NIHR BioResource
Rare Diseases

Genomics england

The 100 000 Genomes Project

how can it apply to paediatric transfusion ……..

British Blood Transfusion Society

Willem H Ouwehand FMedSci

professor of experimental haematology

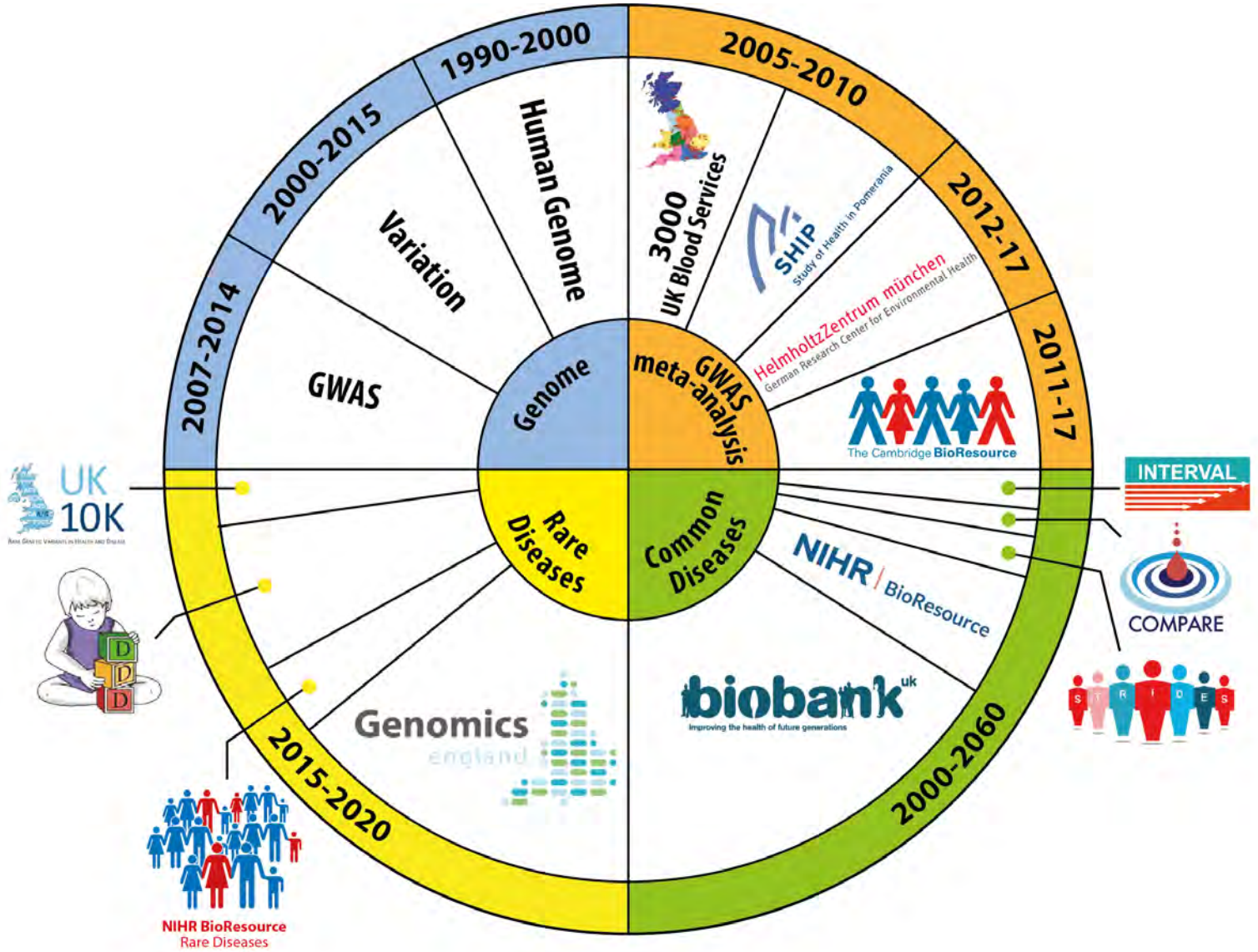
wellcome sanger institute

NHS Blood and Transplant

UNIVERSITY OF CAMBRIDGE

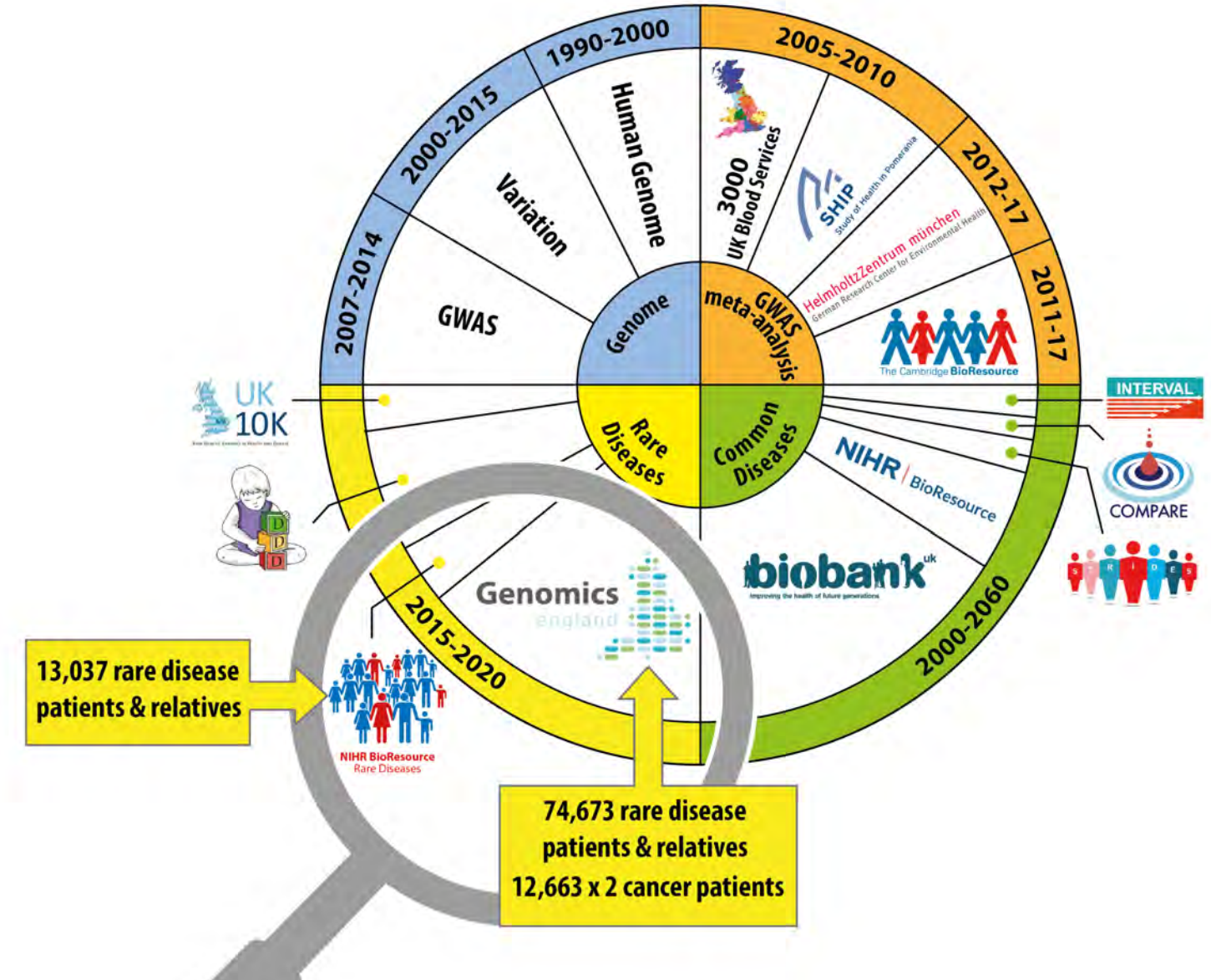
The genomics journey

from genome wide association studies to the genetic roots of rare diseases

