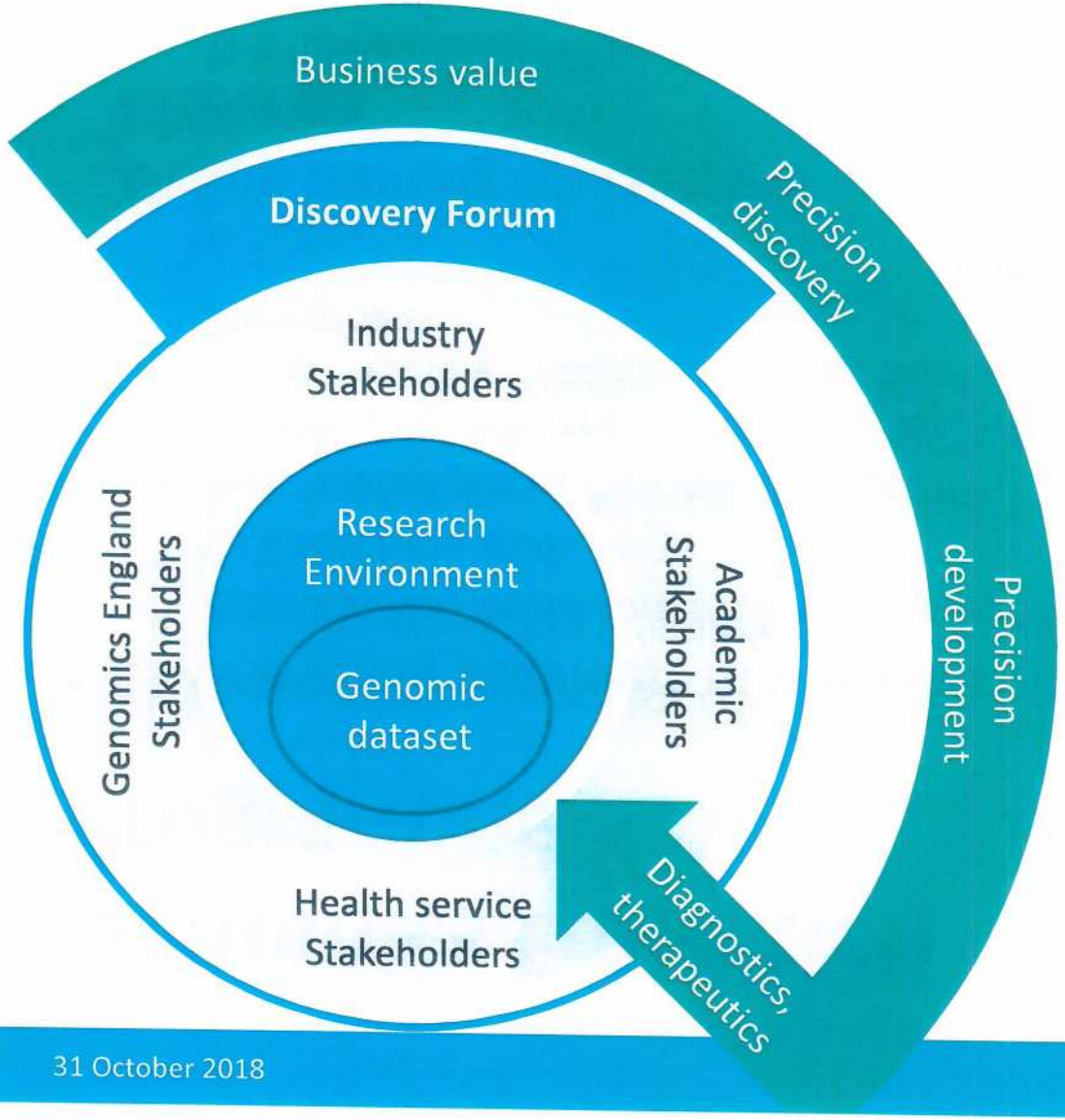
Genomes	**55,681 genomes**	**Primary clinical data**	**71,331 participants**
Secondary data	• Hospital Episode Statistics (HES) • Diagnostic Imaging Dataset (DID) • Patient Reported Outcome Measures (PROMs)		• Mental Health Services Data Set (MHSDS) • Office for National Statistics (ONS) – mortality data and cancer flagging
Clinically interpreted data	• **7,095 families** with Tier 1, 2 and 3 variants from interpretation pipeline • **1,478 families** with GMC exit questionnaires	**Quick view tables**	• Key information from different LabKey tables, merged and filterable • Merged with QC data • Will facilitate cohort-building and project feasibility assessment

