Genomics england

From the 100,000 genomes project to the UK NHS Genome Medicine Service

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FEAM Conference on

Precision Medicine and Personalized Health 2018

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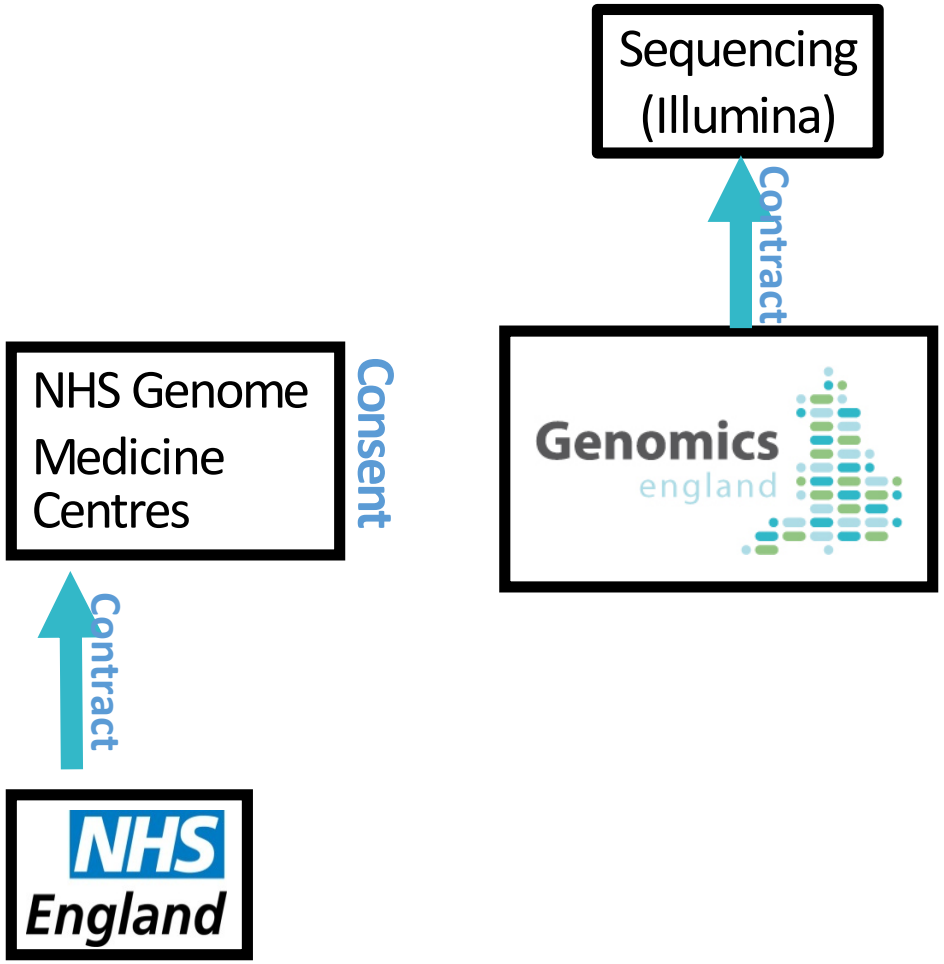
100,000 genomes project

Announced end 2012; Genomics England created 2013

- Primarily a treatment project
  - NHS transformation project
- All whole genome sequencing (clinical grade >30x)
  - Rare disease (3 genomes: affected individual and parent)
  - Cancer (2 genomes: normal tissue/tumour tissue)
- Mission
  - Improve Health of individual NHS patients
  - Create legacy of infrastructure, human capacity and capability in NHS
  - Stimulate wealth generation in the Economy
  - Enable large scale genomics research

Genomics England - Clinical



NHS Firewall

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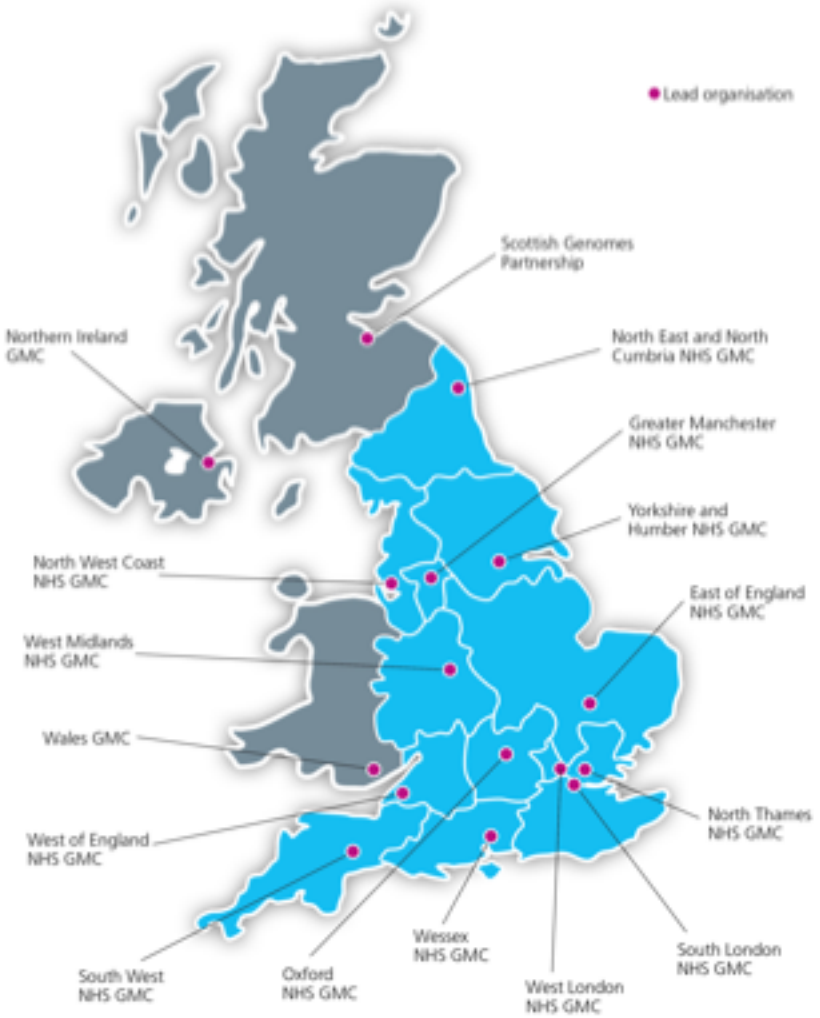
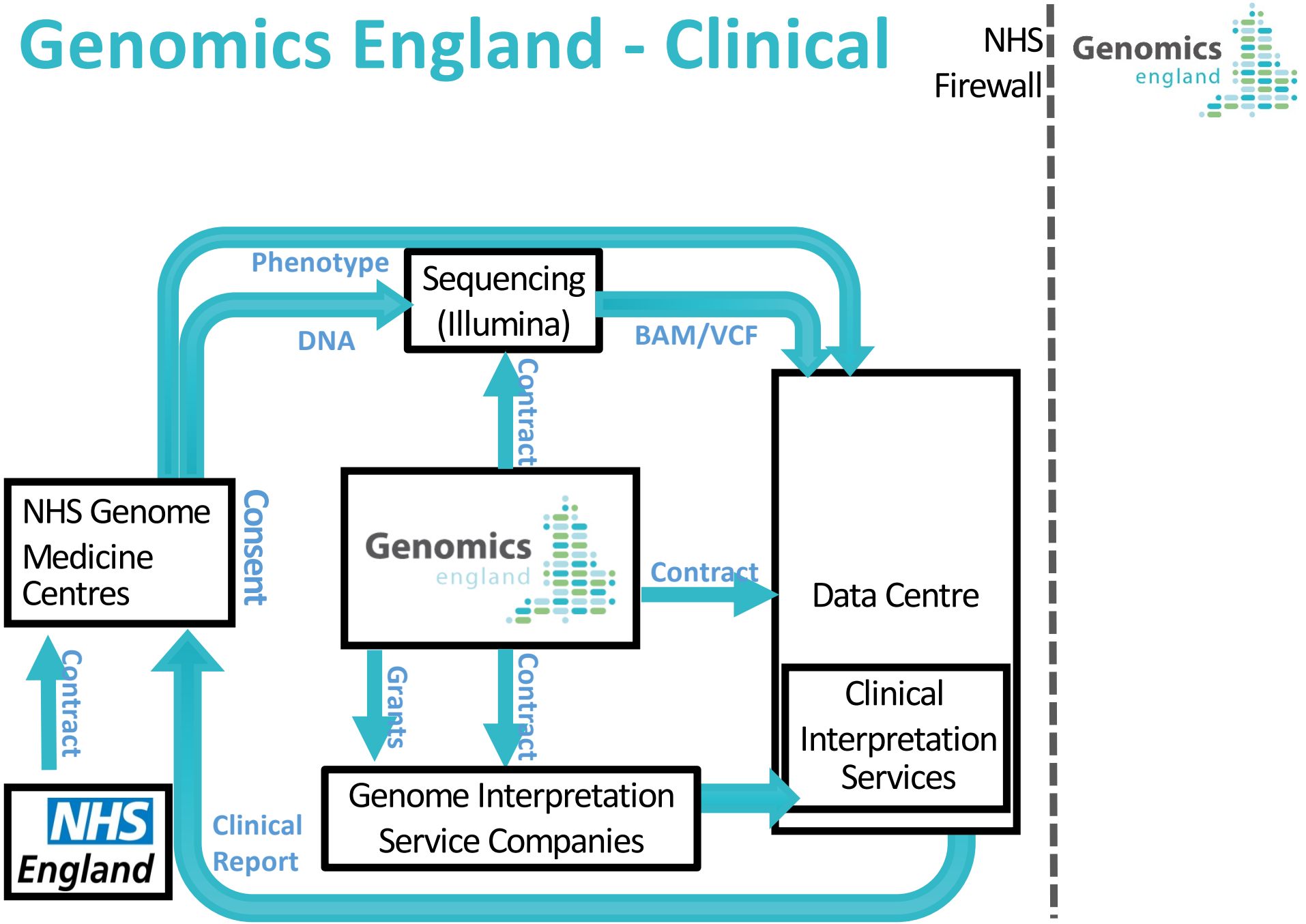
NHS Genomic Medicine Centres

