Genomic Medicine in the UK

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TMF Workshop

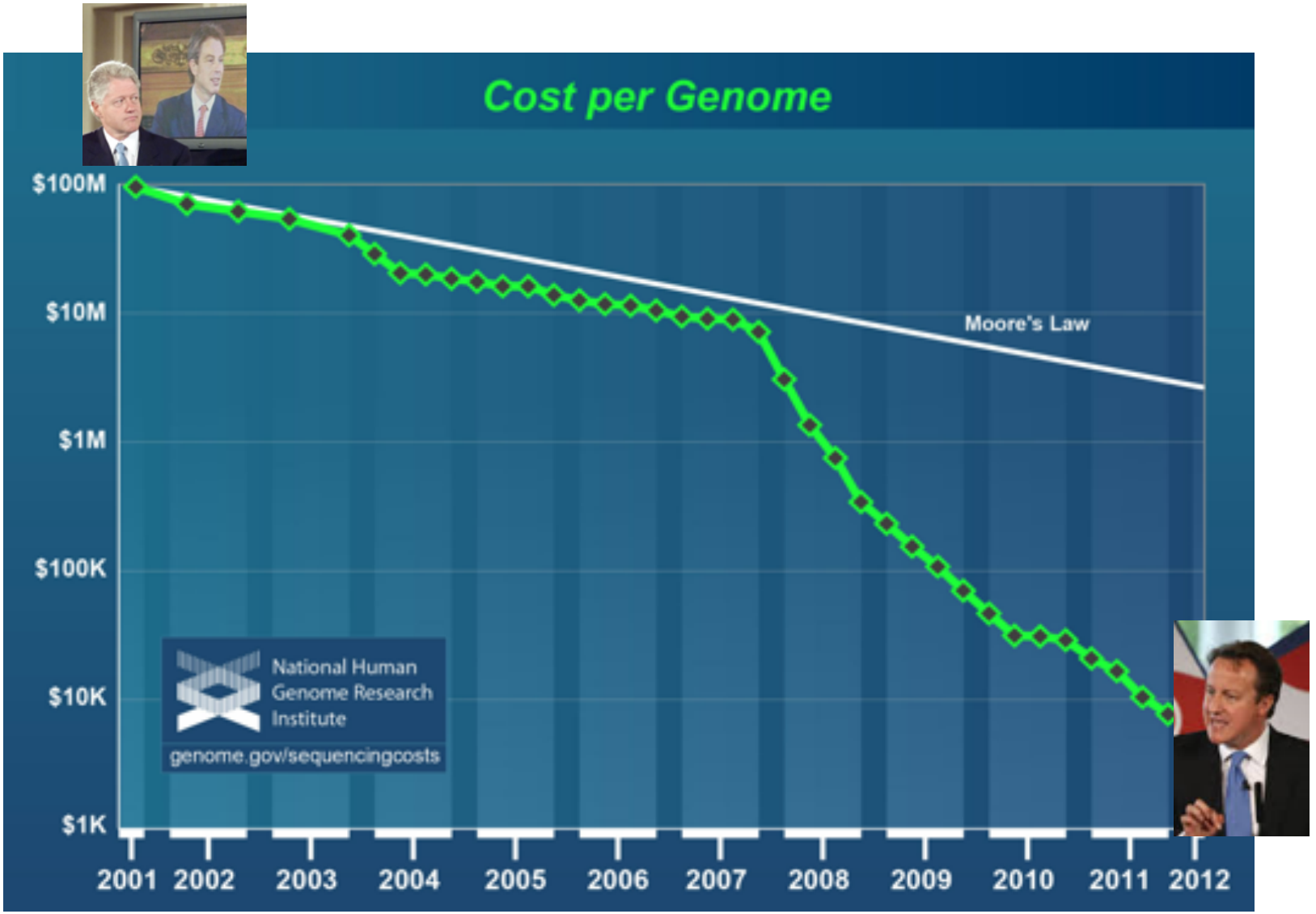
Genomic Medicine in Europe – Blueprints for Germany

27th May 2019

The first human genome sequence

- 26th June 2000 - Cost $3.2 billion
- 100,000 Genomes at Millennium Prices - Cost $320 trillion

Cost per genome



The 100,000 Genomes Project

Background

Announced by the former Prime Minister in December 2012

An Olympic Legacy

Genomics England announced by Secretary of State for Health in speech during NHS 65th Anniversary Celebrations, July 2013

Recommended targets

- 2013 - Professor Dame Sally Davies (CMO) established a **Strategic Priorities Working Group** for the Project - chaired by Professor David Lomas (UCL)
- Recommended rare diseases, certain cancers, and infections
- Areas where they believe the introduction of genomic technology will have the greatest benefit for patient health

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

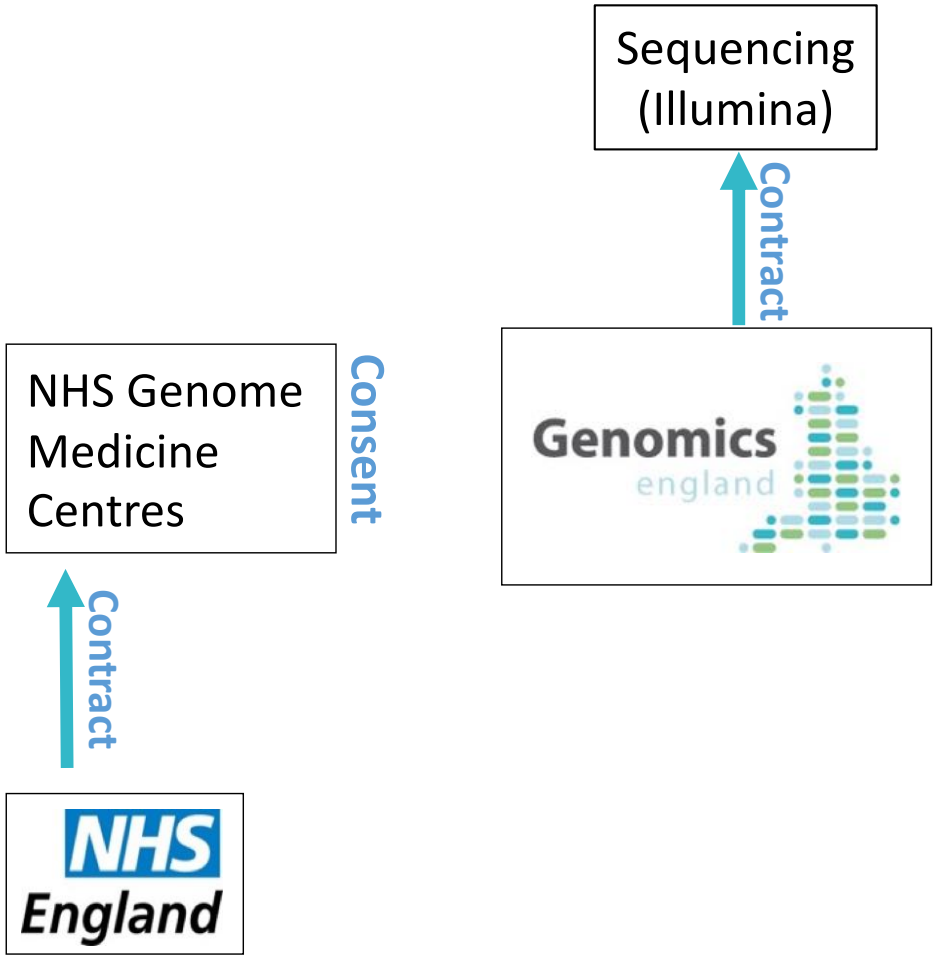
100,000 genomes project

Three phases towards sustainability

- Pilot (2014)
  - Through Biomedical Research Centres
- Main Programme (2015-2018)
  - Through Genome Medicine Centres
- NHS Genome Medicine Service (2018-)
  - Through NHS testing directory:
    National Genomic Information Service (NGIS);
    Genome Laboratory Hubs

Result: sustainable framework for genomic medicine embedded in NHS for clinical care and research