The Discovery Forum

A driver of translational research



- **Exploring** the business value of genomic medicine data.
- **Connecting** industry stakeholders to the Genomics England community.
- Providing a **gateway** to our Research Environment and dataset.
- Leading to **discovery** and development of precision methods, diagnostics, and therapeutics.

Genomics Education Programme

- 11 University providers of a Masters in Genomic Medicine
  - Aimed at NHS healthcare professionals working in England
  - Full/part time study
  - Fully funded places available through HEE
  - Individual (CPPD) modules available for range of professional backgrounds and groups (e.g. medicine, nursing, healthcare scientists and technologists).

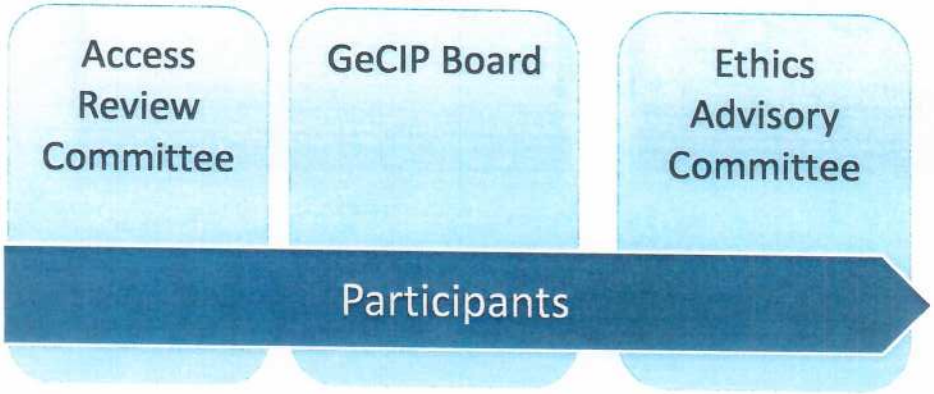
- Online training courses and resources
  - The fundamentals of genomics
  - Bioinformatics
  - The consent process

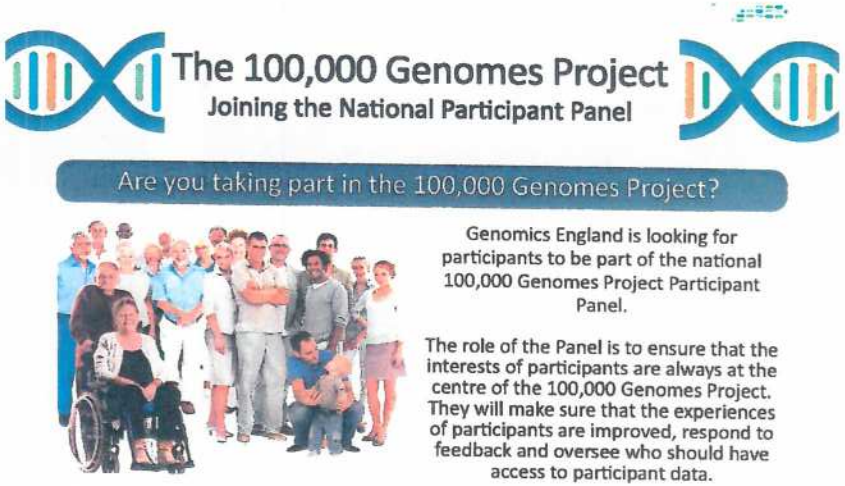
Patient involvement - the National Participant Panel

Role of the Panel is to ensure the interests of participants are always at the centre of the 100,000 Genomes Project.