- 13 Genomic Medicine Centres covering England
- Joined by NHS in Scotland, Northern Ireland and Wales
- Responsibilities:
  - identifying and recruiting participants
  - clinical care following results



Genomics England - Clinical



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)

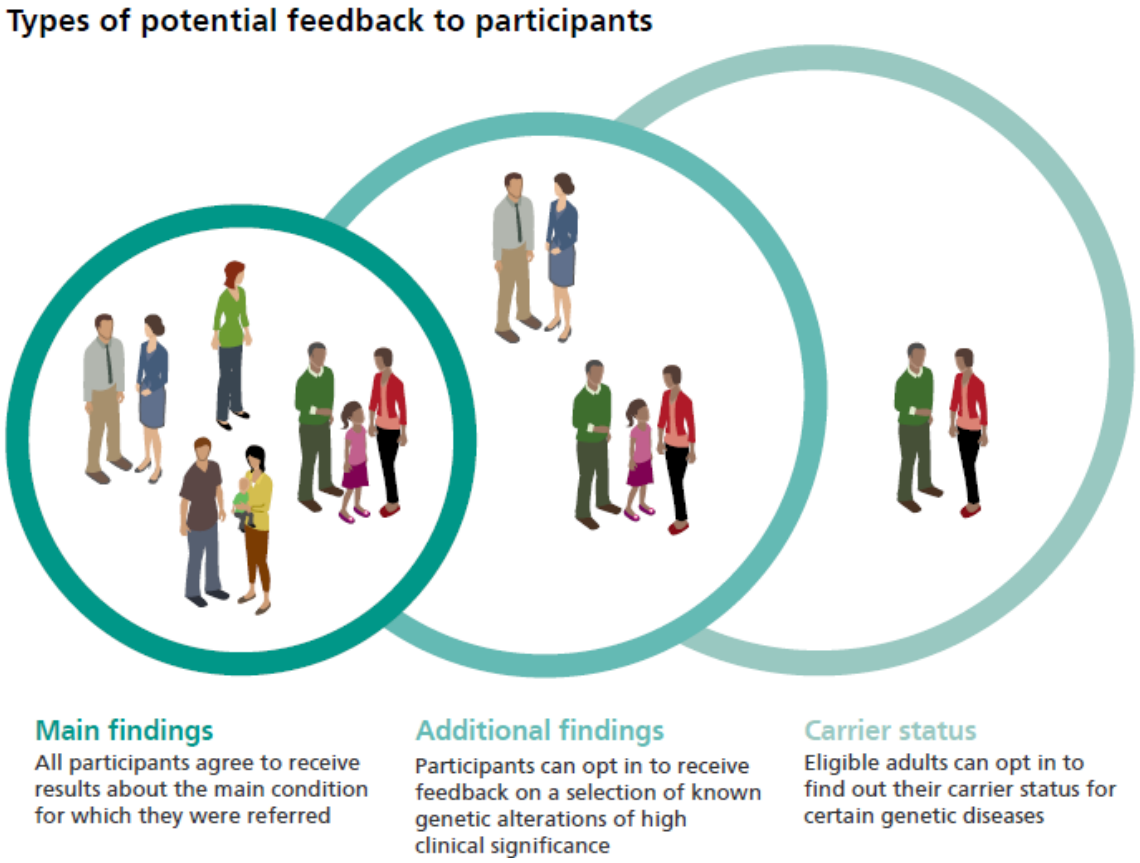
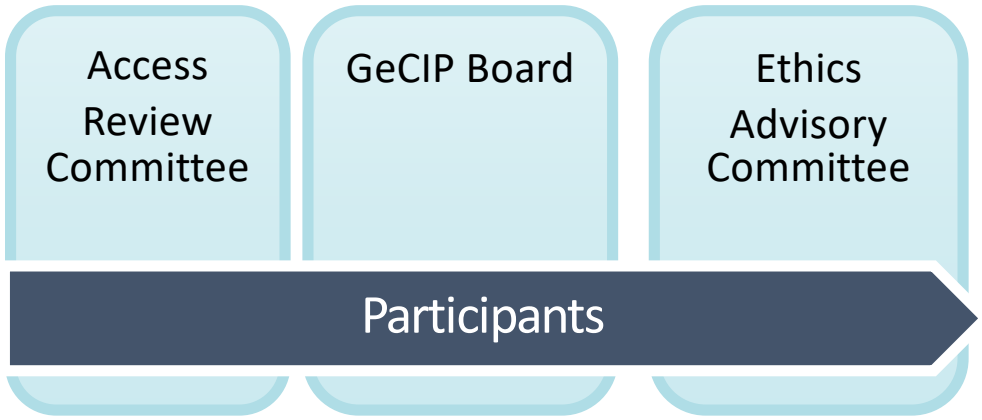


Image courtesy of Health Education England

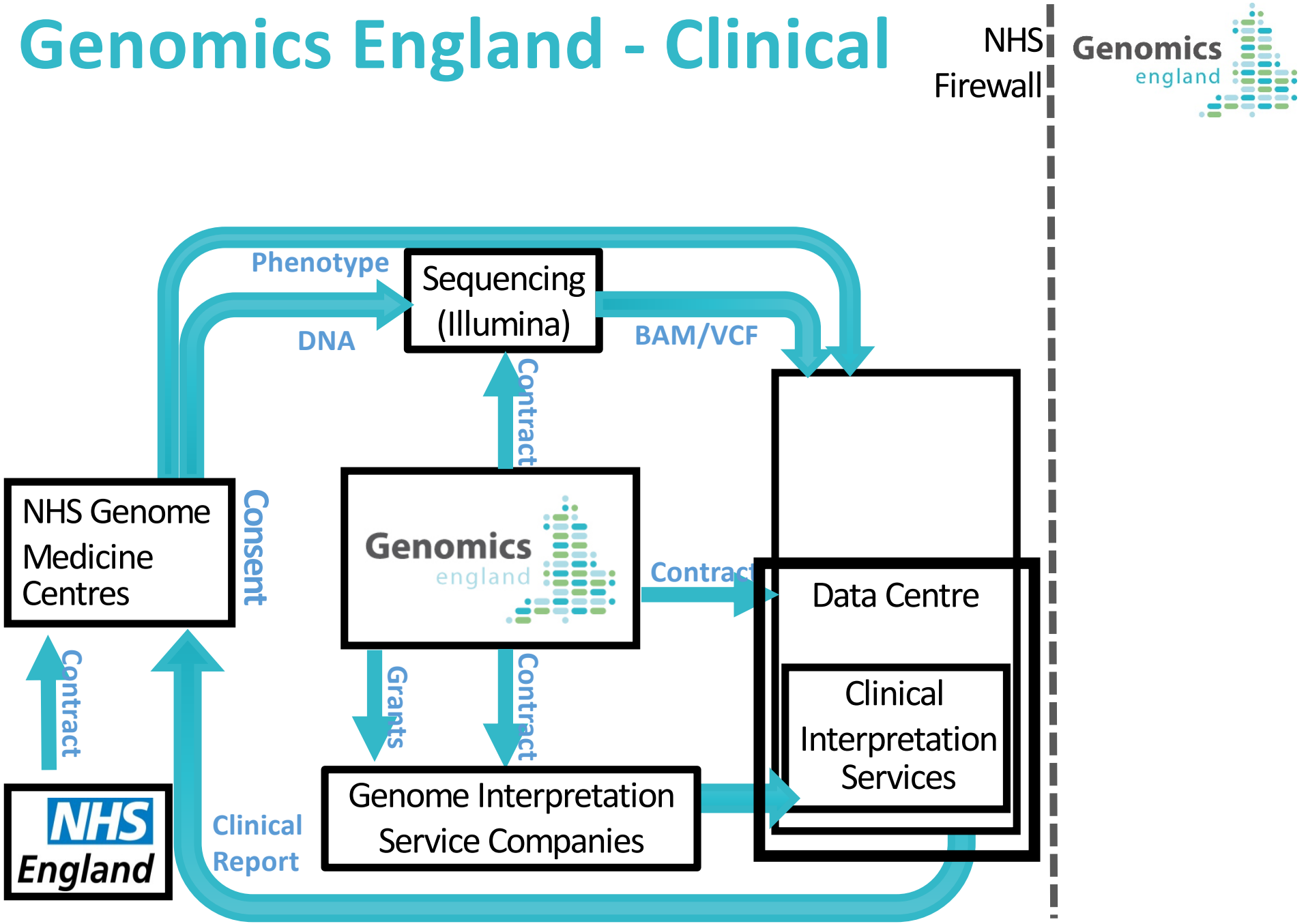
Patient involvement - the National Participant Panel

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:

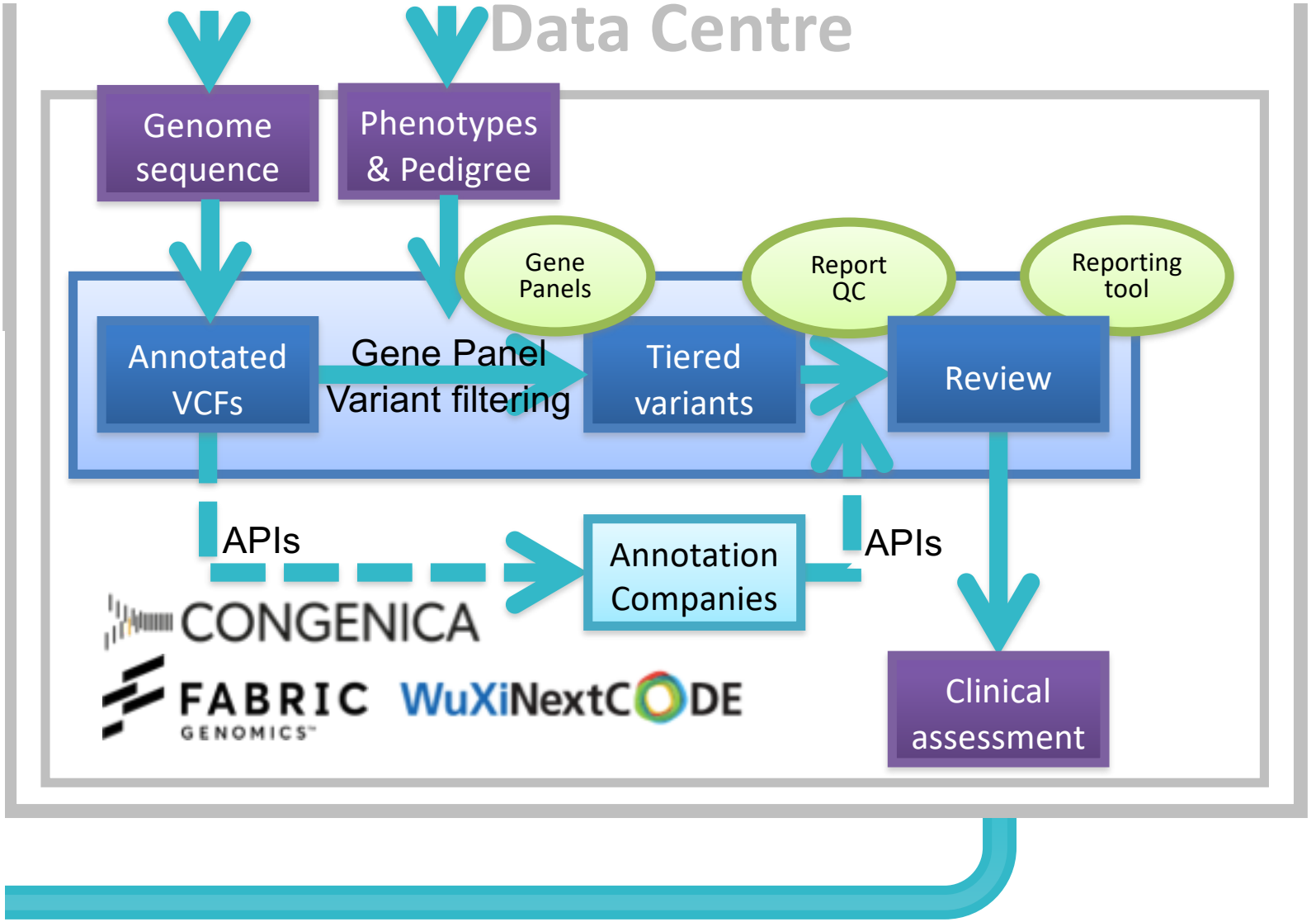
- Making sure experiences of participants are at the heart of the project
- Responding to feedback.
- Overseeing who should have access to participant data



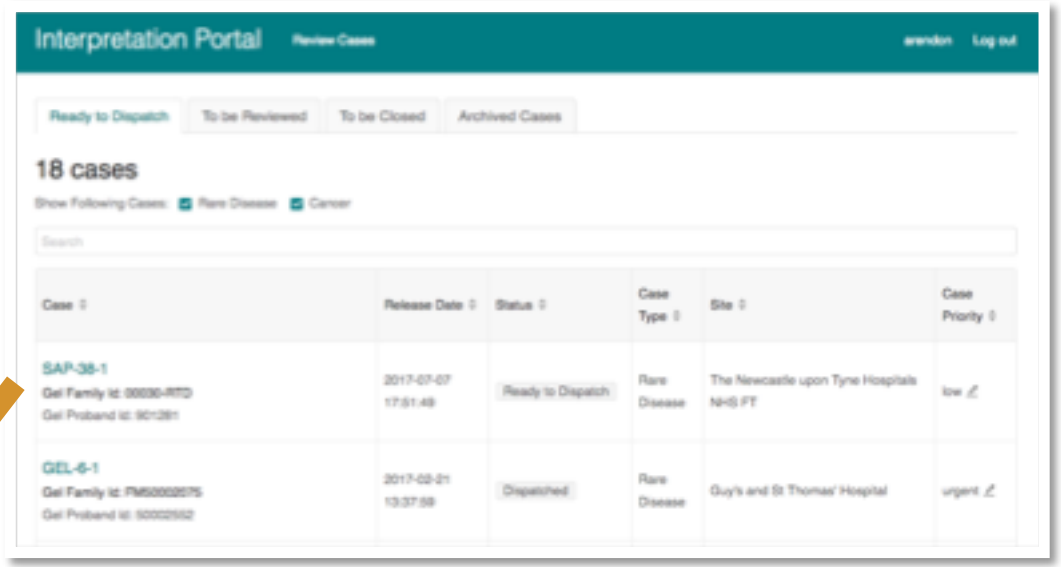
Genomics England - Clinical



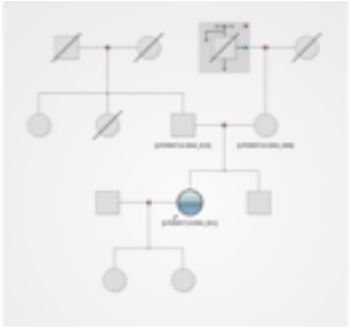
Scalable rare disease diagnostics



Reporting back to the NHS



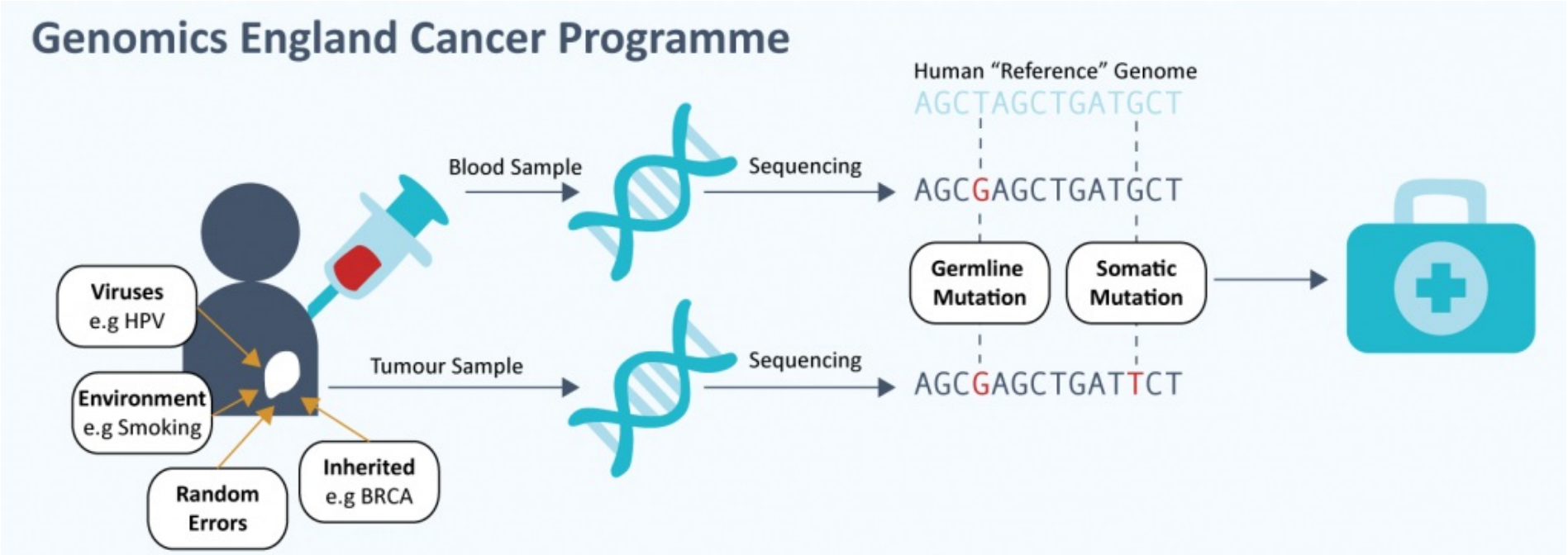
1. View family pedigree



2. Review variants and close case

3. Download the report

Cancer



Common cancers included initially:

- Lung, Breast, Ovarian, Prostate, Colorectal

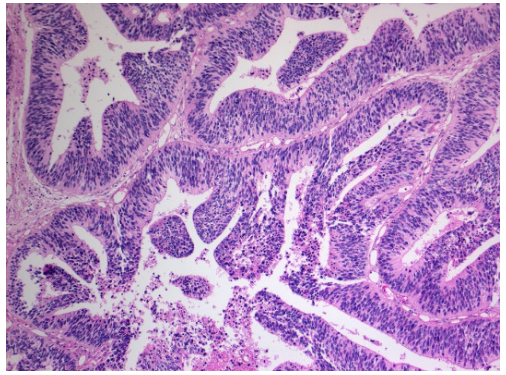
Now included:

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

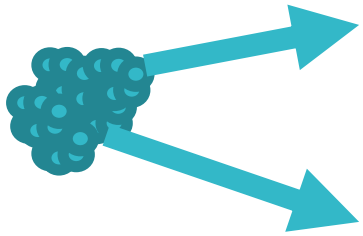
Molecular pathology

Complex NHS transformation underway

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:

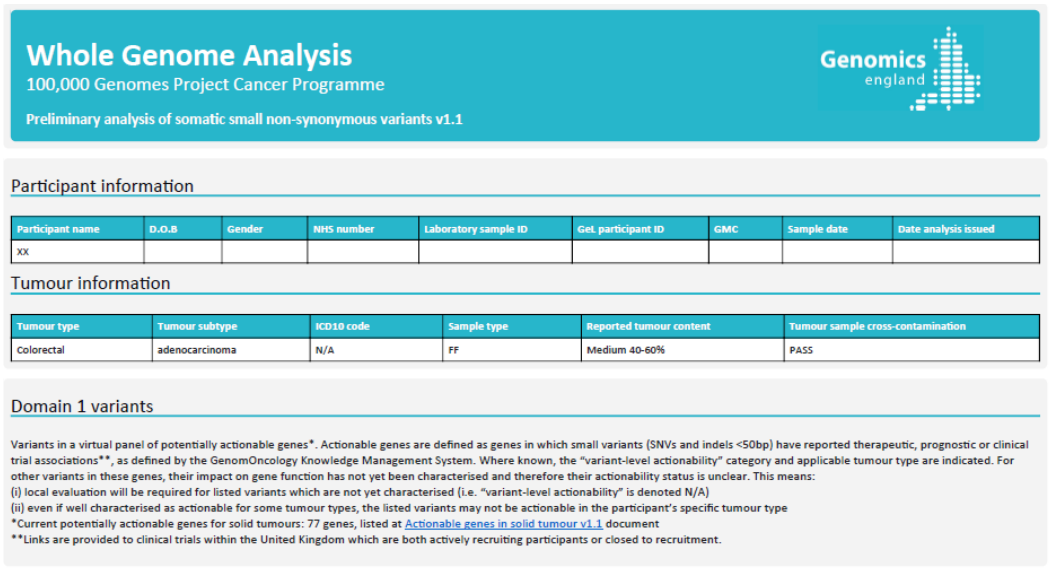
- Domain 1 variants - directly relevant to cancer treatment
- Domain 2 variants – other cancer related genes

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

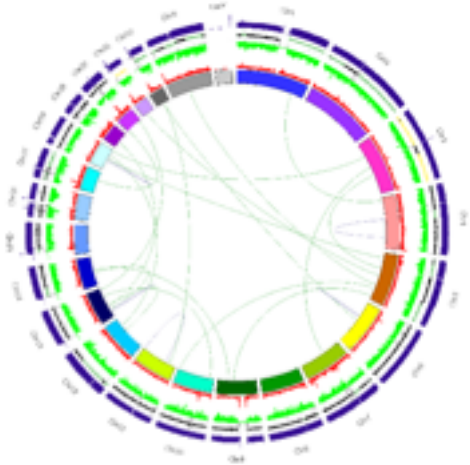
Participant name	D.O.B	Gender	NHS number	Laboratory sample ID	GeL participant ID	GMC	Sample date	Date analysis issued
XX								

Tumour information

Tumour type	Tumour subtype	ICD10 code	Sample type	Reported tumour content	Tumour sample cross-contamination
Colorectal	adenocarcinoma	N/A	FF	Medium 40-60%	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.



Progress to date

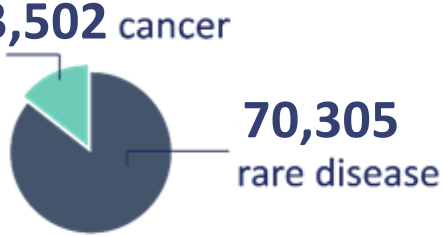
Figures as at 3/09/2018

Samples

93,807
Samples received at the UK Biocentre

23,502 cancer

70,305 rare disease

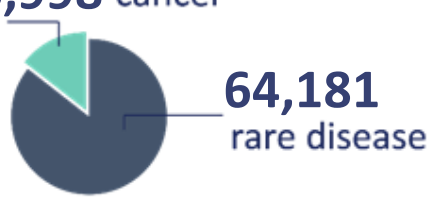


Genomes

81,179
Genomes sequenced

16,998 cancer

64,181 rare disease



+5,627 genomes since last month

Analysis and Results

Results for **28,386** genomes sent to NHS GMCs

Equivalent to **6,330** cancer genomes and **22,056** rare disease

20-25% actionable findings for Rare Disease

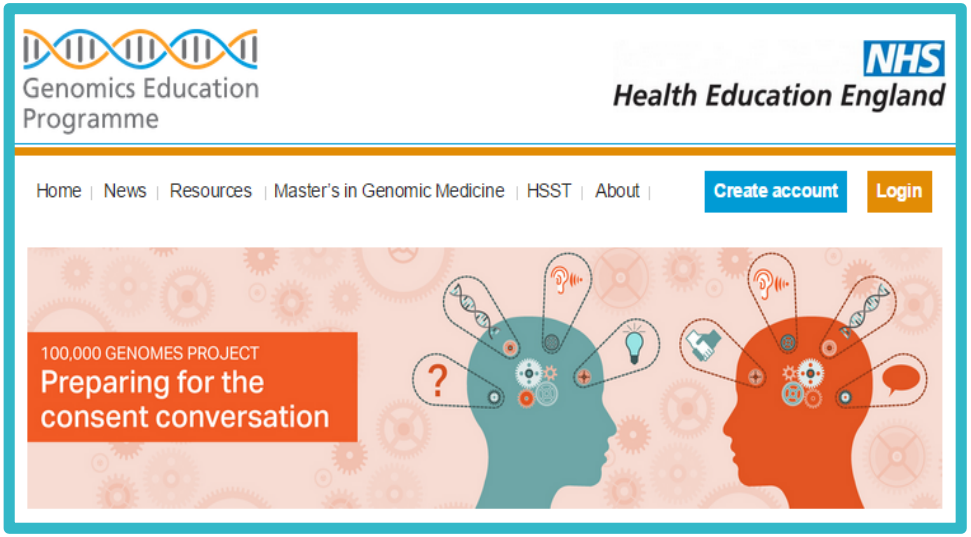
Infections and Pathogens

- 3000 Multi-drug resistance TB strains
- NHS implementing TB sequencing for diagnosis
- Global registry of TB resistance

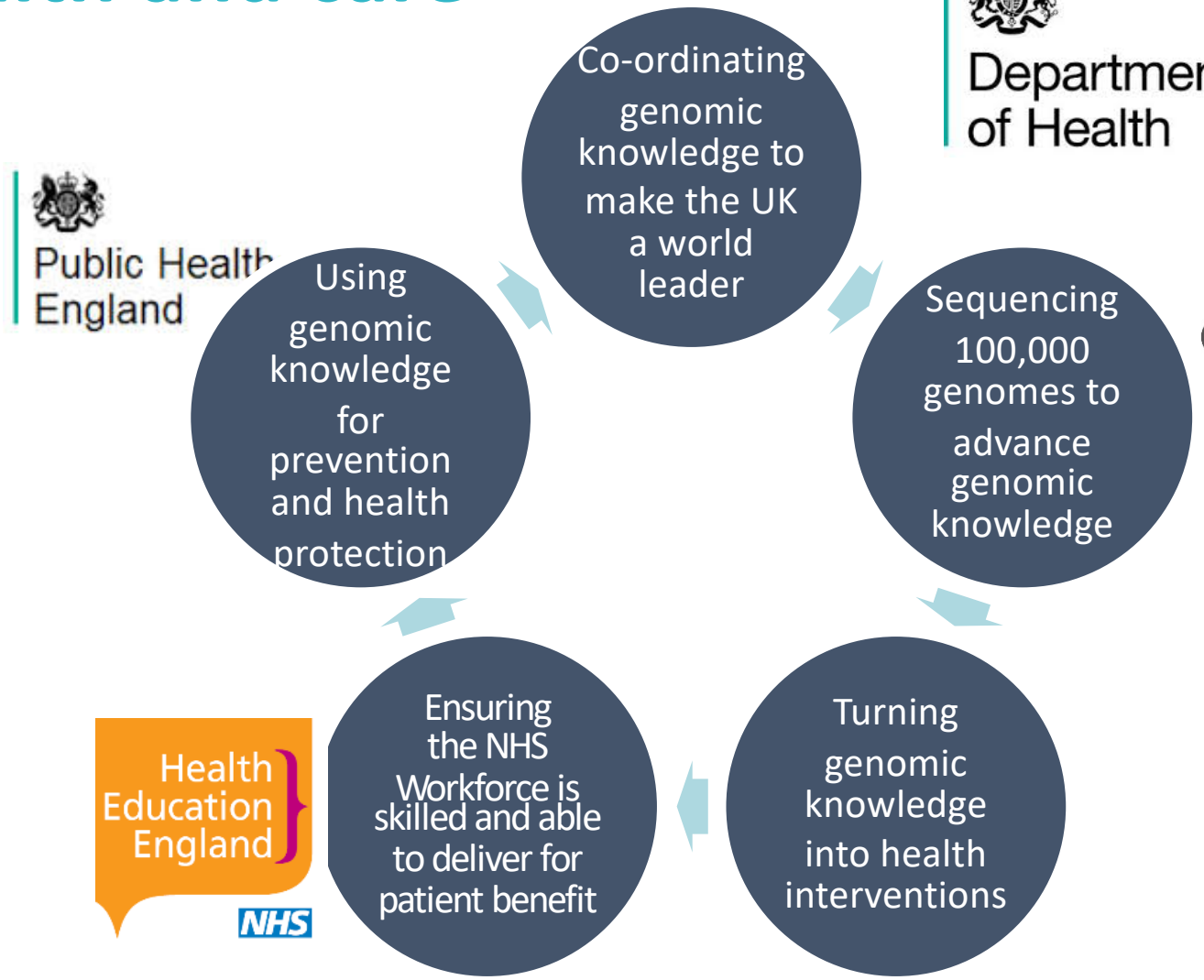
Health Education England

Genomics Education Programme

- 10 University providers of MSc 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