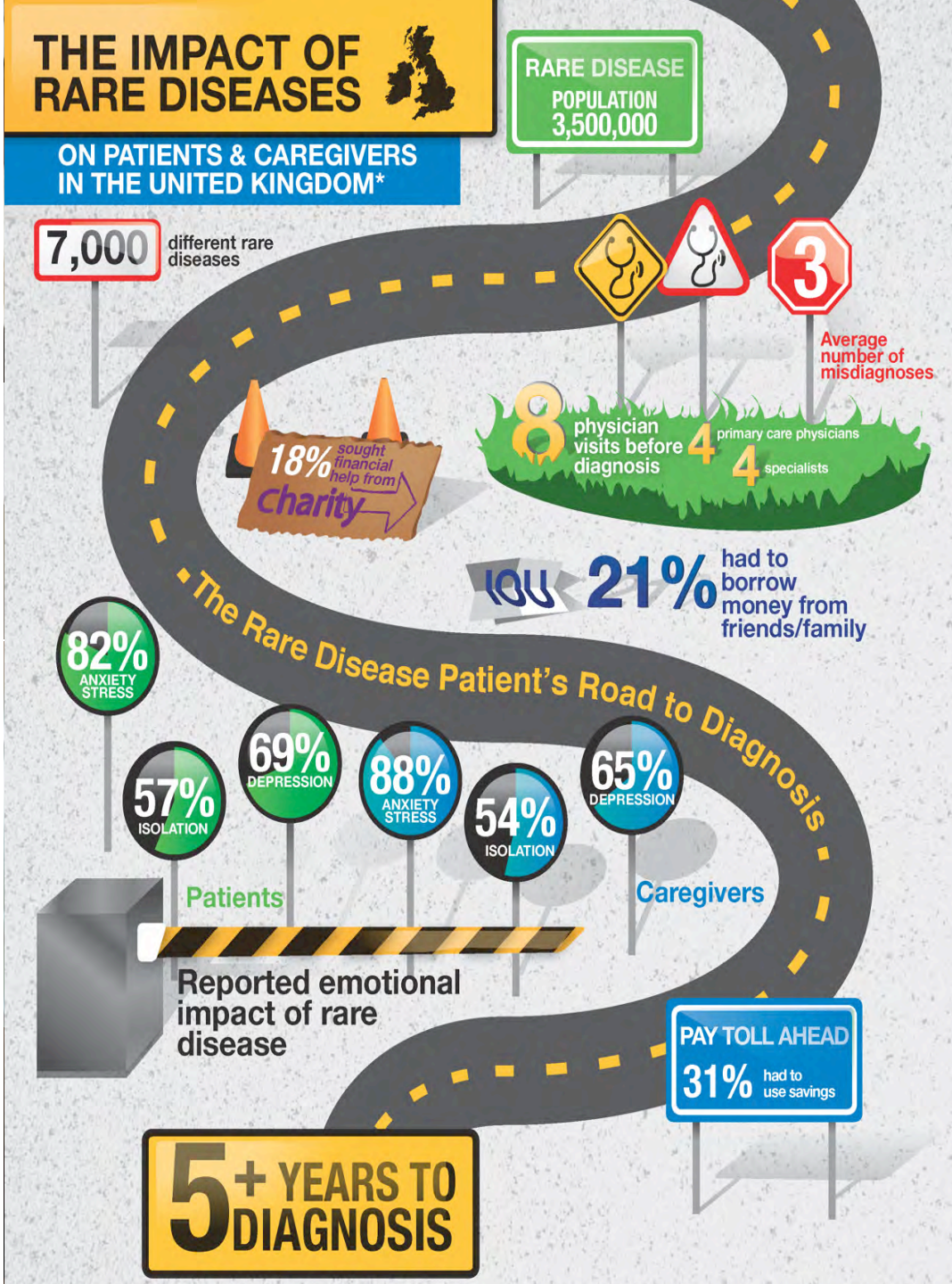


The 100 000 genomes project

bringing whole genome sequencing to the bedside



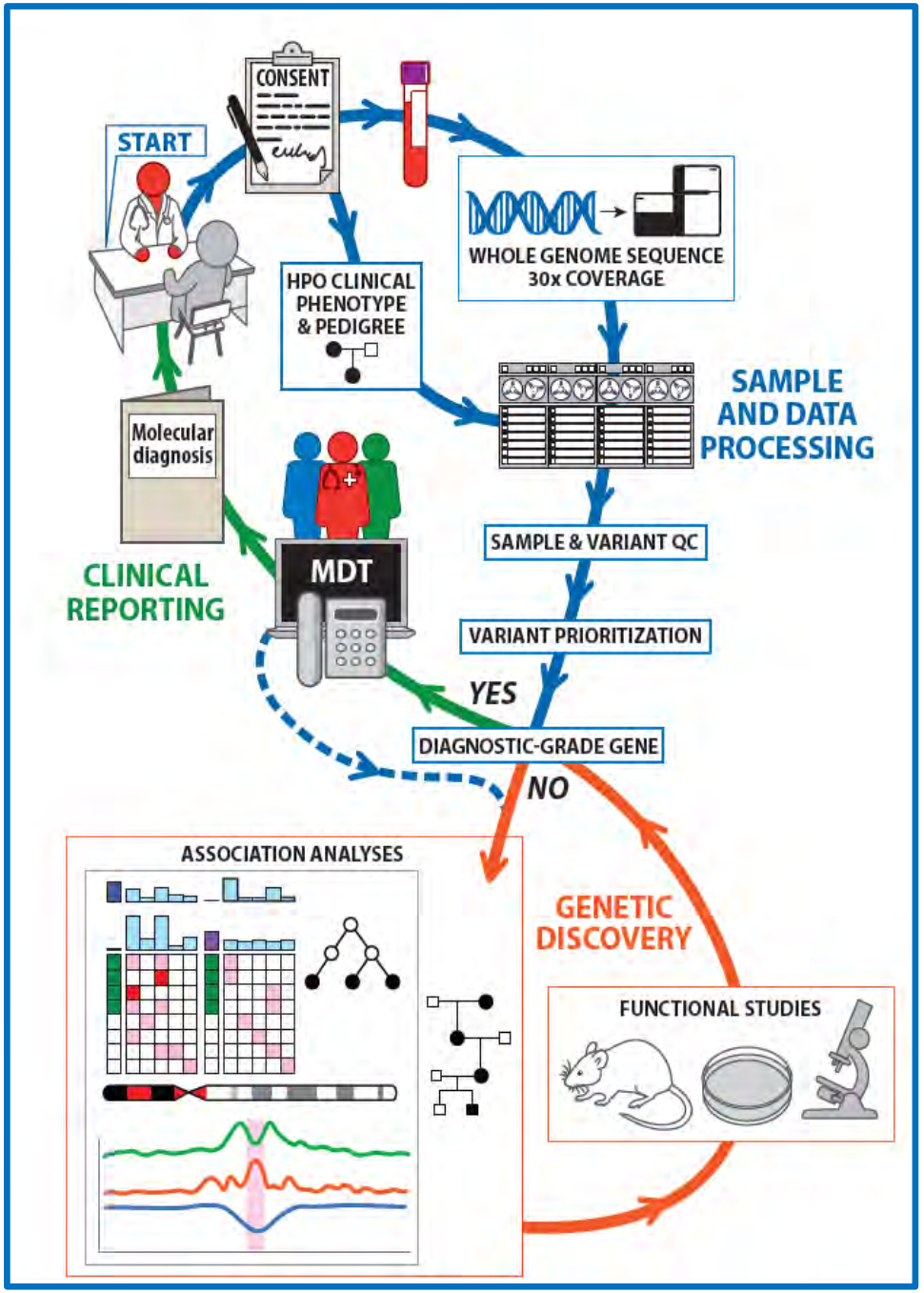
- **7,000** Rare Diseases, most are caused by changes in the DNA code
- **3.5 Million** (**5%**) of UK citizens have ill-health because of Rare Diseases
- Underlying genes have been identified for **halve** of the Rare Diseases

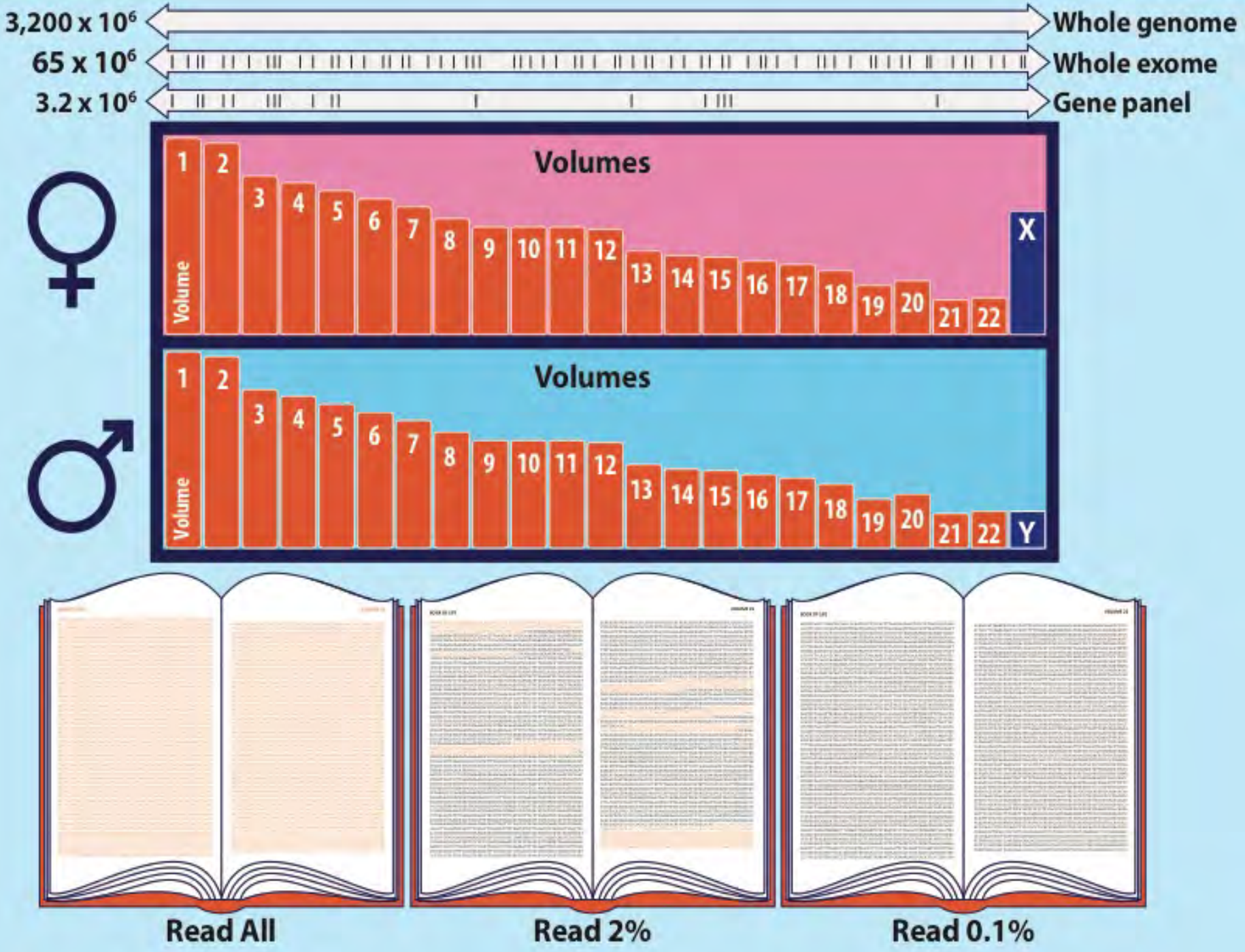



© BBC

100 000 Genomes Project Main Aims

- **Reduce** diagnostic delay
- By embedding **whole genome sequencing** in the NHS
- Report **pertinent findings**
- **Identify** the missing causal genes
- **Develop** new interventions




3,200 x 10⁶
Whole genome
65 x 10⁶
Whole exome
3.2 x 10⁶
Gene panel
Volumes
Volume
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X
Volumes
Volume
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 Y
Read All
Read 2%
Read 0.1%

Your genome

is found in almost every cell of your body and it is the instructions for making you.