Genomics England - Clinical

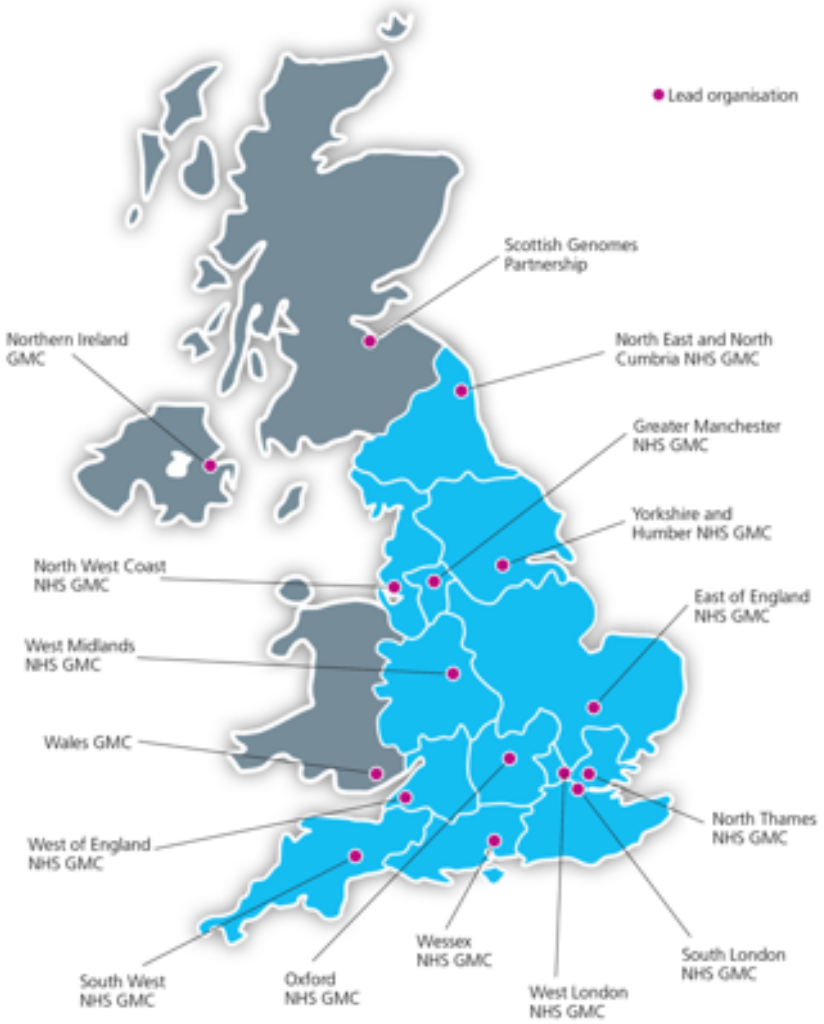


NHS Firewall

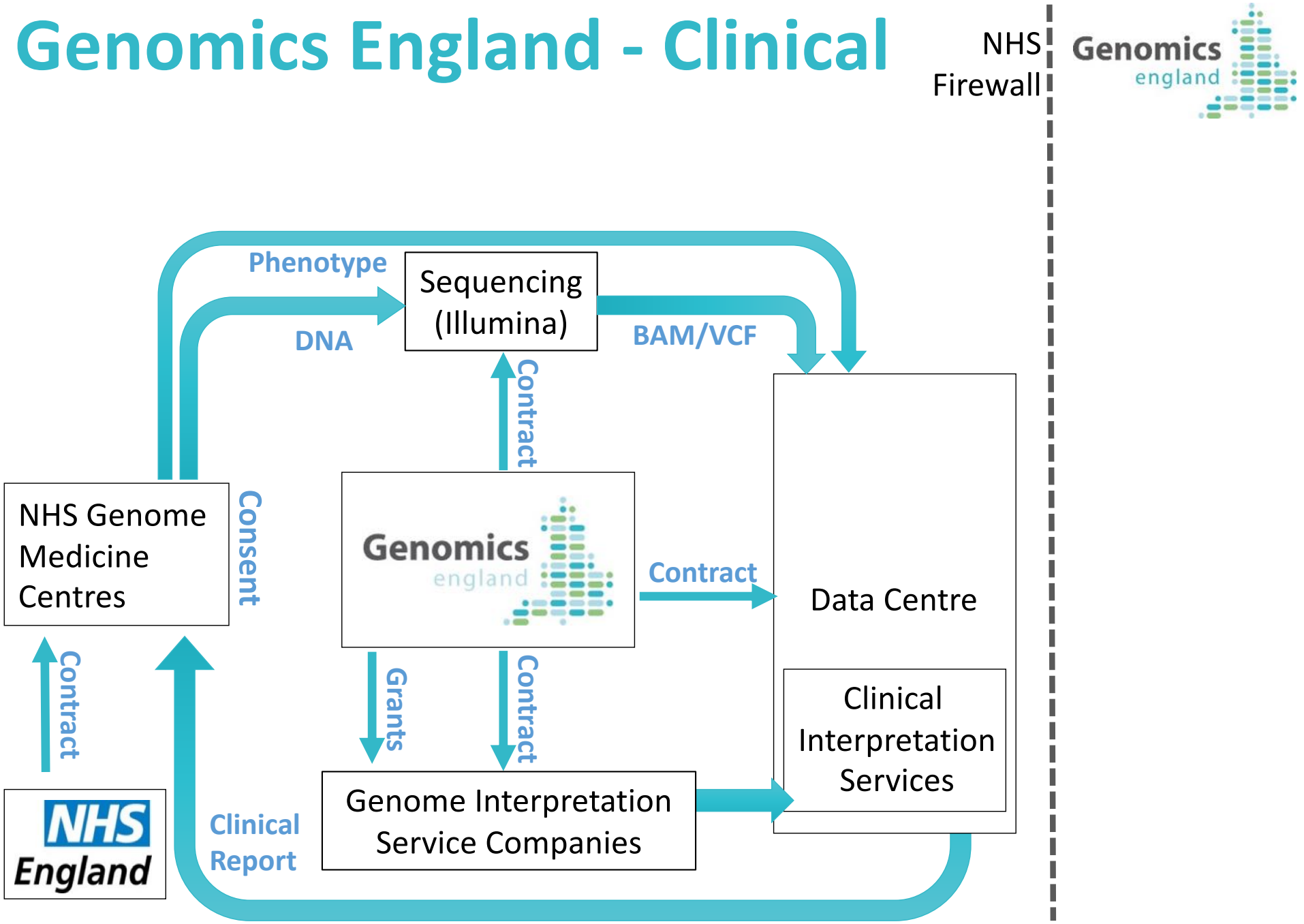
Genomics england

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)

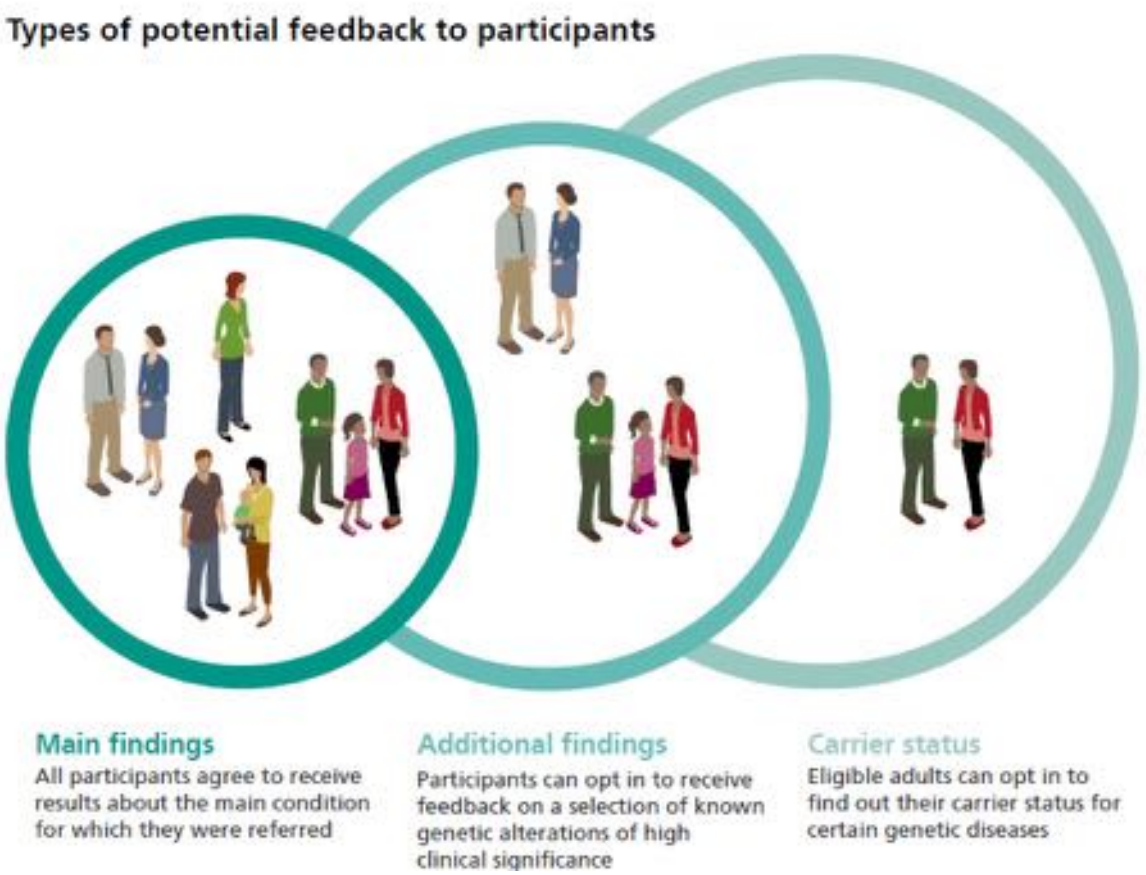


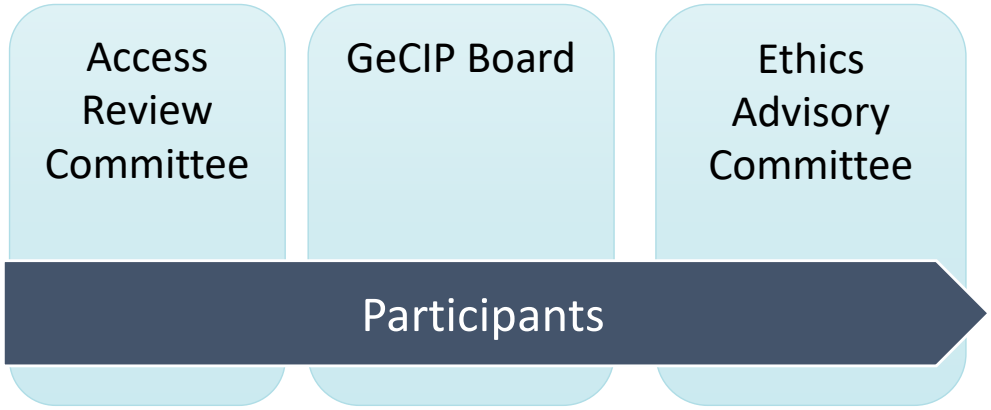
Image courtesy of Health Education England

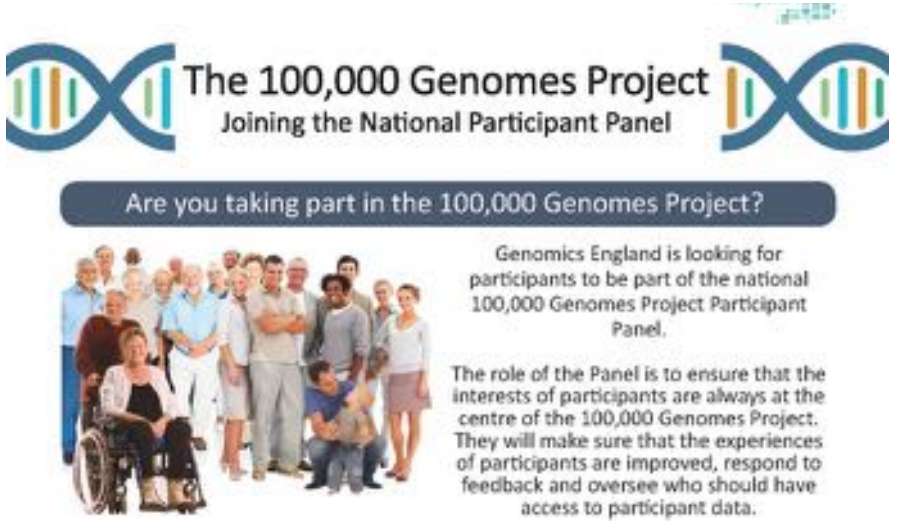
Patient involvement - the National Participant Panel