A co-ordinated response across health and care



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Department of Health

Public Health England

Genomics england

Health Education England NHS

NHS England

Diagnosis success rates

Rare:

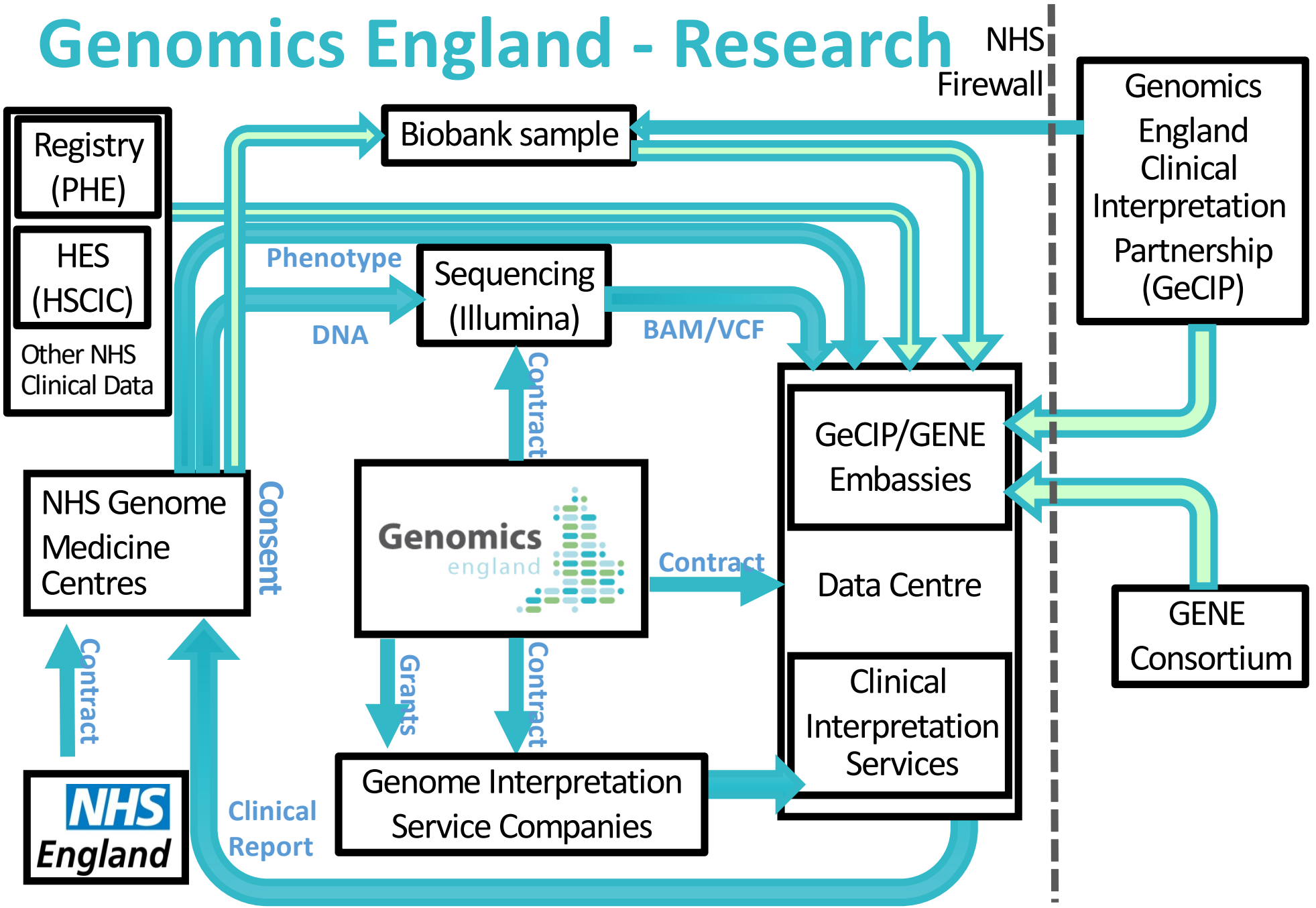
- Current clinical genetics services:
  - Single gene tests, panels: 15-20% diagnosed
- 100,000 genomes project:
  - Whole Genome sequence: Another ~25% diagnosed

Cancer:

- No existing systematic cancer genetics service in NHS
- 100,000 genomes project:
  - Whole Genome sequence: ~60% of reports identify variants in "actionable genes"

- What about ~50% not diagnosed?

Genomics England - Research



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

Genomics England Research Environment at a glance

Genomics england

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
4th release: July 2018 [3 monthly updates]

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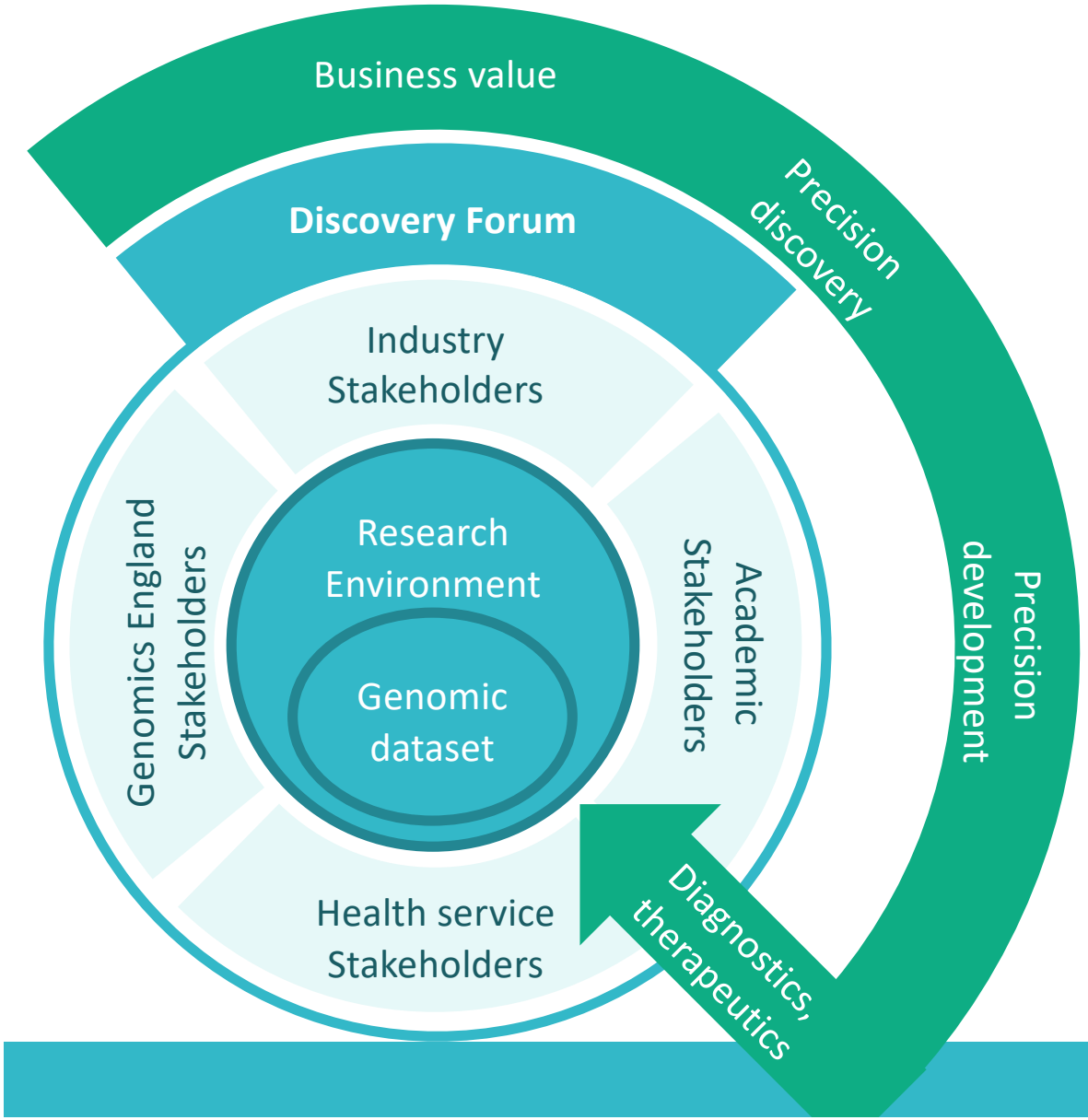
Genomes	**55,681 genomes**	**Primary clinical data**	**71,331 participants**
Secondary data	• Hospital Episode Statistics (HES) • Diagnostic Imaging Dataset (DID) • Patient Reported Outcome Measures (PROMs)	• Mental Health Services Data Set (MHSDS) • Office for National Statistics (ONS) – mortality data 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