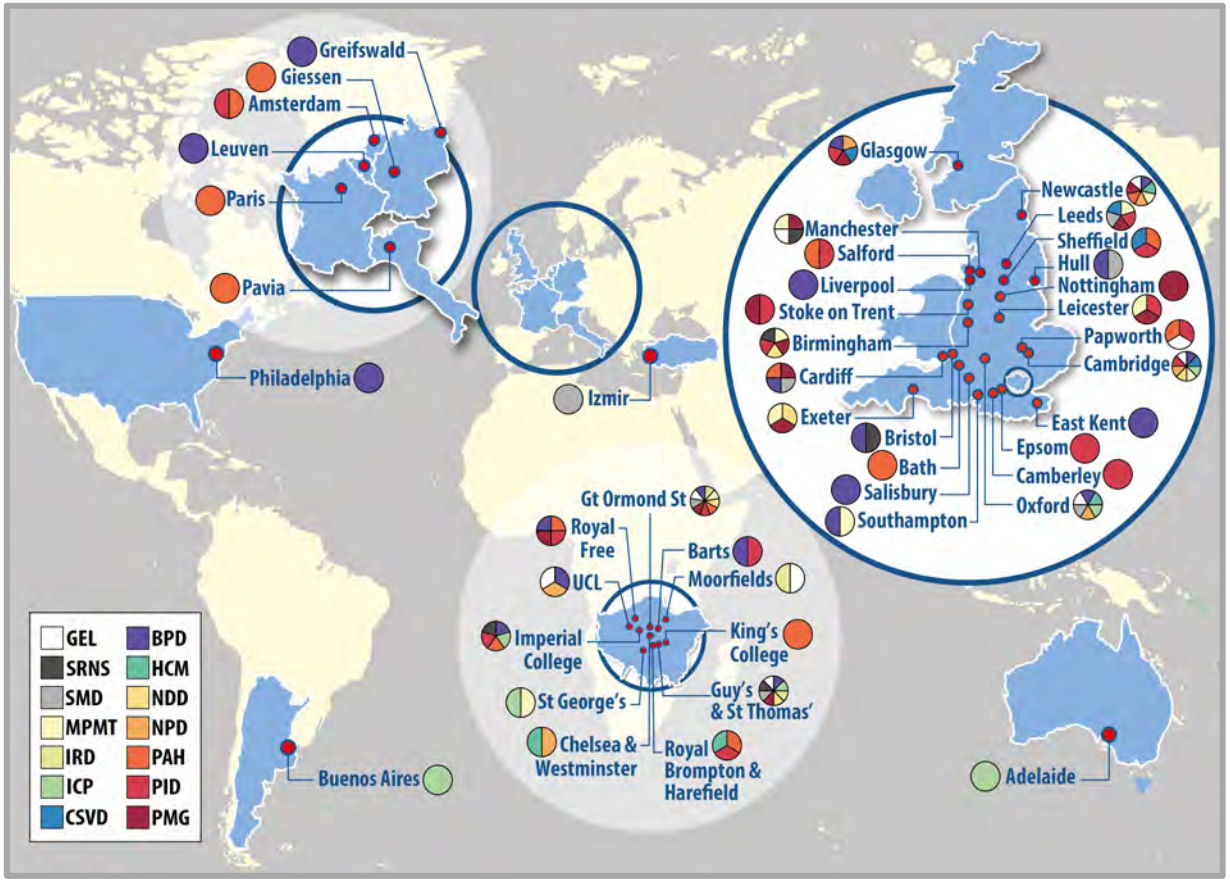
It contains all your **20,000 genes**

It is all **3.2 billion** letters of your DNA

1 genome = 3.2 billion letters of DNA. If it was printed, your genome would fill a stack of paperback books 61m high or fill 200 telephone directories!

The Rare Diseases pilot study

enrolment at 83 hospitals



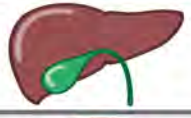
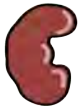
- **57** NHS Hospitals and **26** non-UK Hospitals
- **360** Clinical Care Teams
- **13,037** Patients & Relatives
- Whole Genome Sequencing (WGS) in a single **Accredited** laboratory
- Clinical **Feedback** + Research

NIHR BioResource, Nature (in review)