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

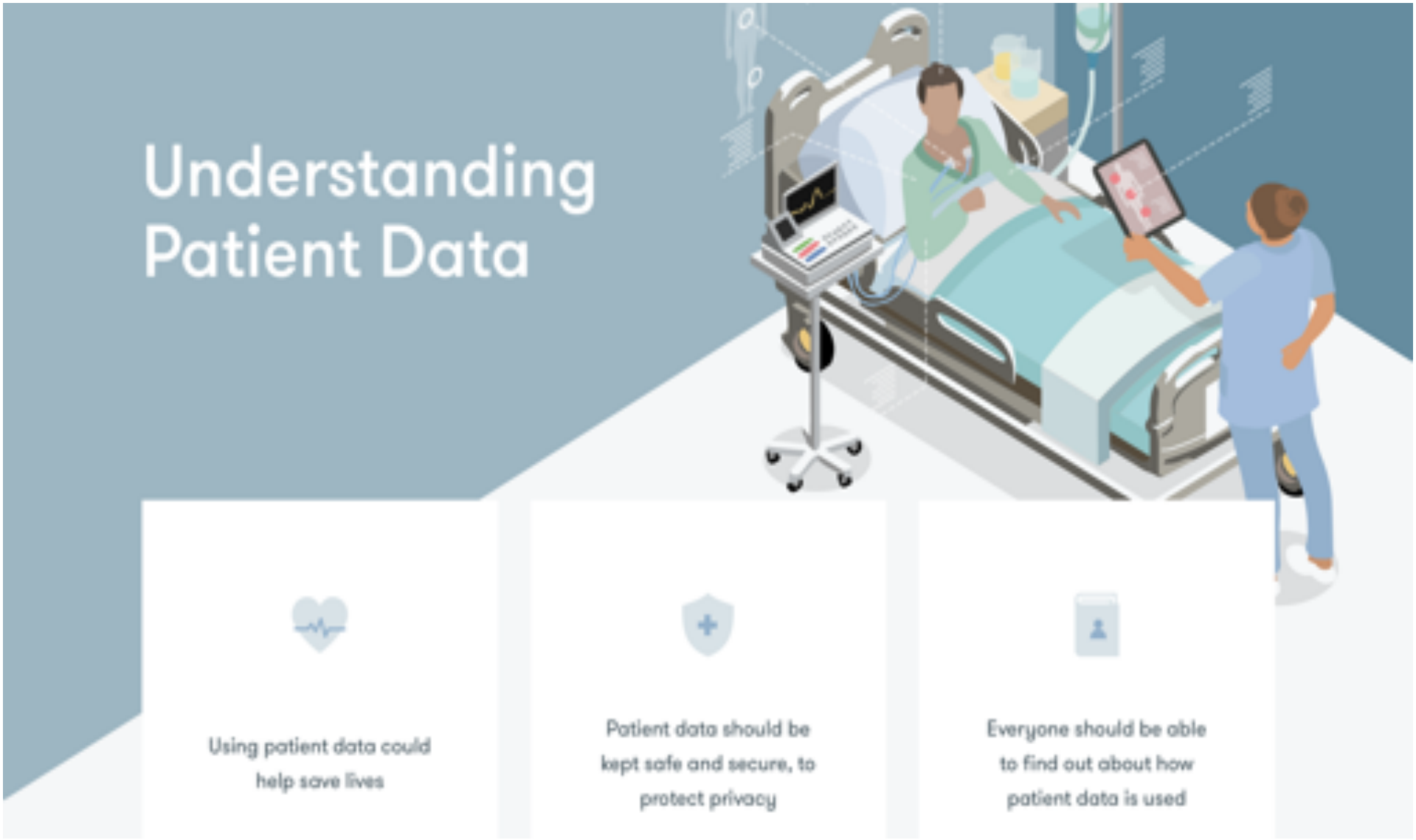




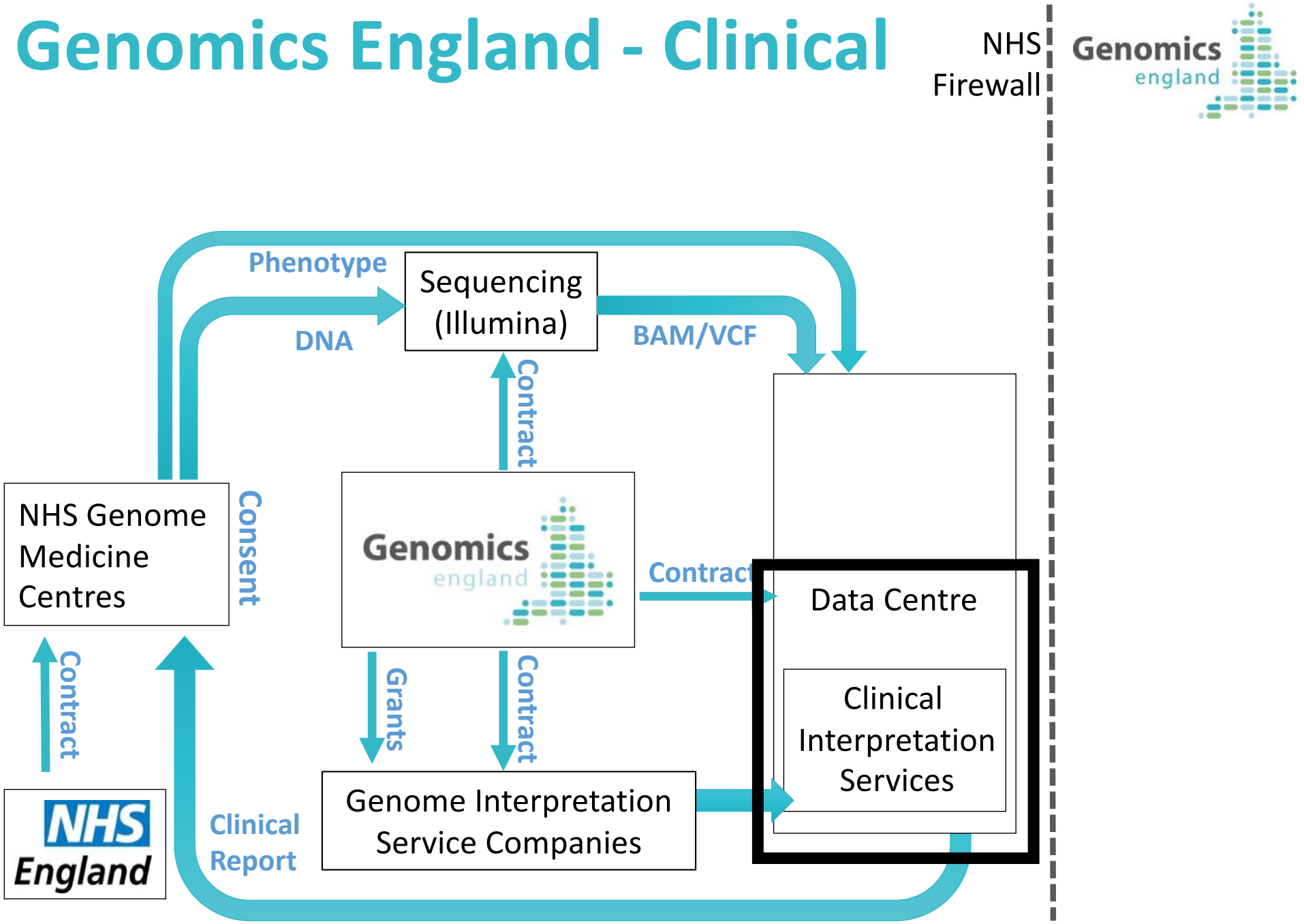
Regulation: GDPR

#DataSavesLives

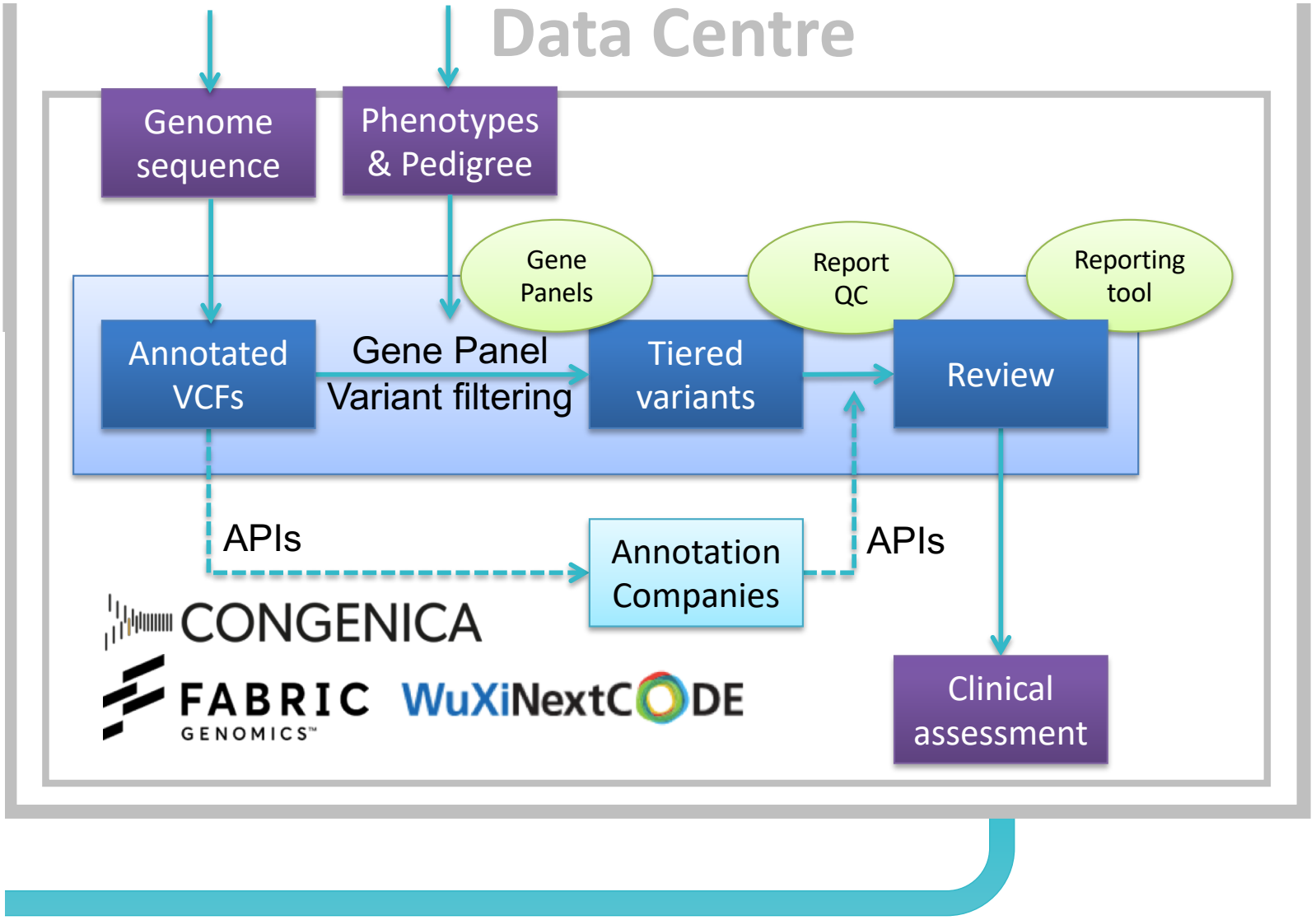
https://understandingpatientdata.org.uk



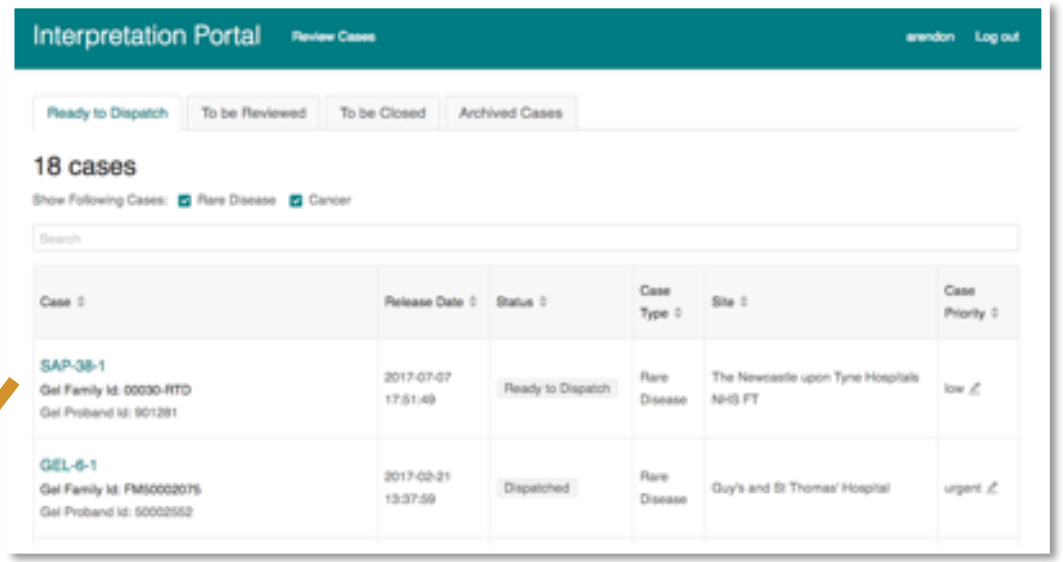
Genomics England - Clinical



Scalable rare disease diagnostics



Reporting back to the NHS



1. View family pedigree

2. Review variants and close case

3. Download the report

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

- 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

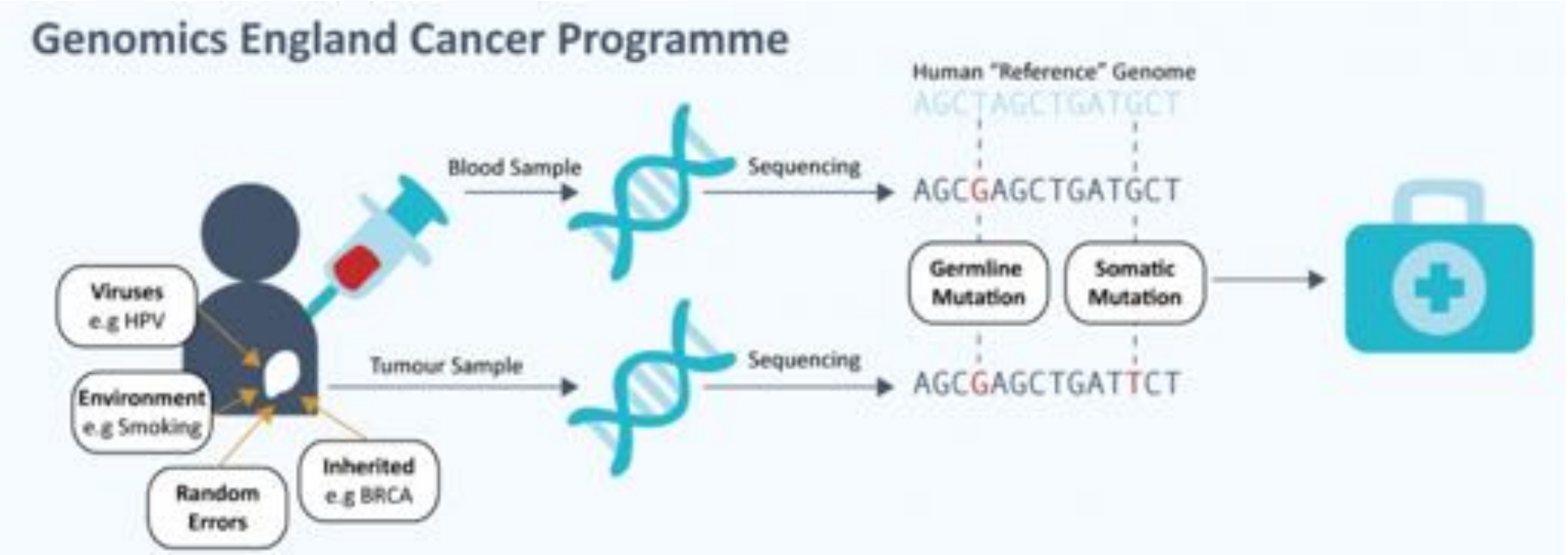
- Developmental delay
- Multiple medical problems
- Sees >5 hospital specialist services
- Seen in two genetic centres
- No cause known despite extensive testing
- Now 4 years old