They do this by:

- Making sure experiences of participants are at the heart of the project
- Responding to feedback.
- Overseeing who should have access to participant data





Progress to date

Figures as at 01/10/2018

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Samples

102,216
Samples collected and received at the UK Biocentre

25,913 cancer

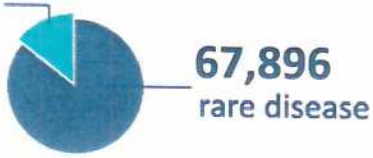
76,303 rare disease

Genomes

87,231
Genomes sequenced

19,335 cancer

67,896 rare disease



+6,052 genomes since last month

Analysis and Results

Results for **32,784** genomes sent to NHS GMCs

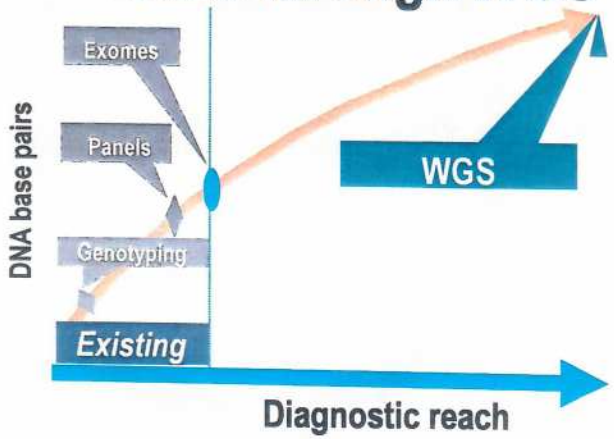
Equivalent to **7,832** cancer genomes and **24,952** rare disease

20-25% actionable findings for Rare Disease

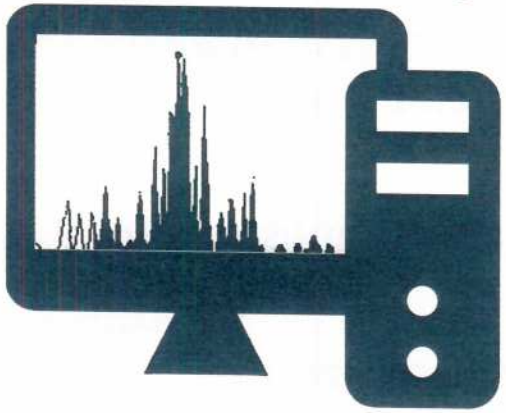
NHS Genomics: Why now?

The time is right because:

- **Huge increase in diagnostic reach through WGS**



- **Improved technologies for biomedical analysis**



- **New tools for managing large datasets**

- **Significant variation in existing services**
  - quality, efficiency & access
  - commissioning & funding model

Building the future NHS genomic medicine service

By the end of 2018 the NHS will have:

- A national Genomic Medicine Service providing consistent & equitable care for 55 million population
- Operating to common national standards, specifications & protocols
- Standardised genomic consent for NHS care and Research
- Delivering an approved national testing directory covering use of single gene to WGS
- Building a single UK Genomic Knowledgebase
- national NHS database with all tests that will enable care, effectiveness, and outcomes
- De-identified data for academic & industry research