Diseases of the blood stem cell and haemostasis

4,643 DNA samples from patients across four domains

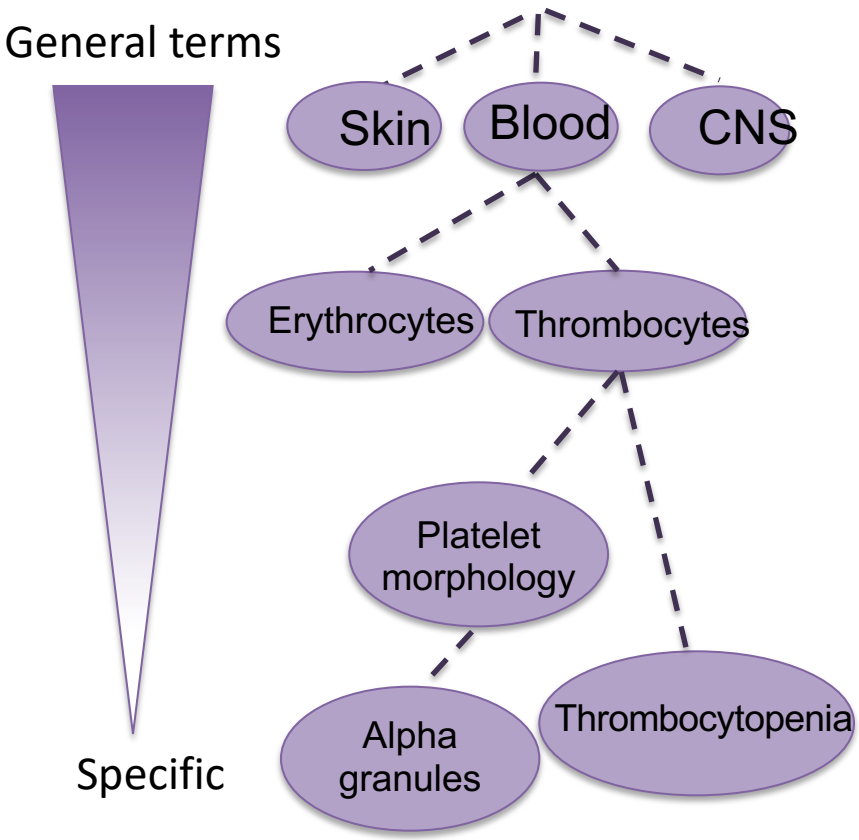
NIHR BioResource Rare Diseases

	Bleeding, thrombotic and Platelet Disorders	BPD		Multiple Primary Malignant Tumours	MPMT
	Cerebral Small Vessel Disease	CSVD		Neurological and Developmental Disorders	NDD
	Ehler-Danlos Syndromes	EDS		Neuropathic Pain Disorders	NPD
Genomics england	Rare Diseases Pilot-II	GEL		Pulmonary Arterial Hypertension	PAH
	Hypertrophic Cardiomyopathy	HCM		Primary Immune Disorders	PID
	Intrahepatic Cholestasis of Pregnancy	ICP		Primary Membranoproliferative Glomerulonephritis	PMG
	Inherited Retinal Disorders	IRD		Stem cell and Myeloid Disorders	SMD
	Leber Hereditary Optic Neuropathy	LHON		Steroid Resistant Nephrotic Syndrome	SRNS
biobank uk Improving the health of future generations				UK Biobank – Extreme Red Cell Traits	UKBio