- 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

Cancer



Common cancers included initially:

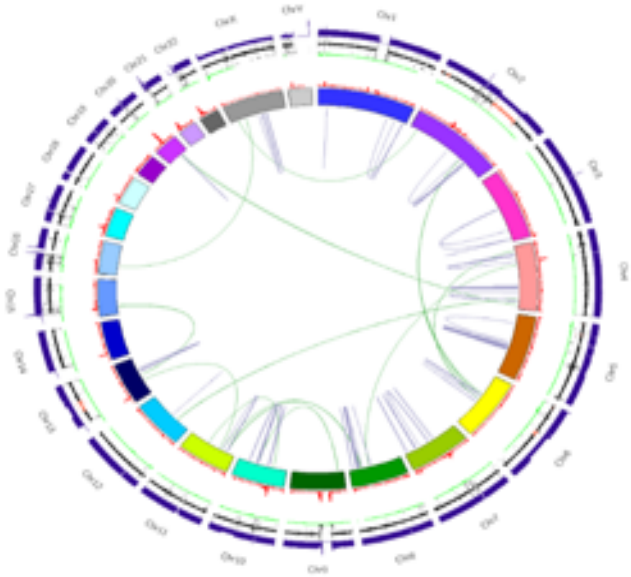
- Lung, Breast, Ovarian, Prostate, Colorectal

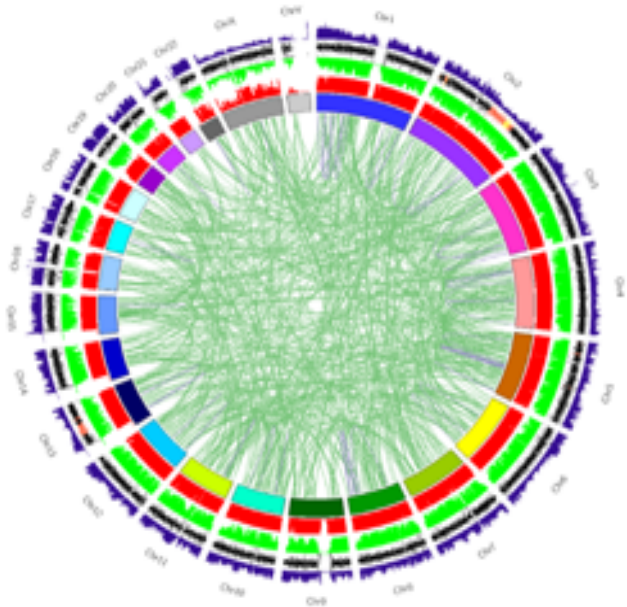
Later expanded to include:

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

Cancer Programme

Optimised FFPE – still has AT loss and CNV drop out
Newer fixation methods – PaxGene
Vacuum Packing/ preservation in a bag at 4 degrees C adequate histo-morphology for diagnosis
Biopsy, Shaken Biopsy, Fine Needle Aspiration
Re-engineer molecular pathology toward a fresh tissue supply in the NHS



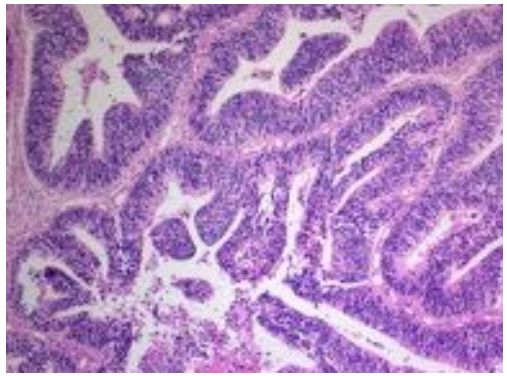


	AT dropout	CG dropout	Evenness of coverage	Chimeric reads, %	SNVs	Indels
GL	2.61	1.91	6.77	0.32	NA	NA
FF	5.22	2.48	11.56	0.65	10083	1573
FFPE	17.30	-17.30	41.26	1.27	698797	41645

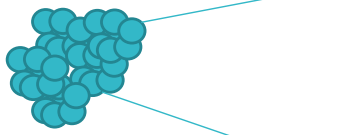
Molecular pathology

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:

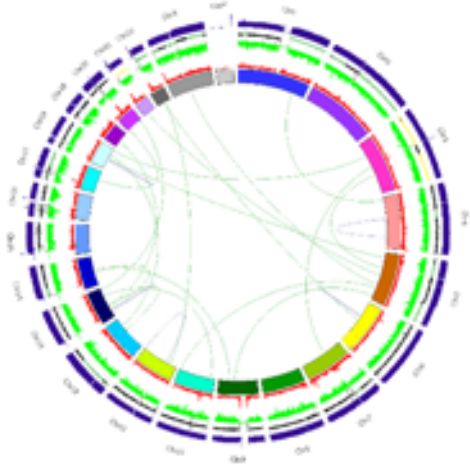
- Domain 1 variants - directly relevant to cancer treatment
- Domain 2 variants – other cancer related genes

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



100,000 Genomes Current status

Genomics england

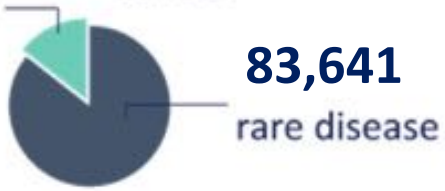
Samples

120,500

Samples collected from NHS GMCs and sent to biorepository

36,859 cancer

83,641 rare disease



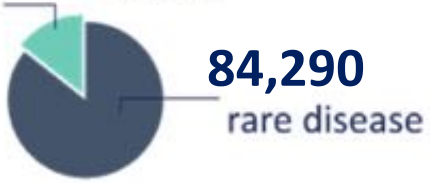
Genomes

109,072

Genomes sequenced

24,782 cancer

84,290 rare disease



Analysis and Results

76,527

Genome analyses sent to NHS GMCs

Research

Data release of genomes in RE **71,860**

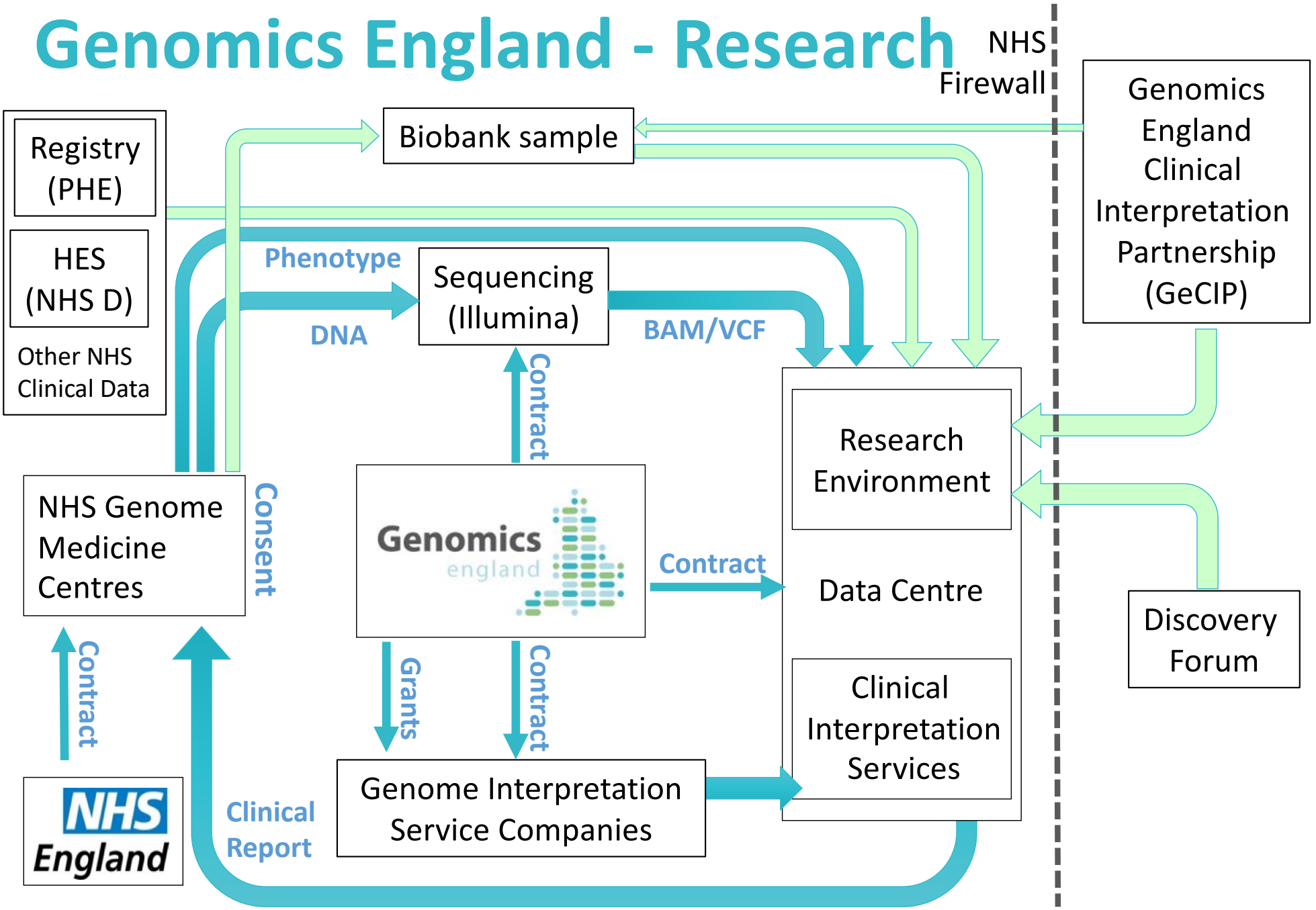
1,800 GeCIP members with access to RE

Over **100** Discovery Forum members (9 full members)

Rare Disease 20-25% potential actionability in the NHS
Cancer up to 50% could access a trial or receive a therapy on the NHS

Figures as at 01/04/2019

Genomics England - Research



Genomics England Clinical Interpretation Partnership (GeCIP)

- A research consortium
- Partnership between **over 3,300** researchers from academia and the NHS, trainees, plus international collaborators (**405** academic institutions) **2,424** currently have access to research environment
- 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
- **£24** million successful grant applications

Genomics England Research Environment at a glance

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

6th release: February 2019 [3 monthly updates]

Genomes	**91,271 genomes** • **22,091 Cancer** • **69,172 Rare Disease**	**Primary clinical data**	**94,285 participants** • **20,475 Cancer** • **73,810 Rare Disease**
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) • Systemic Anti-Cancer Therapy Data Set (SACT)		
Clinically interpreted data & QC	• **21,873 families** with Tier 1, 2 and 3 variants from interpretation pipeline • **4,763 families** with GMC exit questionnaires • **45,743** tiered and quality checked rare disease genomes; **19,098** quality checked cancer genomes	**Quick view tables**	• Key information from different tables, merged and filterable • Merged with QC data • Allow cohort-building and project feasibility assessment