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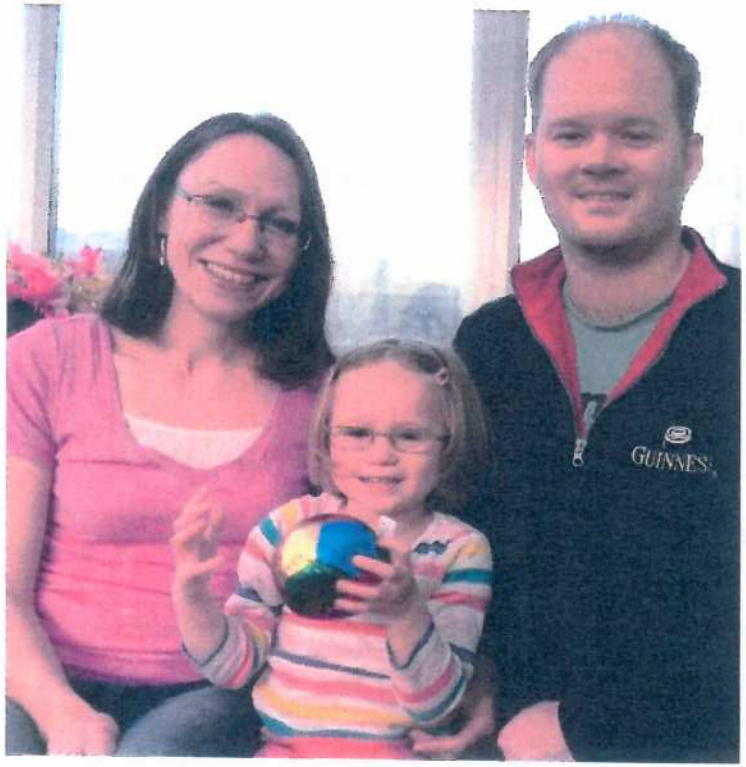
Patient stories

Jessica Wright



- Jessica, aged 4
- Rare condition that causes epilepsy and affects her movement and general development.
- Took took part in the 100,000 Genomes Project rare disease programme with parents at Great Ormond Street Hospital.
- Found that she had a genetic variant in the SLC2A1 gene - makes a protein that transports a certain type of sugar into the brain. Mistakes in the SLC2A1 gene can cause '**Glut1 deficiency syndrome**' –Jessica's diagnosis.

- In some patients who have Glut1 deficiency syndrome a very **low-carbohydrate diet (ketogenic)** can help reduce the number of seizures.
- Thanks to WGS analysis, Jessica's clinician **was able to recommend this diet** for her, which helped with her seizures.

A 10 year-old girl with life threatening chicken pox

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- Ten year old girl admitted to intensive care in Manchester because of life threatening chicken pox
- She had previously had other unusual infections. Detailed immune testing had not determined why.
- Mutations in *CTSP1* gene found via 100KGP
- Likely benefits of diagnosis
  - A (curative) bone marrow transplant is now planned for the girl
  - Her siblings have been tested and shown not to be at risk of these infections
  - The gene wasn't recognised by immunologists as a cause of bad chicken pox. A change in practice is now planned to test many more children for changes in this gene to identify others with the condition

A family with kidney problems

- 57-year-old man with kidney failure; he had other relatives who had had kidney failure too
- His genome was sequenced and the genetic cause of his kidney failure was identified
- His daughter already had signs of kidney failure, and she also shared the genetic variant
- His teenage granddaughter was having yearly checks on her kidneys as she had a 1 in 2 chance of also getting kidney failure
- Genetic tests showed she didn't have the variant found in her mother and grandfather, so she doesn't have to go for check-ups or worry about her kidneys any more