infarcts and leukoencephalopathy (CARASIL); Cerebroretinal microangiopathy with calcifications and cysts; Charge syndrome; Chediak-Higashi syndrome; Chediak-Higashi syndrome; Cherubism; Chronic granulomatous disease; Chronic infections; Chronic Mucocutaneous Candidiasis (CMC); CINCA syndrome; Muckle-Wells syndrome; Cohen syndrome; Combined factor V and VIII deficiency; Combined immunodeficiency; Complement factor 8 defect; Complement factor B deficiency; Complement factor D deficiency; Complement factor H deficiency; Complement factor I deficiency; Congenital amegakaryocytic thrombocytopenia (CAMT); Congenital disorder of glycosylation; Congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD); Coronin-1A deficiency; CVID; DCLRE1C (Artemis) deficiency ; Deficiency of phospholipase A2, group IV A; Dense deposit disease, Macular degeneration, Membrano-proliferative Glomerulonephritis. Complement factor H deficiency; Dense granule abnormality; Di George syndrome; Diamond Blackfan anemia 15 with mandibulofacial dysostosis; Diamond-Blackfan anemia; Diamond-Blackfan anemia 10; DNA ligase I deficiency; DNA Pkcs deficiency; Dock 2 deficiency, Immunodeficiency 40; Dursun syndrome; Dyserythropoietic anemia; Dyserythropoietic anemia, congenital, type Ia; Dyskeratosis congenita; Dyskeratosis congenita; Dyskeratosis congenita, autosomal dominant 1; Dyskeratosis congenita, autosomal recessive 1; Dyskeratosis congenita, autosomal recessive 2; Dyskeratosis congenita, X-linked; Dyskeratosis congenita; Pulmonary fibrosis and/or bone marrow failure; Dyskeratosis congenita; Revesz syndrome; E47 TF deficiency; Early onset inflammatory bowel disease; Ectodermal dysplasia; Ehlers-Danlos syndrome; Ehlers-Danlos syndrome; Encephalopathy; Epidermodysplasia verruciformis; Fabry disease; Factor V deficiency; Factor VII deficiency; Factor X deficiency; Factor XI deficiency; Factor XIII deficiency; Familial cold autoinflammatory syndrome; Familial hemophagocytic lymphohistiocytosis; Familial Mediterranean fever; Familial platelet disorder with predisposition to acute myelogenous leukemia; Fanconi anemia; Fanconi anemia, complementation group B; Fanconi anemia, complementation group E; Fanconi anemia, complementation group T; Fever Syndromes and Related Diseases, Aicardi-Goutieres syndrome 6 (AGS6); Fibrinogen deficiency; FILS syndrome; Folate malabsorption, hereditary; Ghosal syndrome; Glanzmann thrombasthenia; Glycogen storage disease Ia; Glycogen storage disease Ib; Granulomatous disease; Gray platelet syndrome; Gray platelet-like syndrome; Griscelli syndrome; Growth hormone insensitivity with immunodeficiency; Haemophilia A; Haemophilia B; Hemolytic anemia, CD59-mediated; Hemolytic disease of the newborn; Hemolytic uremic syndrome; Hemophagocytic lymphohistiocytosis; Hemorrhage, intracerebral, susceptibility to ICH; Hennekam lymphangiectasia-lymphedema; Heparin cofactor 2 deficiency; Hepatic venoocclusive disease with immunodeficiency; Hepatocellular carcinoma; Hereditary hemorrhagic telangiectasia; Hermansky-Pudlak syndrome; Hermansky-Pudlak syndrome; Herpes simplex encephalitis; Histidine-rich glycoprotein deficiency; Histiocytosis-lymphadenopathy plus syndrome; Hoyeraal-Hreidarsson syndrome; Hoyeraal-Hreidarsson syndrome/ Dyskeratosis congenita, autosomal dominant 4; Dyskeratosis congenita, autosomal recessive 5; Hyper-IgD syndrome; Hyper-IgE recurrent infection syndrome; IBD-1, inflammatory skin; IL7Ra deficiency; Immunodeficiency; Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX); Infections, recurrent, with encephalopathy, hepatic dysfunction, and cardiovasuclar malformations; Inflammatory bowel disease; INO80 deficiency, HIGM; Interleukin-1 receptor antagonist deficiency; Interleukin-2 receptor, alpha chain, deficiency of; IRAK4 deficiency; IRF7 deficiency; Isolated congential asplenia; JAK3 deficiency; Kappa light chain deficiency; Leukemia, acute myeloid; Platelet disorder, familial, with associated myeloid malignancy; Leukocyte adhesion deficiency; Leukocyte integrin adhesion deficiency, type III; LIG4 syndrome; LIG4 syndrome; Lupus; Lymphedema-distichiasis syndrome; Lymphoproliferative syndrome; Macrothrombocytopenia; Macrothrombocytopenia ; Macrothrombocytopenia and sensorineural hearing loss; Macrothrombocytopenia, Beta-tubulin 1 related; Malignant hyperthermia susceptibility 6; MASP2 deficiency; May-Hegglin and other MYH9 disorders; MHC class II deficiency, complementation group B; Migraine, familial hemiplegic; Mismatch repair cancer syndrome; Multiple coagulation factor deficiency type 2; Multiple coagulation factor deficiency type 3; Multiple intestinal atresia and severe combined immunodeficiency (MINAT); Myeloperoxidase deficiency; Myopathy associated with thrombocytopenia; Natural killer cell and glucocorticoid deficiency with DNA repair defect; Nephropathy due to CFHR5 deficiency, Hemolytic uremic syndrome, atypical, susceptibility to; Netherton syndrome; Neutropenia; Neutropenia; Neutropenia; Neutrophil immunodeficiency syndrome; Neutrophilia; Nijmegen breakage syndrome; Nik deficiency, Primary Immunodeficiency with Multifaceted Aberrant Lymphoid Immunity; Papillon-Lefevre syndrome; Paris-Trousseau thrombocytopenia and Jacobson syndrome; Periodic fever, familial; Periodontitis; Pityriasis rubra pilaris; Plasminogen activator Inhibitor 1 deficiency; Plasminogen deficiency; Platelet-type bleeding disorder 18; Poikiloderma with neutropenia; Poikiloderma with neutropenia; Polyarteritis nodosa, childhood-onset, recurrent fever, early-onset stroke, low IgM, Hypogamma, lymphopenia; Polyglucosan body myopathy, early-onset; Porokeratosis; Properdin deficiency; Protein C deficiency; Protein S deficiency; Prothrombin deficiency; Pseudoxanthoma elasticum ; Psoriasis, generalized pustular; Pulmonary fibrosis and/or bone marrow failure; Pulmonary hypertension; Pulmonary venoocclusive disease 2 ; Pyogenic bacterial infections; Pyogenic sterile arthritis; Quebec platelet disorder; RAG1 deficiency; RAG2 deficiency; Ras associated lymphoproliferative disease (RALD); Reticular dysgenesis, AK2 deficiency; Reticular skin hyperpigmentationdystrophic nails, osteoporosis, premalignant leukokeratosis of the mouth mucosa, palmar hyperkeratosis, anemia and pancytopenia; RhoH deficiency; RIDDLE syndrome; Schimke immunoosseous dysplasia; SCID; Scott syndrome; Severe combined immunodeficiency; Severe combined immunodeficiency with microcephaly, growth retardation, and sensitivity to ionizing radiation; Severe congenital neutropenia; Shwachman-Bodian-Diamond syndrome; Shwachman-Diamond syndrome; Sickle cell disease; Specific granule deficiency; Spinocerebellar ataxia; STAT2 deficiency; STING-associated vasculopathy, infantile-onset; Stormorken syndrome; Surfactant metabolism dysfunction, pulmonary; Susceptibility to candidasis & Mycobacterial infection; Susceptibility to mycobacterial infection; Susceptibility to pulmonary hypertension ; Systemic lupus erythematous; T-cell immunodeficiency; Telangiectasia, hereditary hemorrhagic; Thrombocytopenia; Thrombocytopenia; Thrombocytopenia 2; Thrombocytopenia-absent radius syndrome; Thrombocytopenia-absent radius syndrome (TAR); Thrombocytopenia, congenital amegakaryocytic; Thrombocythemia; Myelofibrosis with myeloid metaplasia; Thrombocytopenia, red cell macrocytosis and predisposition to lymphoblastic leukaemia; Thrombocytopenia, with or without dyserythropoietic anemia; Thrombocytopenia with beta-thalassemia; Anemia, X-linked, with/without neutropenia and/or platelet abnormalities; Thrombomodulin deficiency; Thromboxane A2 receptor defect; Thyroid dyshormonogenesis; Tissue Plasminogen Activator deficiency; TPP2 deficiency; Transcobalamin-2 precursor ; Trichohepatoenteric syndrome; Trypanosomiasis; Vasculopathy, retinal, with cerebral leukodystrophy; Vici syndrome; von Willebrand disease; WHIM syndrome; WHIM syndrome; Wiskott-Aldrich syndrome; Wiskott-Aldrich syndrome; Wiskott-Aldrich syndrome; Thrombocytopenia; Zap-70 deficiency; 3-methylglutaconic aciduria, type VII, with cataracts, neurologic involvement and neutropenia;

To capture the diversity of symptoms

doctors and nurses were trained to use the library of thousands of HPO terms



Human Phenotype Ontology (HPO)