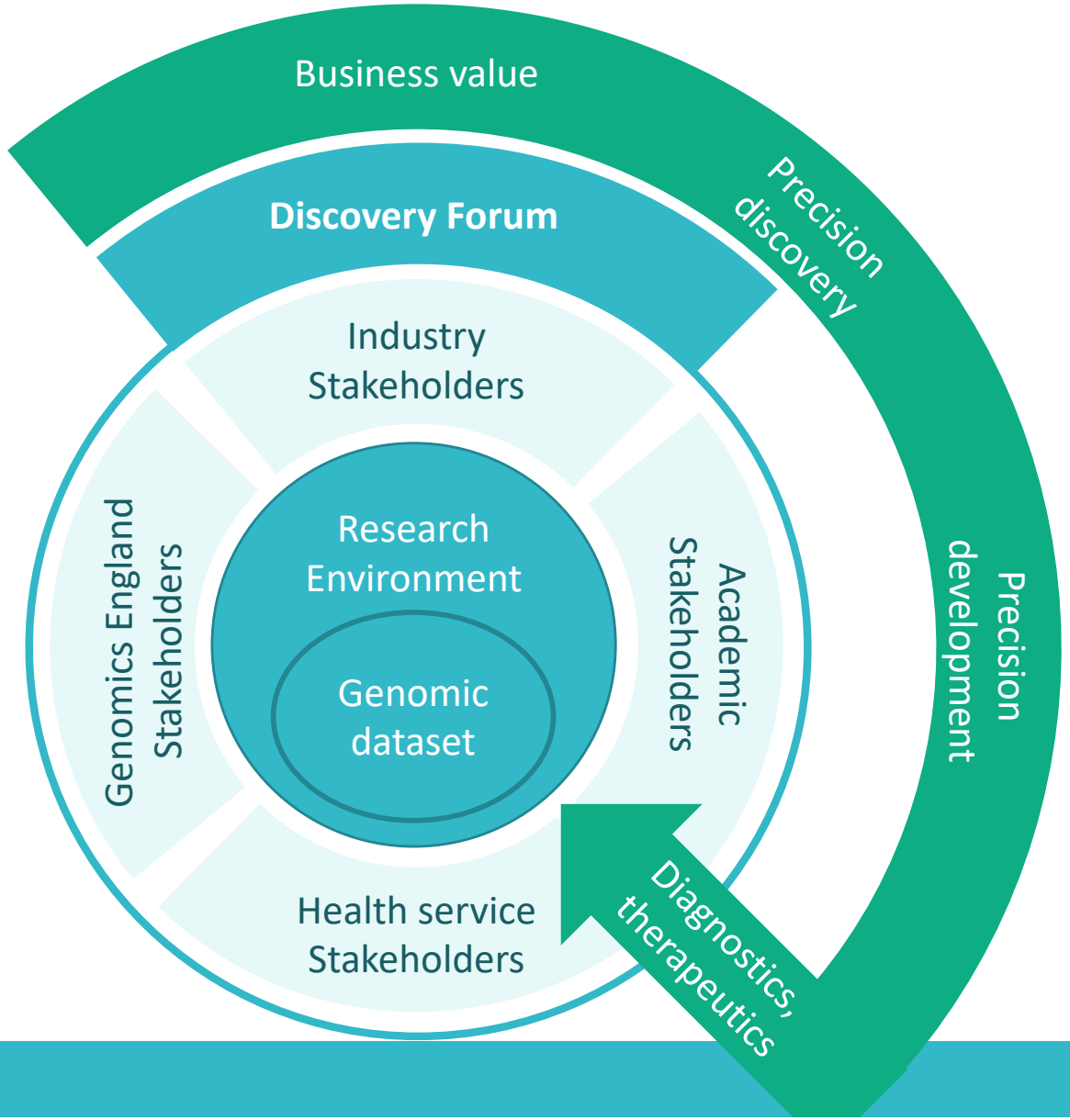
Awaiting – Primary Care, Prescribing Data, Cancer Registries live feed

Opportunities for GeCIPs

- Interpret cases where CIPs (Clinical Interpretation Providers) currently fail
- Develop clinical applications against stored WGS
  - Phamacogenics; Polygenic Risk Scores
- Improved interpretation algorithms
  - machine learning; artificial intelligence
  - using whole genome; predicting variable penetrance
- Experimental investigation of function of variants
  - Is it really the cause? How does it function?

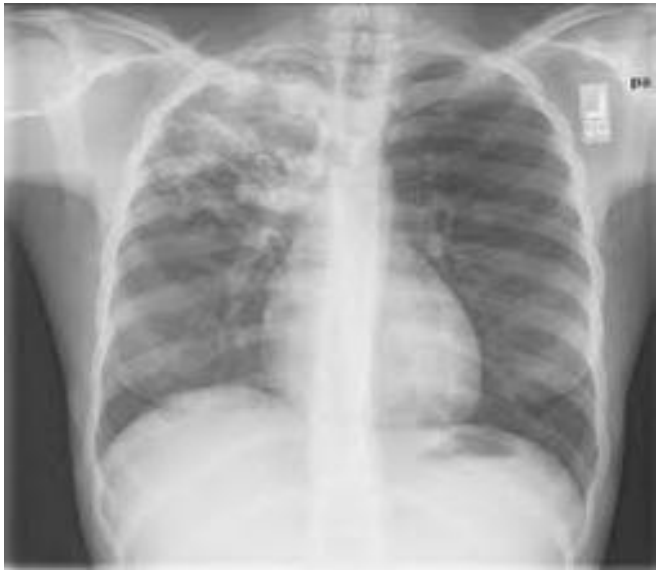
The Discovery Forum

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.

Infections & Pathogens



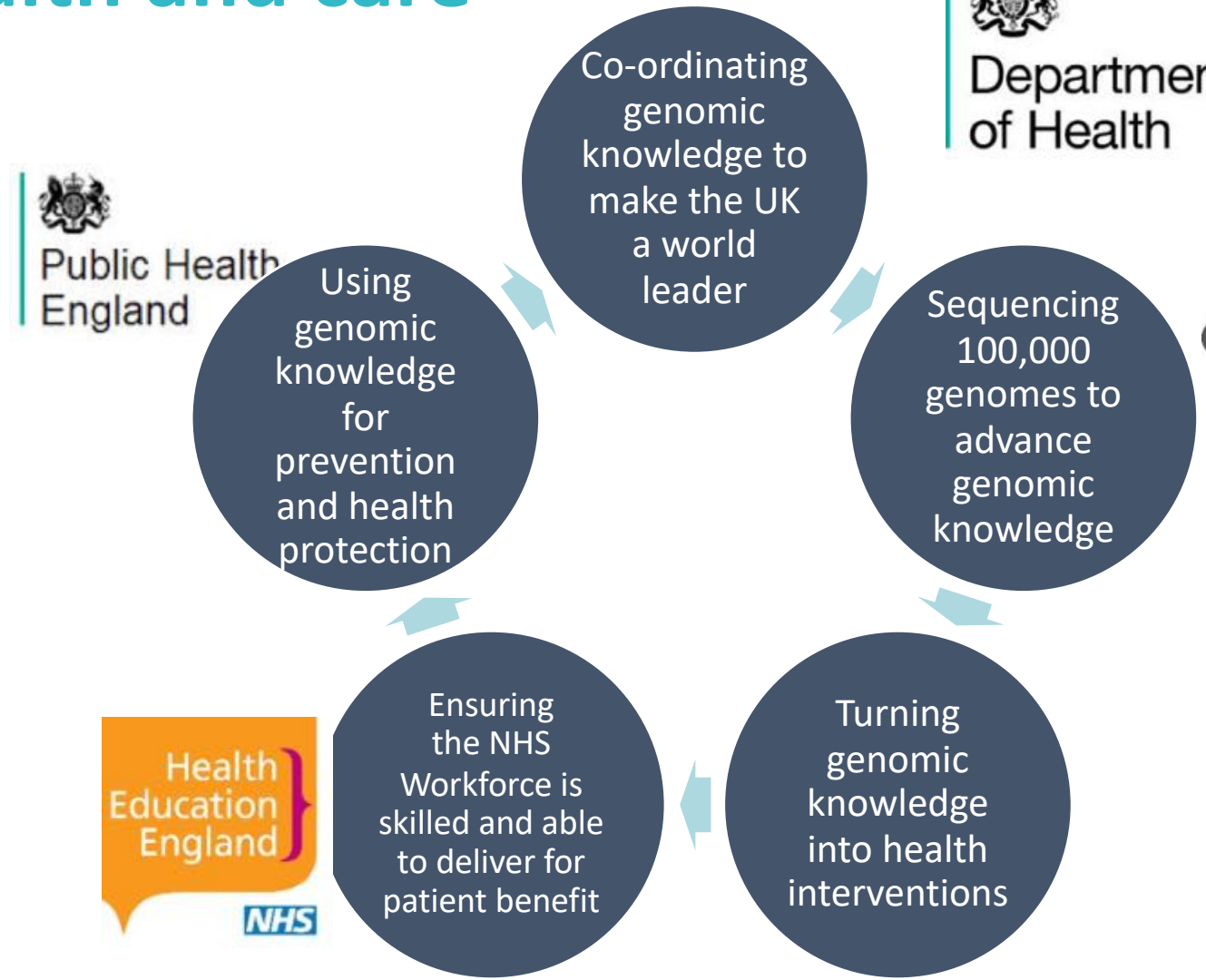
- 10,000 TB strains sequenced
- WGS correctively predicted drug sensitivity enabling precision care for TB
- NHS implemented TB sequencing for diagnosis (1000 organisms/month)
- Global registry of TB resistance