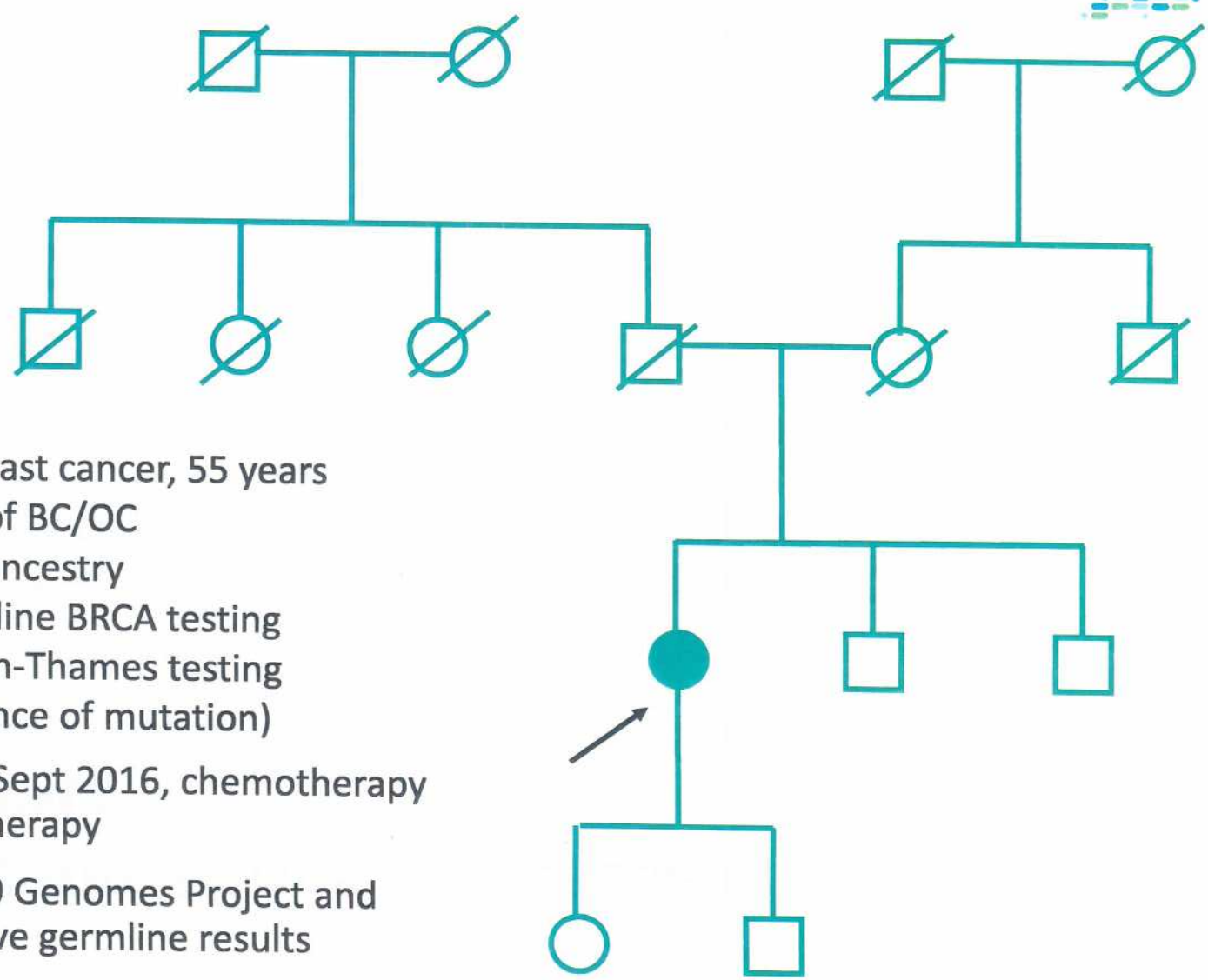
Georgia

KDM5B-related intellectual disability

- Developmental delay
- Multiple medical problems
- Sees >5 hospital specialist services
- Seen in two genetic centres
- No cause known despite extensive testing
- Now 4 years old

- Mutation in *KDM5B* found via 100KGP – newly recognised disease gene
- Mutation not present in either parent (‘*de novo*’)
- Likely benefits of diagnosis
  - Ends 4 year diagnostic odyssey
  - Informs parents on risk of recurrence in another child (very low)
  - This is a newly recognised disease gene. It’s recognition will help diagnose other families
  - A CRISPR-Cas9 mouse model of the mutation is planned as part of the collaboration between Genomics England and MRC Harwell to learn more about the condition

Cancer Case Study



- Triple negative breast cancer, 55 years
- No family history of BC/OC
- No Jewish/Polish ancestry
- Ineligible for germline BRCA testing under previous Pan-Thames testing criteria (<10% chance of mutation)
- Right mastectomy Sept 2016, chemotherapy followed by radiotherapy
- Enrolled in 100,000 Genomes Project and consented to receive germline results

Non-coding mutations as a cause of choroideremia

- A man with choroideremia of unknown cause under the case of Moorfield's Eye Hospital
- A causative non-coding (promoter) mutation upstream of the X chromosome *CHM* gene was found via 100KGP
- A second family with the same mutation has now been found
- Likely benefits of diagnosis
  - Identifies the cause as X-linked and allows cascade testing of at risk relatives
  - No non-coding mutations had previously been found, nor CHM's promoter recognised. Analysis of the promoter region will now become a standard part of diagnostics, allowing diagnosis in other families