Translate clinical picture

Standardised

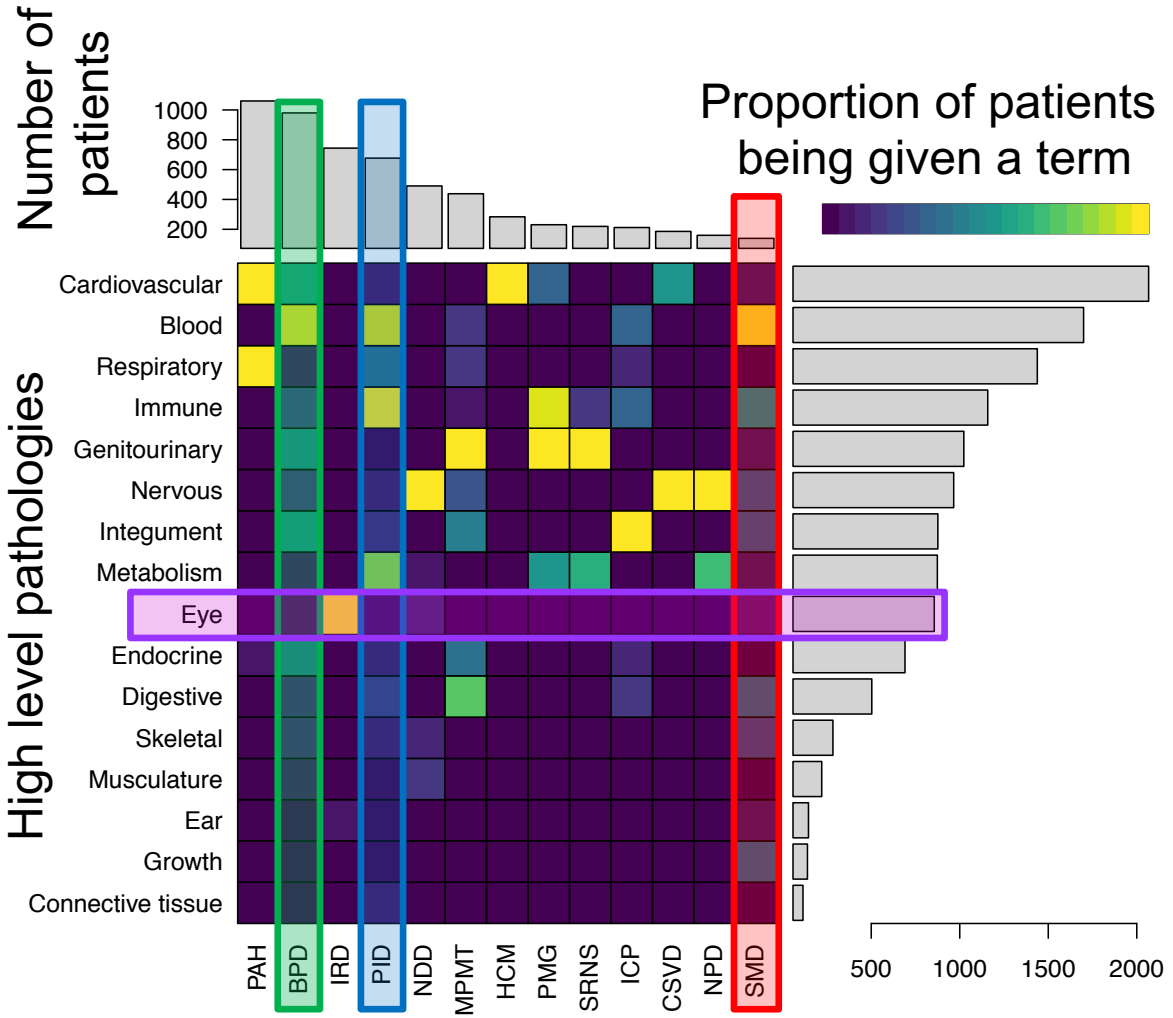
Computable

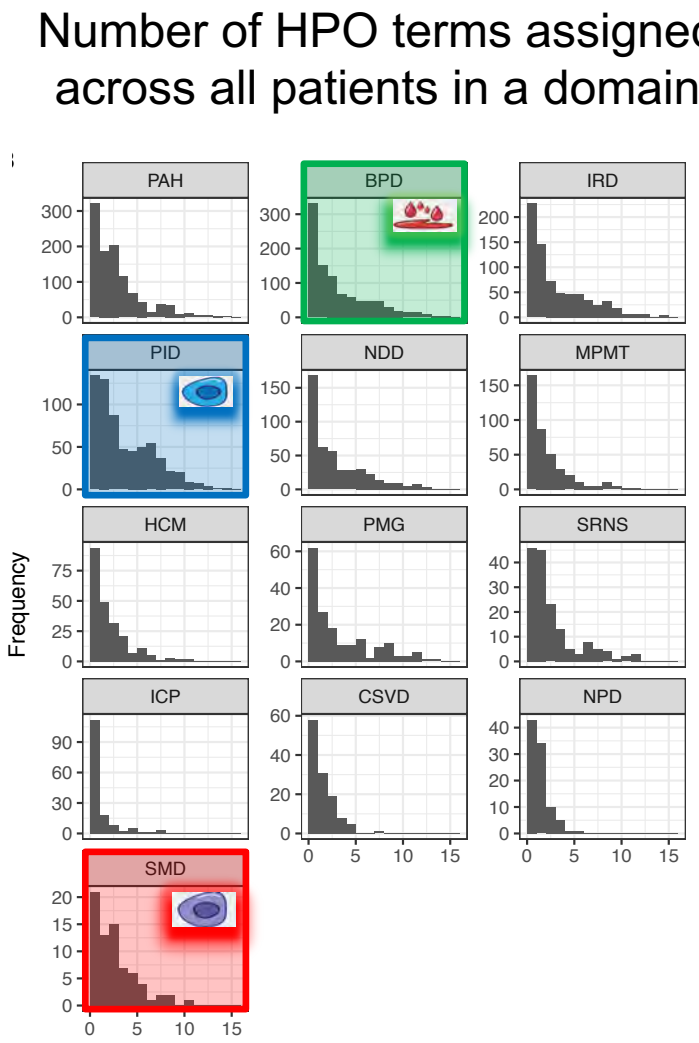
Westbury *et al*, Genome Medicine 2015

Köhler *et al,* NAR 2019

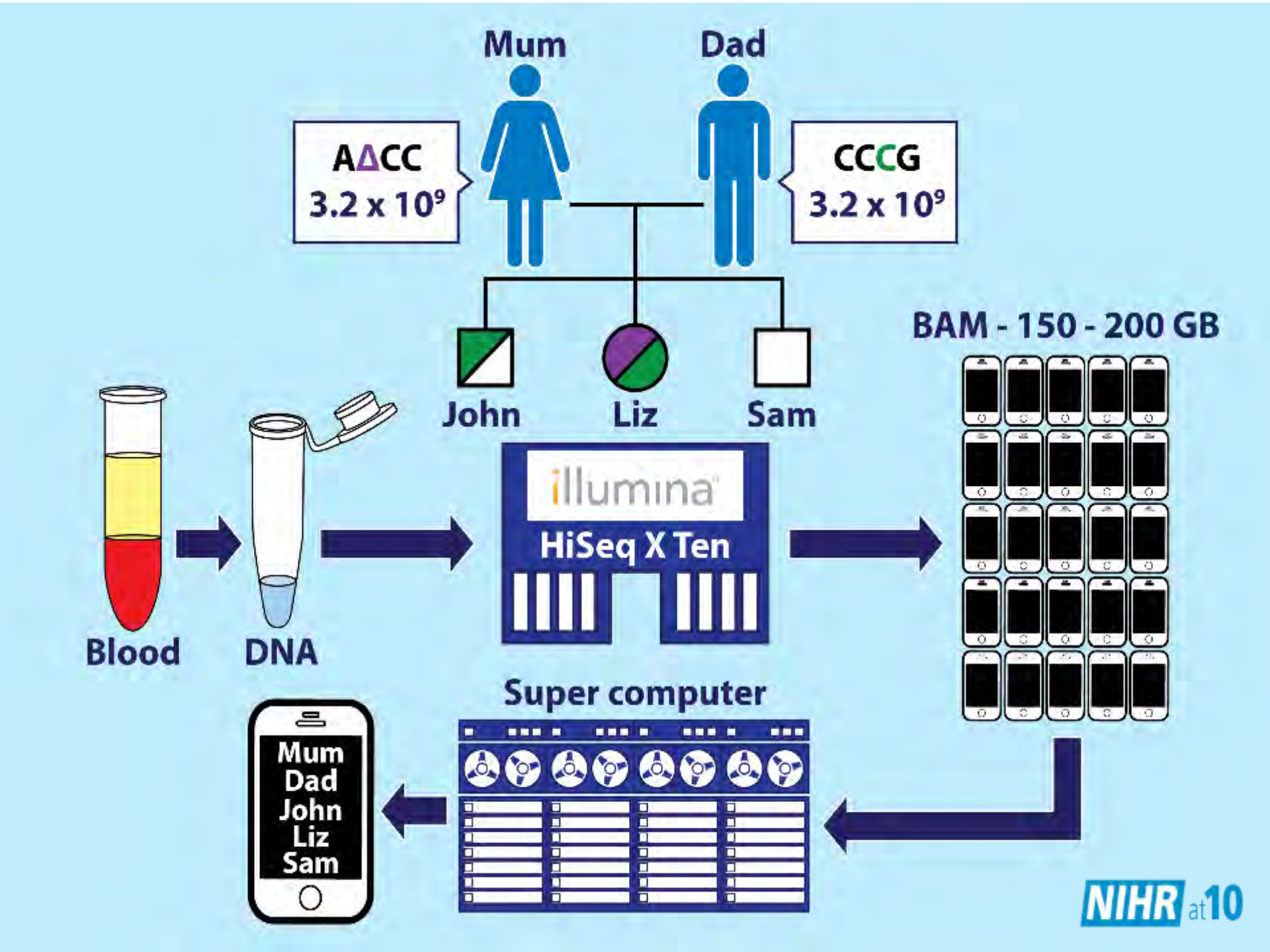
HPO coding of disease phenotypes in rare diseases patients