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



Genomics england

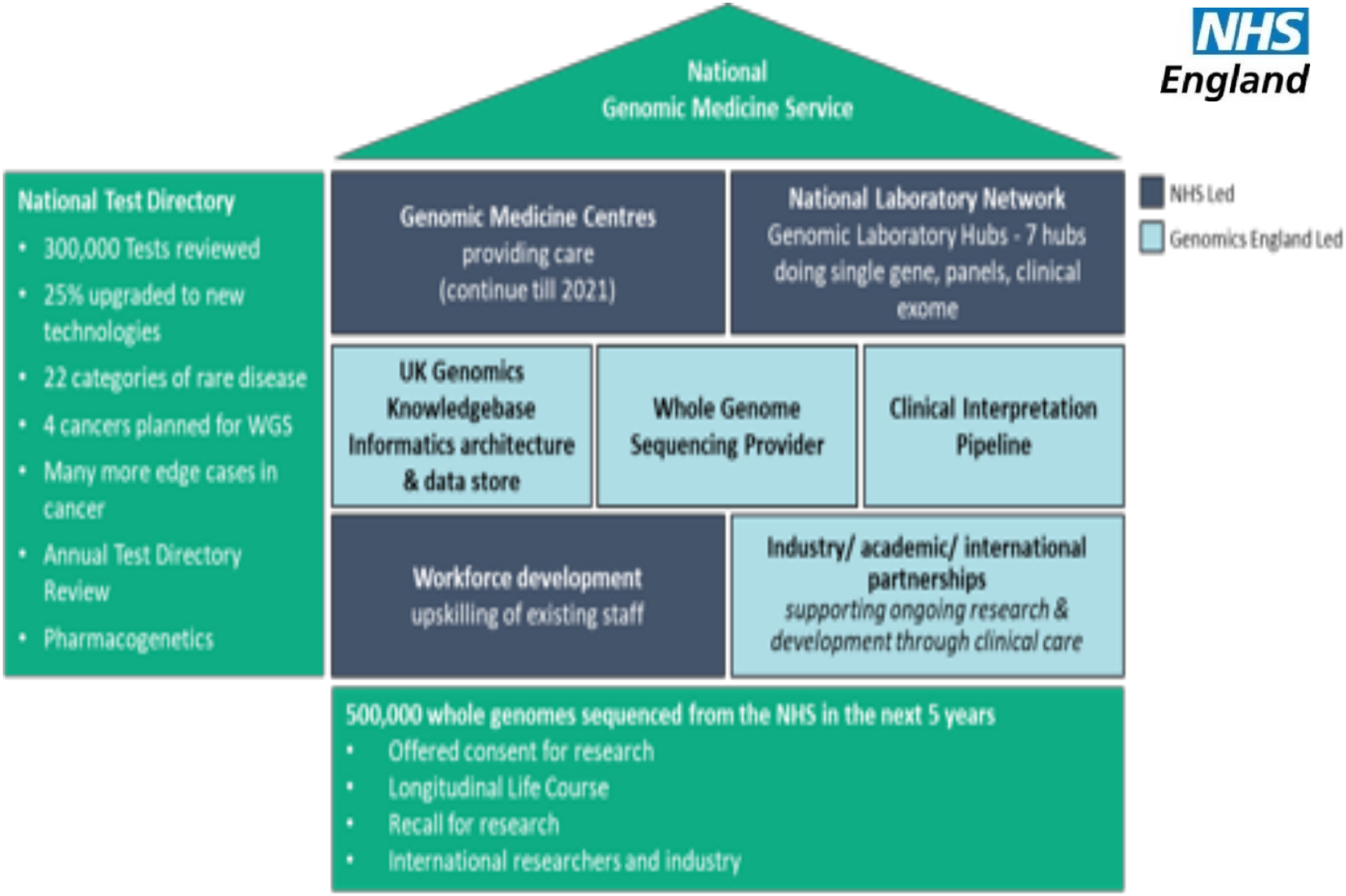
Department of Health

Public Health England

Genomics england

Health Education England NHS

NHS England


National
Genomic Medicine Service
NHS England
National Test Directory
• 300,000 Tests reviewed
• 25% upgraded to new technologies
• 22 categories of rare disease
• 4 cancers planned for WGS
• Many more edge cases in cancer
• Annual Test Directory Review
• Pharmacogenetics
Genomic Medicine Centres
providing care
(continue till 2021)
National Laboratory Network
Genomic Laboratory Hubs - 7 hubs
doing single gene, panels, clinical exome
NHS Led
Genomics England Led
UK Genomics Knowledgebase Informatics architecture & data store
Whole Genome Sequencing Provider
Clinical Interpretation Pipeline
Workforce development
upskilling of existing staff
Industry/ academic/ international partnerships
supporting ongoing research & development through clinical care
500,000 whole genomes sequenced from the NHS in the next 5 years
• Offered consent for research
• Longitudinal Life Course
• Recall for research
• International researchers and industry

Future – UK Life Sciences Strategy

- International Partnerships with
- France, Australia, Hong Kong, British Columbia, Japan

- Cancer Research UK

- Multi-omics and new technologies
- Long read technologies
- cftDNA
- Transcriptomics
- Multi-omics
- Standardisation
- Other disease areas
- Population cohorts

From 100,000 to 5 million

Health and Social Care Secretary Matt Hancock said:

"I'm proud to announce we are expanding our 100,000 Genomes Project so that one million whole genomes will now be sequenced by the NHS and the UK Biobank.

I'm incredibly excited about the potential for this type of technology to improve the diagnosis and treatment for patients to help people live longer, healthier lives – a vital part of our long-term plan for the NHS.

Today's commitments form part of our bold aspiration to sequence 5 million genomes in the UK, using ground-breaking technology to do this within an unprecedented 5-year period."

Industrial Strategy Wave 2

Towards 5 Million Genome Analyses

- 1 Million Whole Genomes (Industrial Strategy)
  500,000 Whole Genomes in UK Biobank
  500,000 Whole Genomes in the NHS

- Circa 1.5 million other genomic tests

- Circa 2.5 million ?whole genomes
- Other diseases connected to the NHS
- Volunteers

- 5 Million Early Detection Cohort
- Longitudinal Life Course Follow Up
- AI, wearables, multi-omics