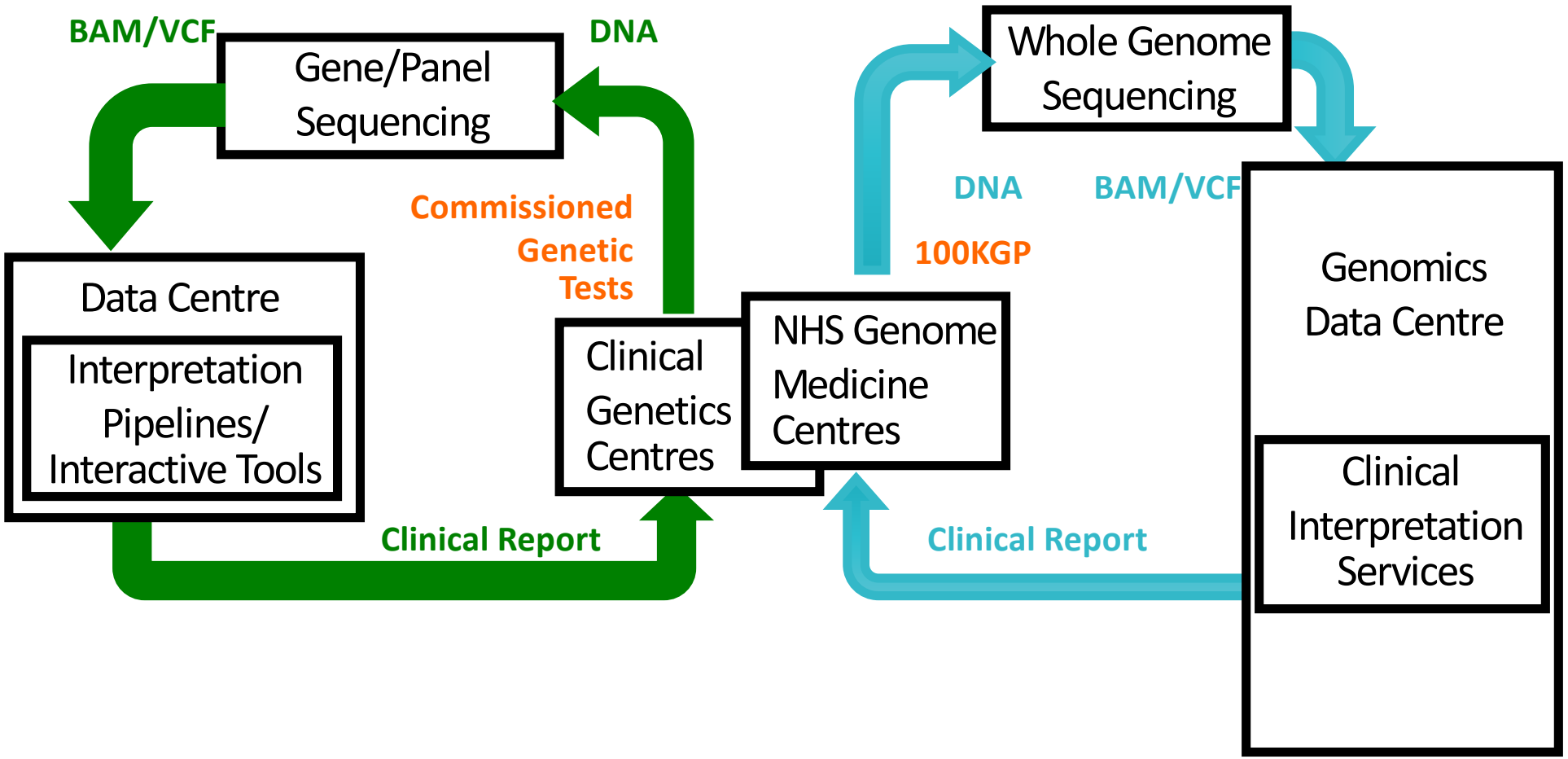


- **Exploring** the business value of genomic medicine data.
- **Connecting** industry stakeholders to the Genomics England community.
- Providing a **gateway** to our Research Environment and dataset.
- Leading to **discovery** and development of precision methods, diagnostics, and therapeutics.

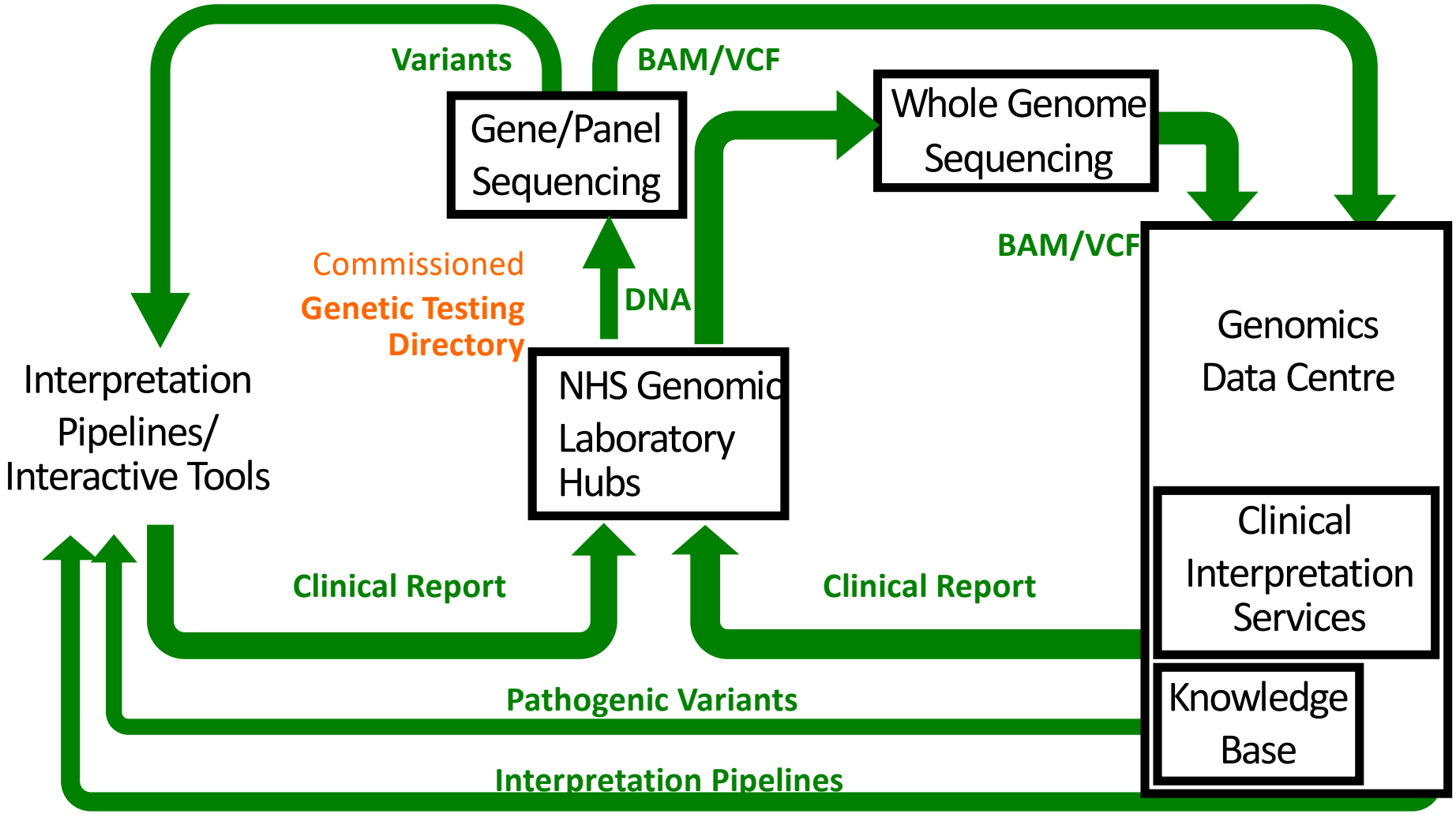
Opportunities for GeCIPs

- Interpret cases where CIPs currently fail
- Improved CIP algorithms
  - machine learning; using whole genome; predicting variable penetrance
- Other clinical apps against stored WGS
  - Phamacogenics; decision support
- Experimental investigation of function of variants
  - Is it really the cause? How does it function?

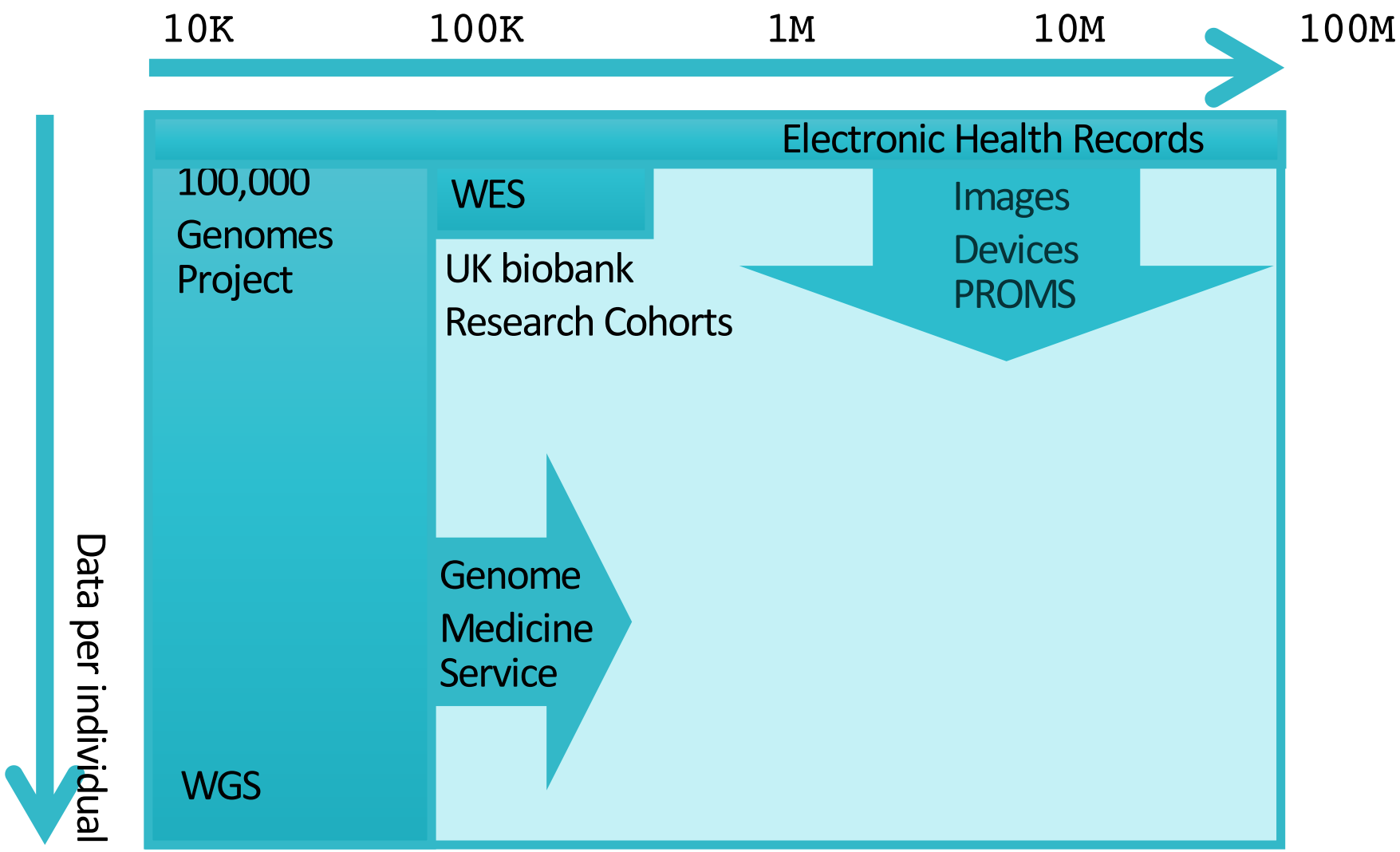
From 100,000 genomes to NHS Genome Medicine Service