Jillian and Sam

- Jillian Hastings Ward gave birth to Sam, almost four years ago.
- Eye condition, not progressing intellectually and has mental development of a six-month-old child.
- After joining the project, we found that Sam had a fault in the **GRIN1 gene**
- Causes intellectual disability, low muscle tone and in some cases seizures.
- By studying the genomes of Sam's parents, doctors were able to show that neither had passed on the GRIN1 gene variant to their son.

"The project has brought tremendous relief and hope"

- Jillian said: "That was tremendously important.. It showed that it is extremely unlikely that his elder sister Kirsty would be affected by the condition. That had been a real worry for us."

Implications of result

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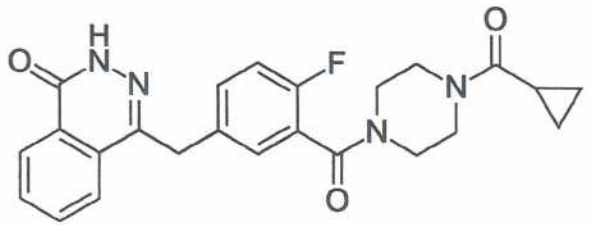
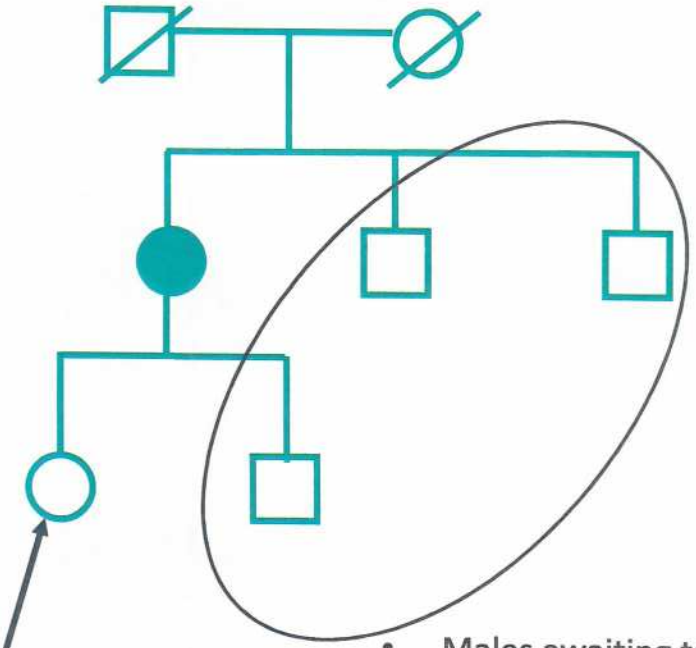
For the patient



- Targeted therapy with Olaparib (PARPi) through clinical trial (OLYMPIA)
- 1-3/10 women develop ovarian cancer
- Offer risk reducing surgery
- 1 in 2 lifetime chance of left sided breast cancer – requires ongoing screening or consideration of risk reducing surgery

For her family



Predictive test
BRCA2 carrier

- Daughter will receive breast screening with MRI yearly from age 30
- consider risk reducing surgery
- consider chemoprevention

- Males awaiting testing
- If carriers, self examination for breast lumps
- Eligible for prostate cancer screening from age 40

Alex's story

- Over the first 18 years of his life, Alex Masterson has had 28 operations, including the removal of tumours and several bouts of heart surgery.
- Originally thought he was suffering from Noonan syndrome.
- But his symptoms did not fit this diagnosis.
- Sequencing revealed he had a related condition known as **LEOPARD syndrome**.
- Diagnoses like Alex's can also bring alleviation from the odysseys of diagnostic visits that families with rare disorders have to go through.

"It has not changed his life expectancy or anything like that. However, it has given us closure and that has been a marvellous relief"