Rare Diseases & Trials

Cancer Trials

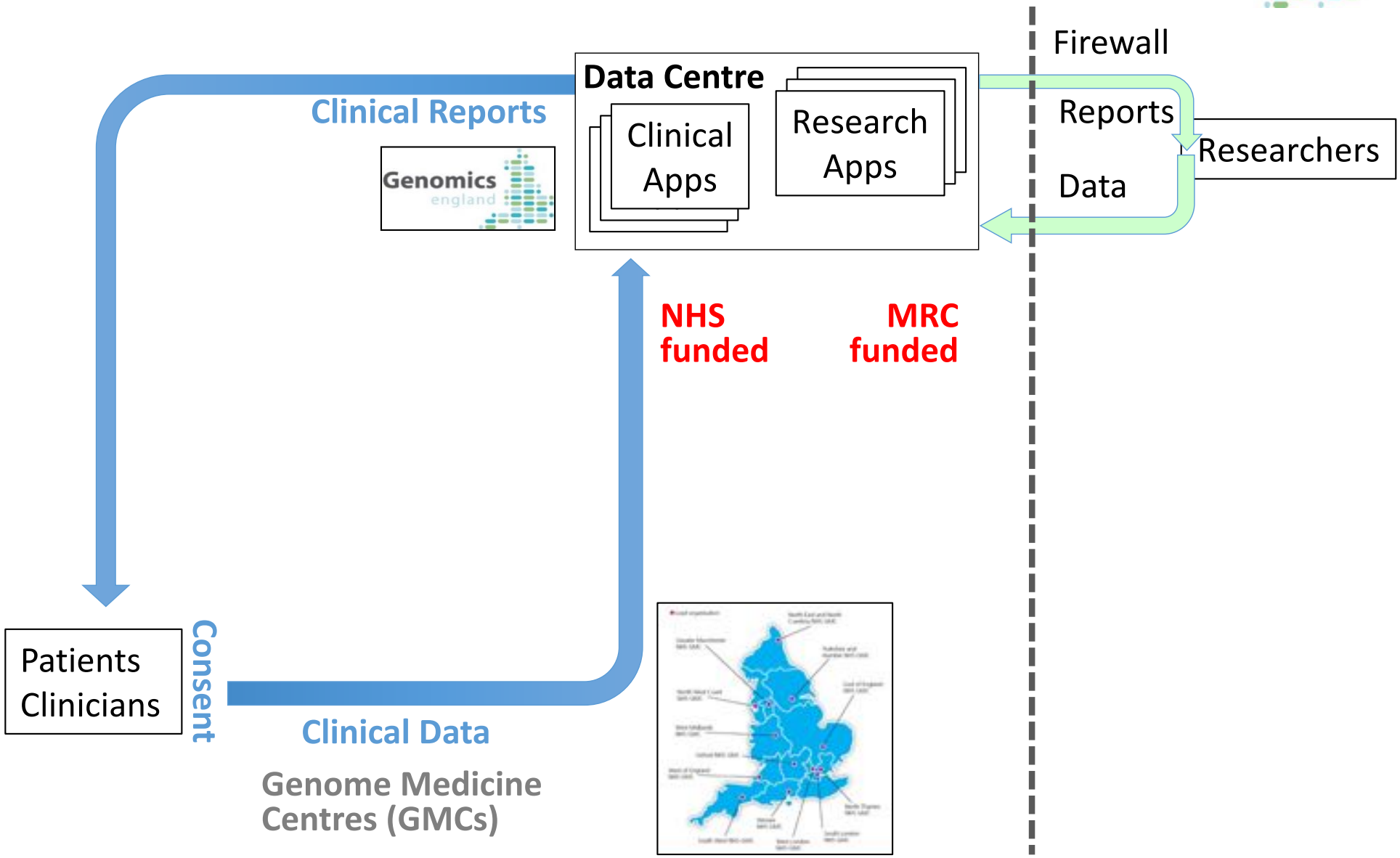
Newborn

Pharmacogenomics
Drug efficacy

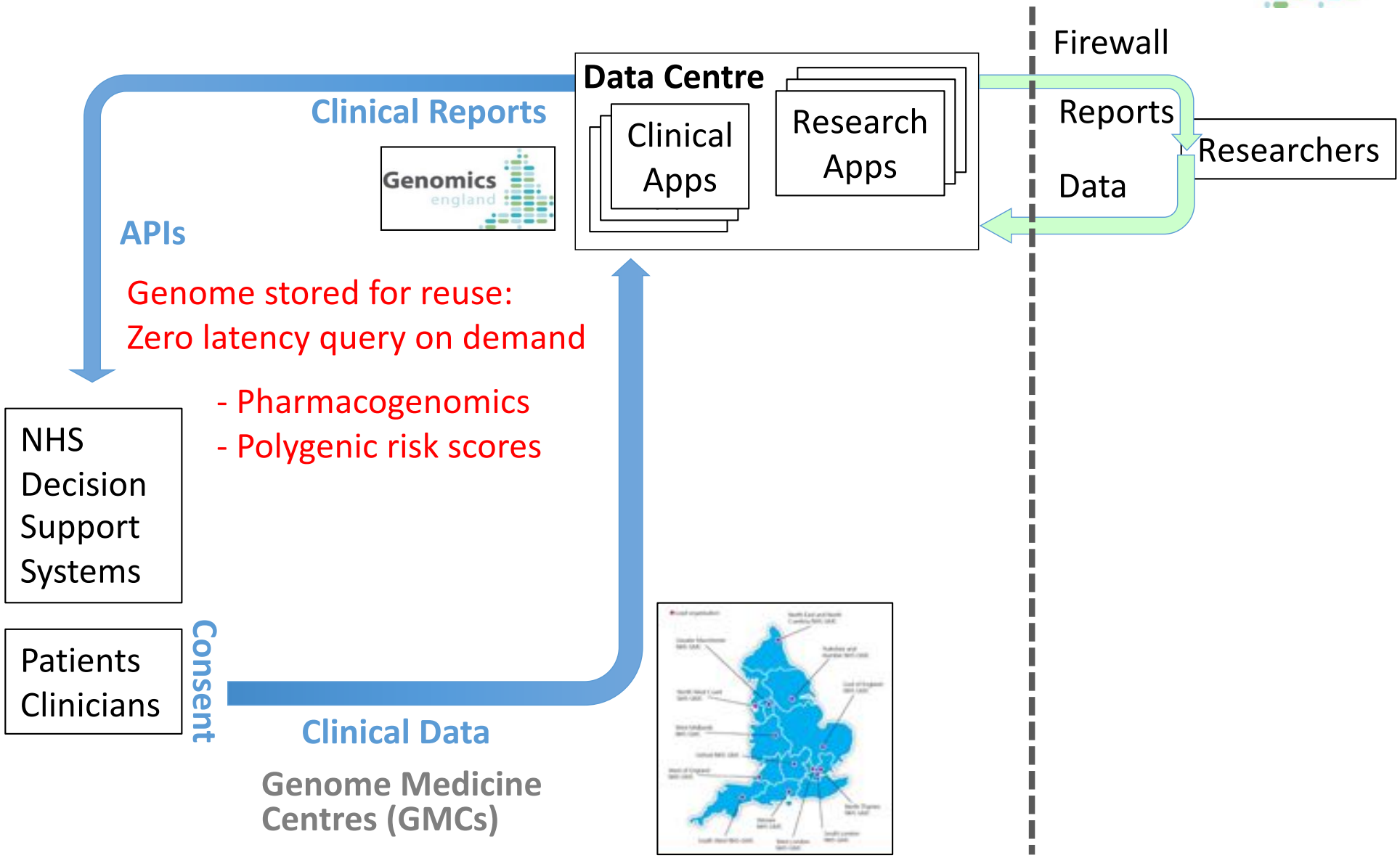
Towards 5 Million consultation

ABPI & our Discovery Forum
Direct industry interaction
Multi-company consortia

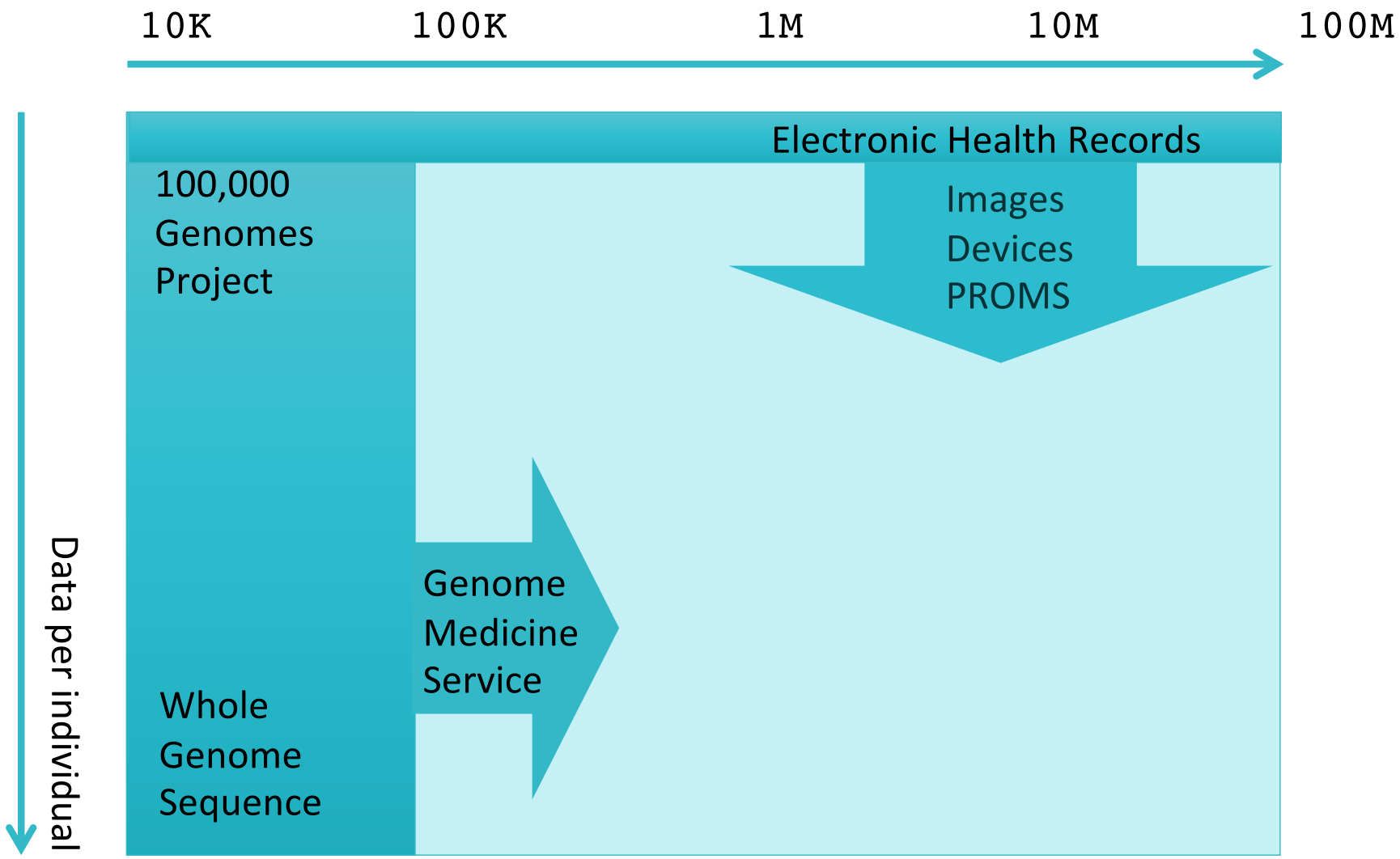
Generic structure for data use



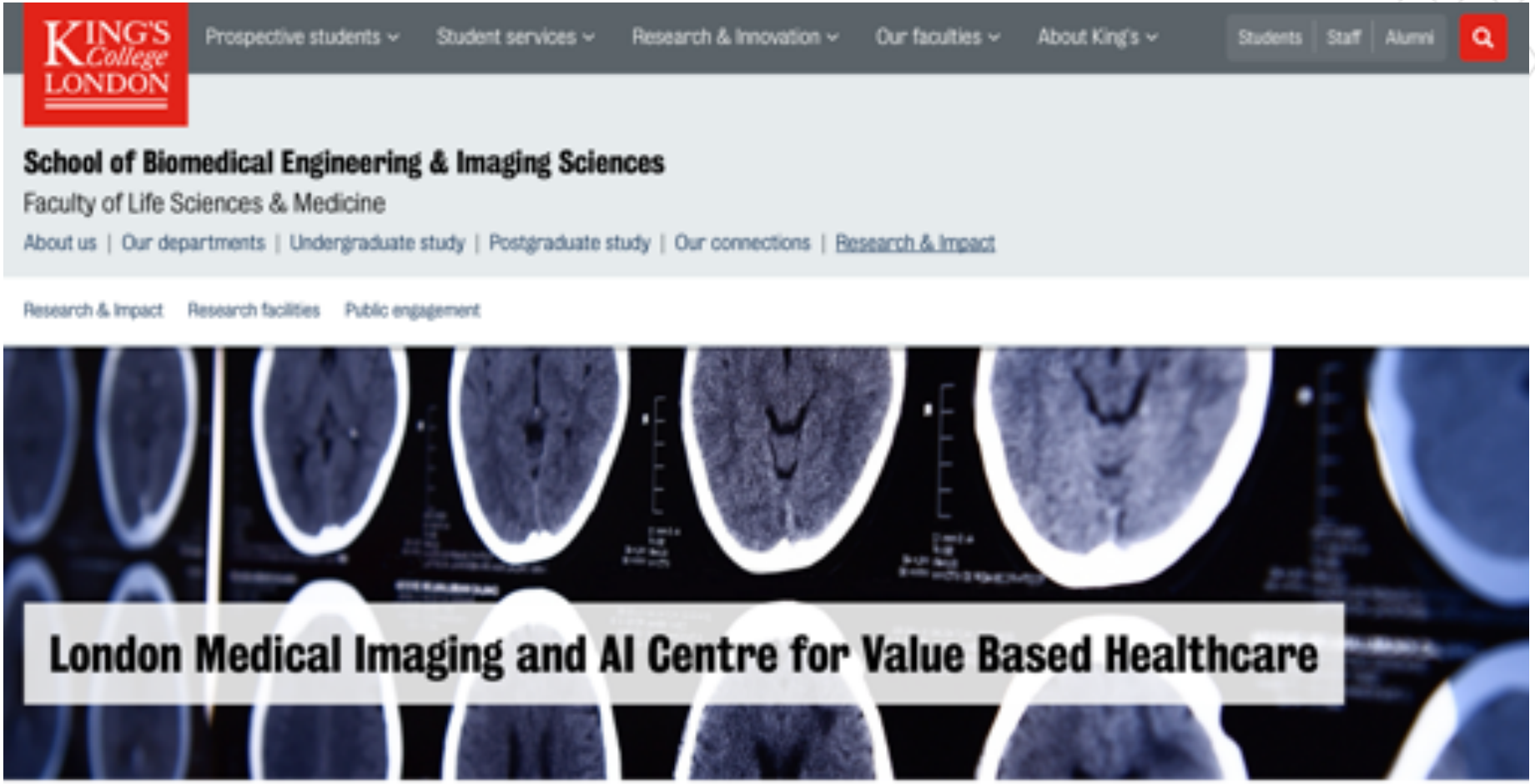
Generic structure for data use



Expanding health data sets

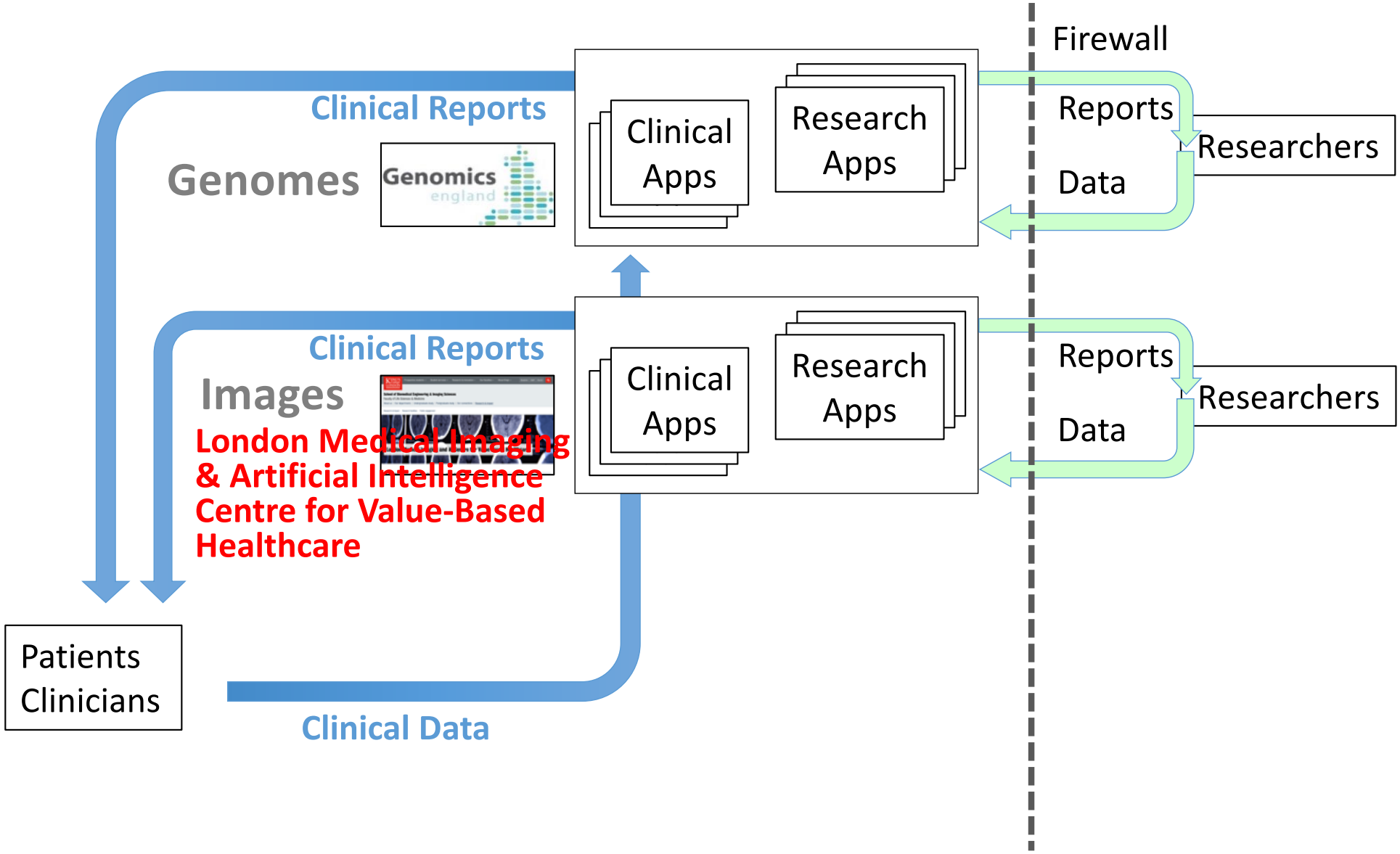


InnovateUK has created five new centres of excellence for digital pathology and imaging, including radiology, using AI medical advances

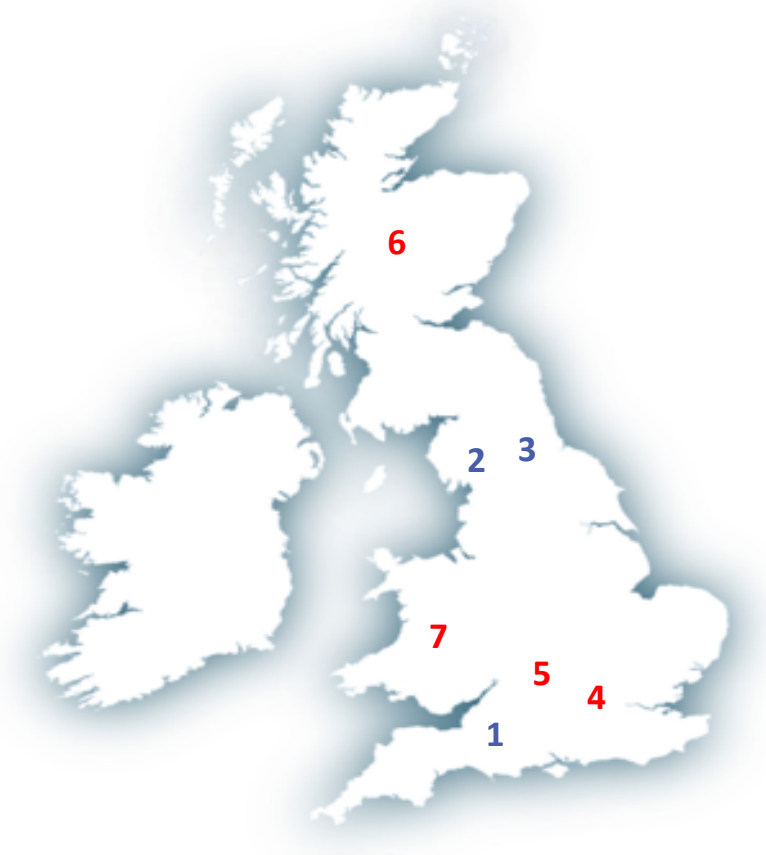


https://www.gov.uk/government/news/artificial-intelligence-to-help-save-lives-at-five-new-technology-centres