From 100,000 genomes to NHS Genome Medicine Service



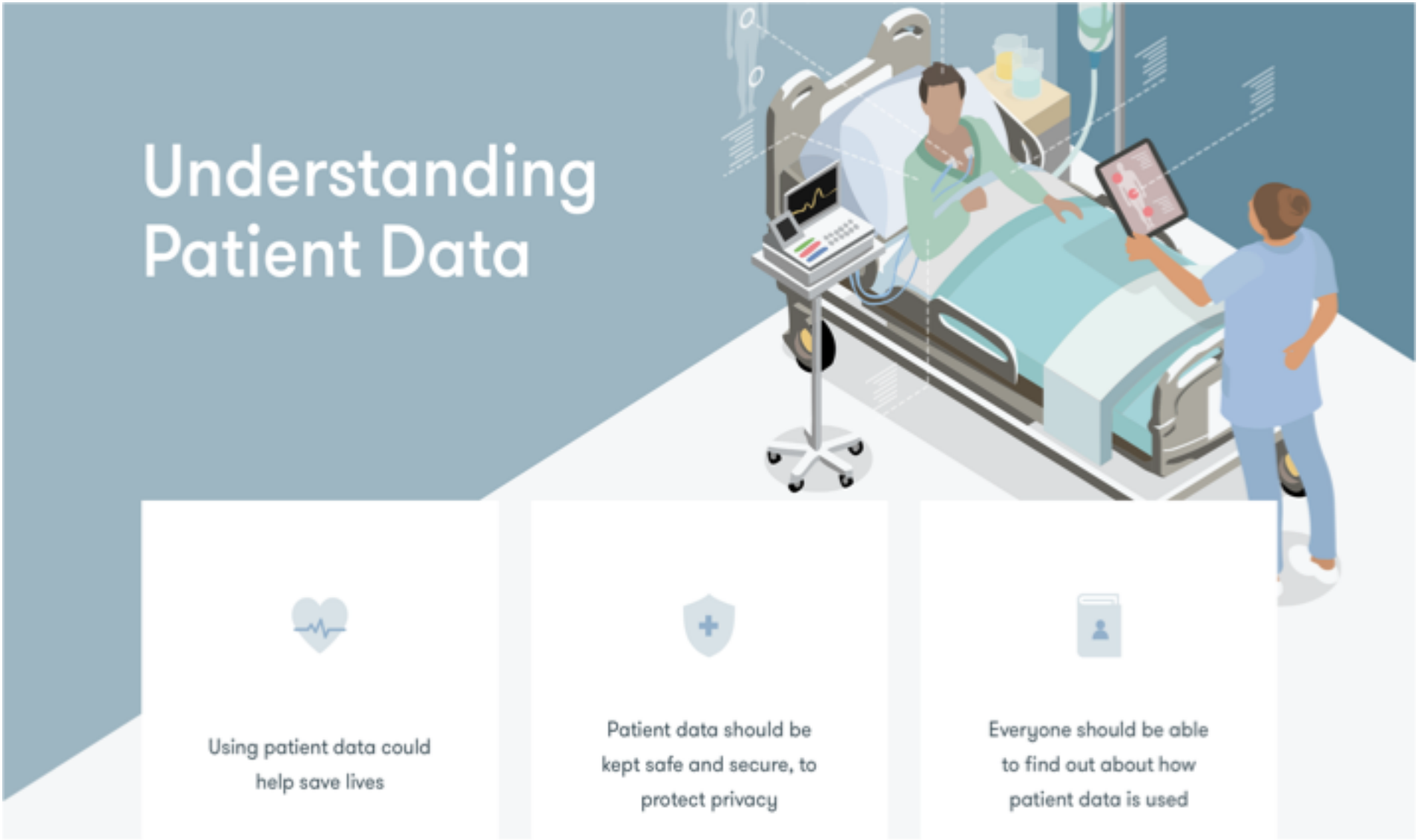
Expanding health data sets



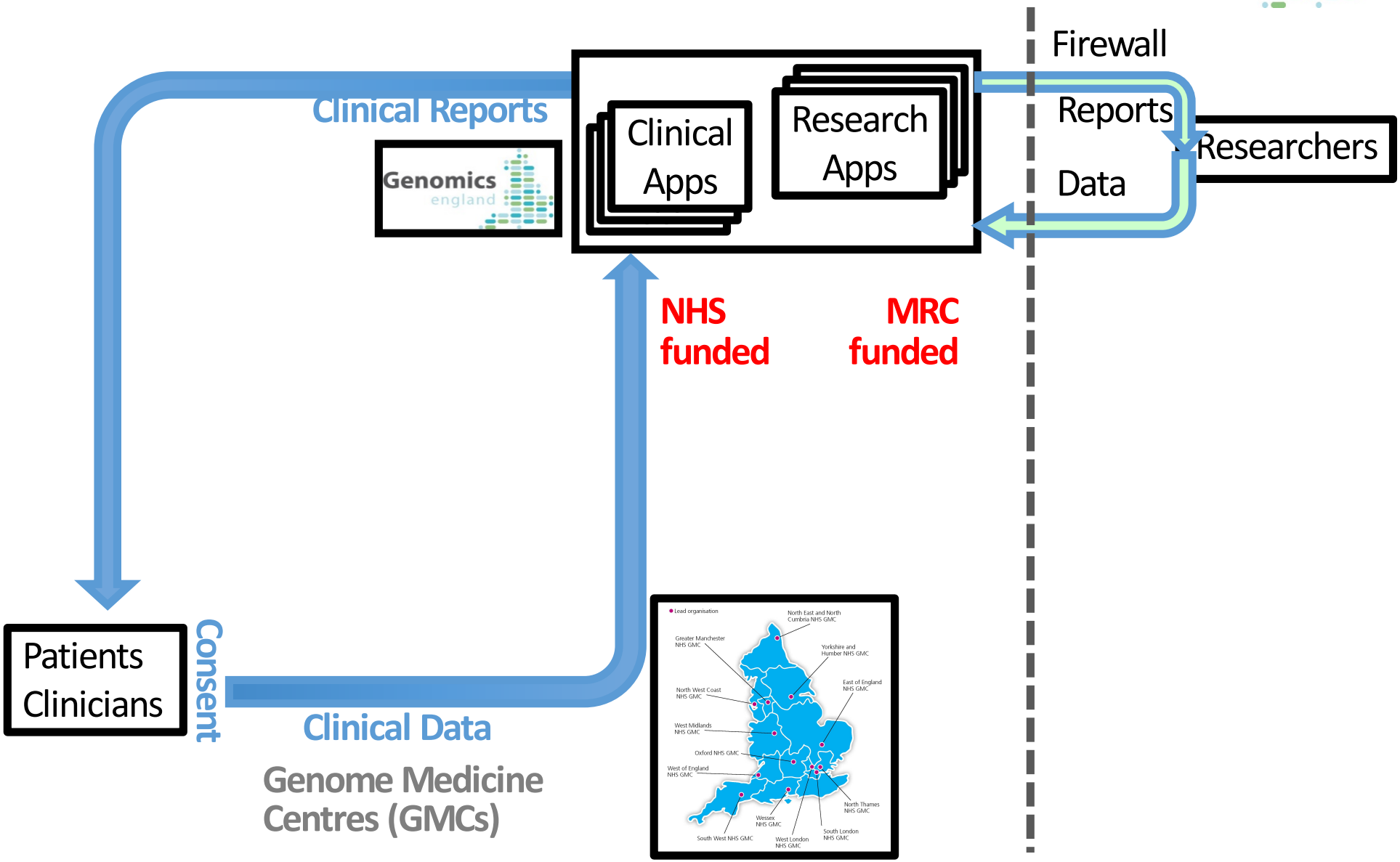
Regulation: GDPR

#DataSavesLives

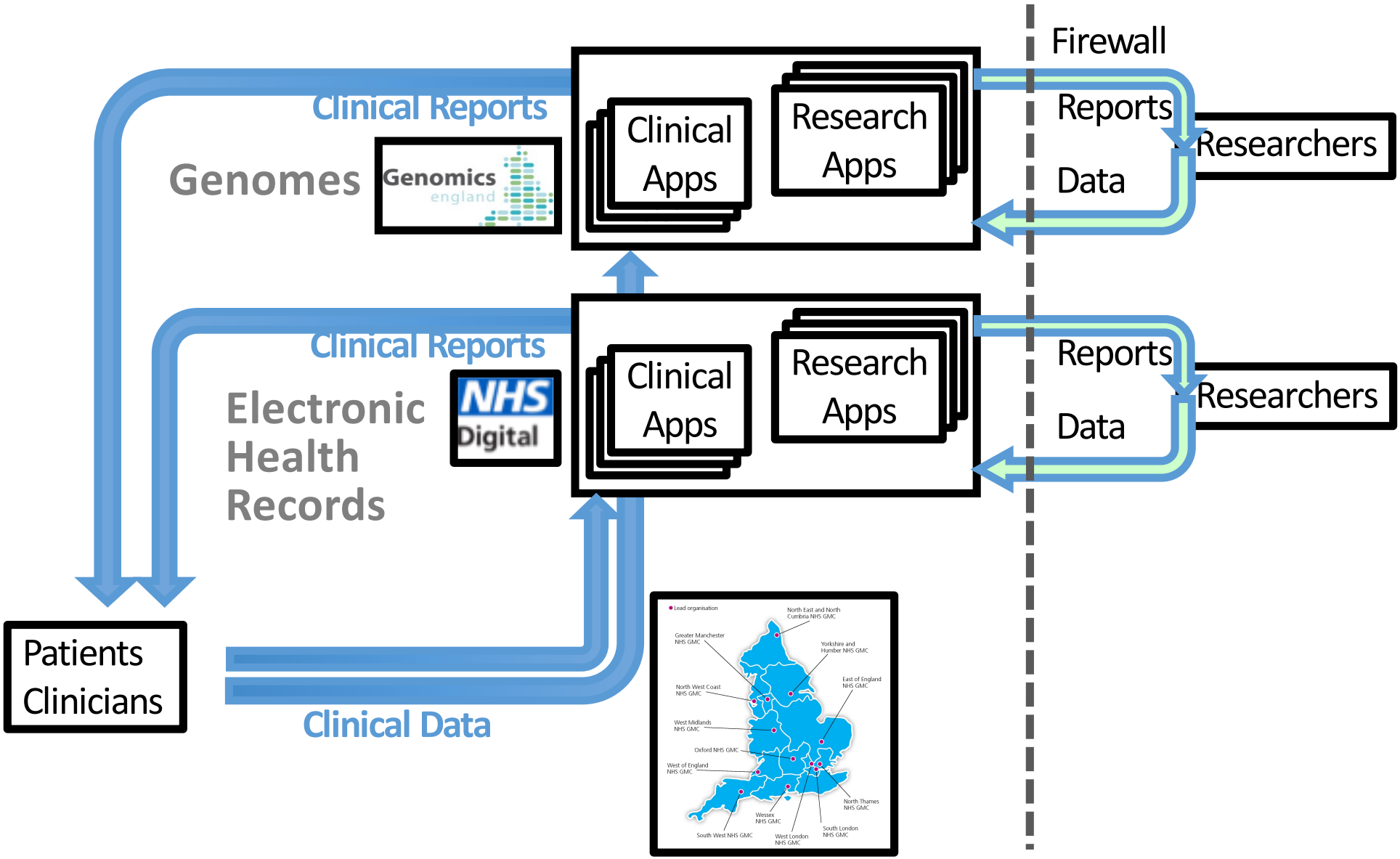
https://understandingpatientdata.org.uk



Generic model for data use



Genome, EHR, Image data



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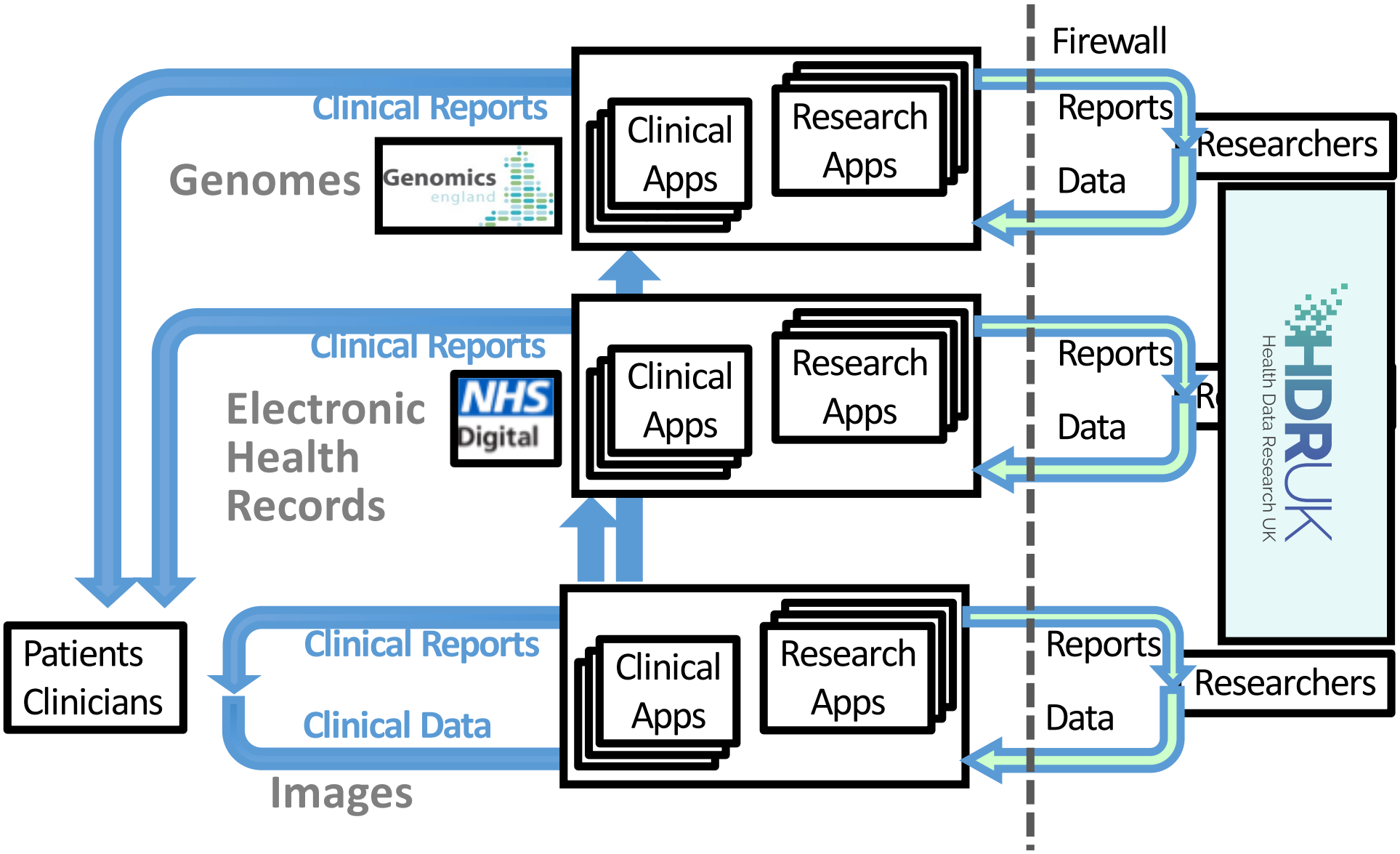

A new national Institute for health data science

HDRUK
Health Data Research UK

History: Launched in April 2018 with selection of six initial sites

Mission: make game-changing improvements in the health of patients and populations through research and innovation.

How: Apply cutting-edge data science approaches to clinical, biological, genomic and other multi-dimensional health data to address the most pressing health research challenges facing the public

Funding: Medical Research Council, the British Heart Foundation, the National Institute for Health Research, the Economic and Social Research Council, the Engineering and Physical Sciences Research Council, Health and Care Research Wales, Health and Social Care Research and Development Division (Public Health Agency, Northern Ireland), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, and Wellcome.

Genomics England - Impact

- *Genome Medicine Centre contracts:* Engine for NHS personalised medicine transformation
- *Phenotype data models for rare and cancer:* Driver standardisation of secondary care data capture
- *Support for interpretation services:* Engine for economic activity around development of genome interpretation applications for decision support
- *Dual purpose data centre:* Pioneering single informatics environments that support clinical interpretation services and research analysis **without data distribution for public trust and patient privacy**