Genome, Image data



NHS England Local Health and Care Record Exemplars and Devolved NHS Partnerships

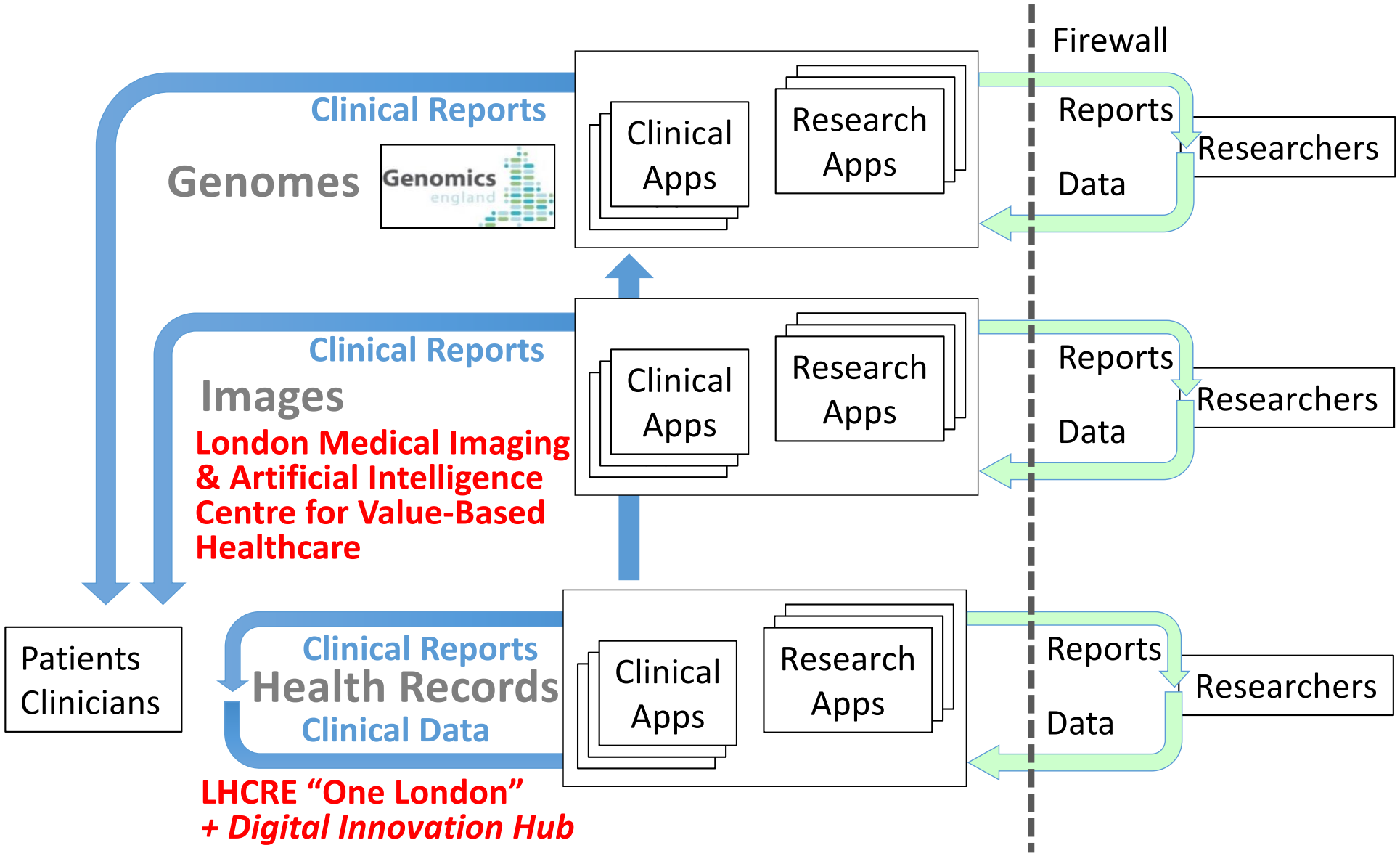


1. Wessex
2. Greater Manchester
3. Yorkshire and the Humber
4. One London
5. Thames Valley and Surrey

6. NES Digital Service

7. NHS Wales

Genome, Image, EHR data



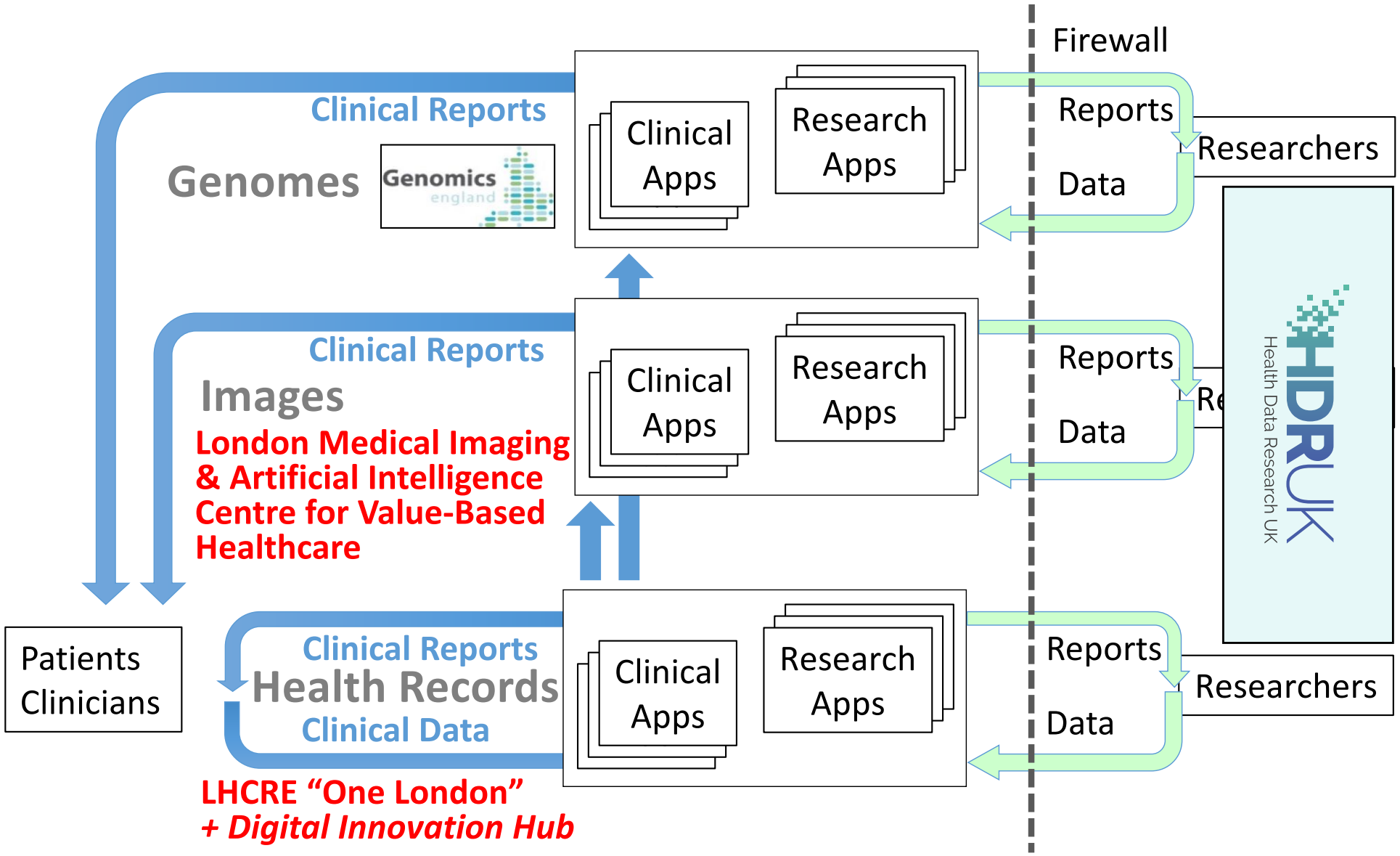
Previous examples represent systems designed to support research and clinical decision support in NHS

- Infrastructure, ethics, engagement designed to facilitate both decision support and research
  - better clinical and patient engagement
  - more immediate clinical benefits from research

- Recognises that most NHS data cannot be moved
  - hardware needs to be hosted within NHS organizations
  - unless funding is sustained, services are shutdown

- Builds on model that Genomics England has tested
  - NHS and MRC jointly funded single data environment that supports both clinical interpretation and research activities

Genome, Image, EHR data



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.

HDR UK triple aim

HDRUK
Health Data Research UK

Scientific programmes	Training the next generation	UK wide expert research data services
Integration of data science with biomedical and health science expertise to perform ground-breaking research, with an initial focus on data analytics, precision medicine, 21st century clinical trials and modernising public health.	To develop novel approaches to research training and mentorship to foster a cadre of health data science researchers, on a substantial scale.	Development and delivery of cutting-edge technologies and trusted research platforms that acquire, store, represent, and process large, multi-dimensional research data.

Trustworthy use of data

We will work in partnership with the public, funders, social scientists and legal/ethical experts to champion the trustworthy use of data.

Initial HDR UK investment supports six sites.

HDRUK
Health Data Research UK

Each works with NHS, industry and the public to translate research into benefits for patients and populations.

1. Wales and Northern Ireland (Swansea and Queen's University Belfast)
2. Midlands (Birmingham, Leicester, Nottingham, Warwick)
3. Scotland (Glasgow, Edinburgh, Dundee, Aberdeen, Strathclyde, St Andrews)
4. London (Imperial, Kings, London School of Hygiene and Tropical Medicine, Queen Mary, UCL)
5. Oxford
6. Cambridge (EBI, Sanger, Cambridge University)

Summary

- Healthcare is a digital outlier
  - Huge potential for health data collection for care and research
  - Behind other people facing industries (Banking, Transport etc.)
- Enough healthcare value to start implementing limited genome medicine in health systems today
  - 100,000 genomes project demonstrates what is possible today
  - Complexity of human biology makes predictive personalized medicine hard
- Research progress will depend on data from more individuals
  - To use healthcare data (largest source) will be dependent on trust
  - Image and monitoring device data will increasingly contribute to personal health record alongside personal genomic data

The 100,000 Genomes Team

- Tom Fowler, Richard Scott, Ellen Thomas, Helen Brittain, Emma Baple, Ariana Tucci, Nirupa Murugaesu, Louise Jones, Clare Craig, Clare Turnbull, Anna Need, Freya Boardman Pretty, Sarah Watters, Lea Lahnstein, Tim Rogers, Ryan Weir, Atul Hatwall, Pete Goddard
- James Holman, Andy Paynton, Mark Brundrett, David Ardley,
- Chris Patch, Fiona Maleady-Crowe,
- Lisa Dinh, Katrina Nevin-Ridley, Yufan Chen
- Katherine Smith, Kristina Ibanez Garikano, Chris Odhams, Alex Stuckey, Ellen McDonagh, Marta Bleda, Alona Sosinsky, Augusto Rendon,
- Mark Caulfield, Peter Counter, Graham Colbert, Nick Maltby, Mark Bale, John Mattick, Sir John Chisholm and 200 GEL Staff.

- Dame Sue Hill, Sandi Deans, Ellen Graham and the NHS in England, the 1500 NHS Staff @13 Genomic Medicine Centres, 7 Genomic Lab Hubs, Northern Ireland, Scotland, Wales and the 3000 Researchers worldwide

This is an NHS Transformation Programme by the NHS for the NHS

Genomics england

Other funders include : Department of Health, NIHR, Wellcome, CRUK, MRC, Illumina and the Devolved administrations of Scotland, Northern Ireland, Wales, NHS England

Thank you to everyone who has taken part in the 100,000 Genomes Project

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