Building the future of genomic medicine

- Deliver 100,000 WGS on NHS patients and pathogens
- Concentrate the UK Genomics Knowledgebase in one location
- Partnership of the NHS, academics and industry at the outset to drive Genomic Medicine into the NHS and create wealth
- Build human capacity and capability
- Add value through international partnerships
- Opportunities for new diagnostics and therapies for patients
- Legacy of NGS Centres, sample pipeline and biorepository, large-scale data store that makes this usable by the NHS
- Transition to commissioned WGS service in NHS in 2018 as part of new Genomic Medicine service

Acknowledgements

The patients and their families

Genomics England Team

NHSE- Sue Hill, Malcolm Grant, Bruce Keogh

HEE- Sue Hill, Val Davison, Anneke Seller

PHE- Derrick Crook

Genomic Medicine Centres in England, Scotland, Wales and Northern Ireland, UK CLL Consortium, CRUK, RCPath, NHSE, DoH, Biobank UK, Sanger, EBI, KCL, UCL and QMUL

NIHR BioResource Rare Disease, DDD

NIHR Translational Research Collaborative

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Jessica

Epileptic encephalopathy type 9 (GLUT1)

- Difficult to treat seizures
- Developmental delay
- Standard tests found no cause
- Now 4 years old

- Mutation in *GLUT1* found via 100KGP
- Mutation not present in either parent
- Likely benefits of diagnosis
  - Ends 4 year diagnostic odyssey
  - Provides possible tailored therapy (ketogenic diet)
  - Informs parents on risk of recurrence in another child (very low)

A 10 year-old girl with life threatening chicken pox

- 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

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

Expanding health data sets