shows disease-causing mutations play out in different organ systems



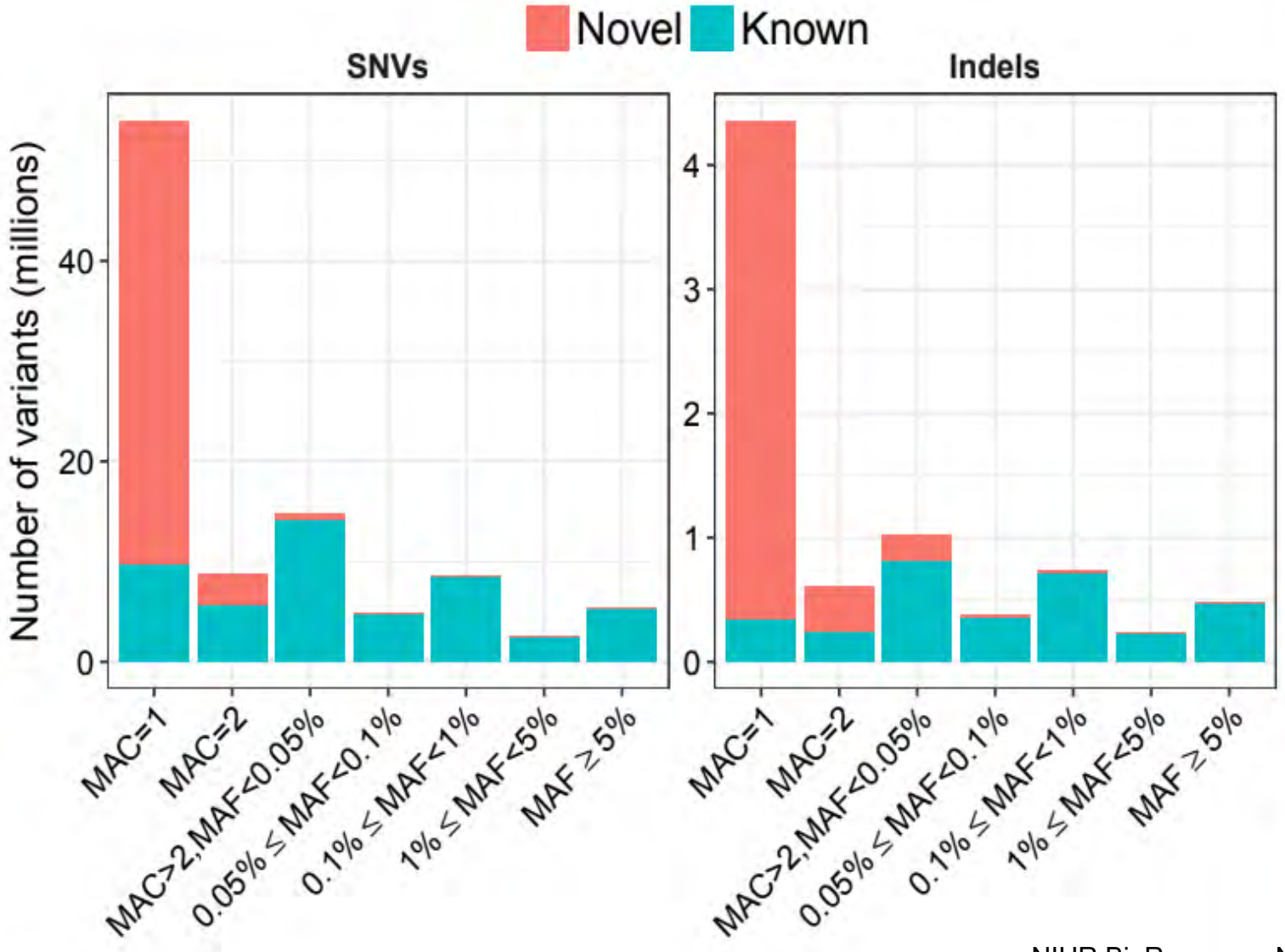


NIHR BioResource, Nature (in review)


Mum
Dad
AΔCC
3.2 x 10⁹
CCCG
3.2 x 10⁹
John
Liz
Sam
BAM - 150 - 200 GB
Blood
DNA
illumina
HiSeq X Ten
Super computer
Mum
Dad
John
Liz
Sam
NIHR at 10

176 million unique variants

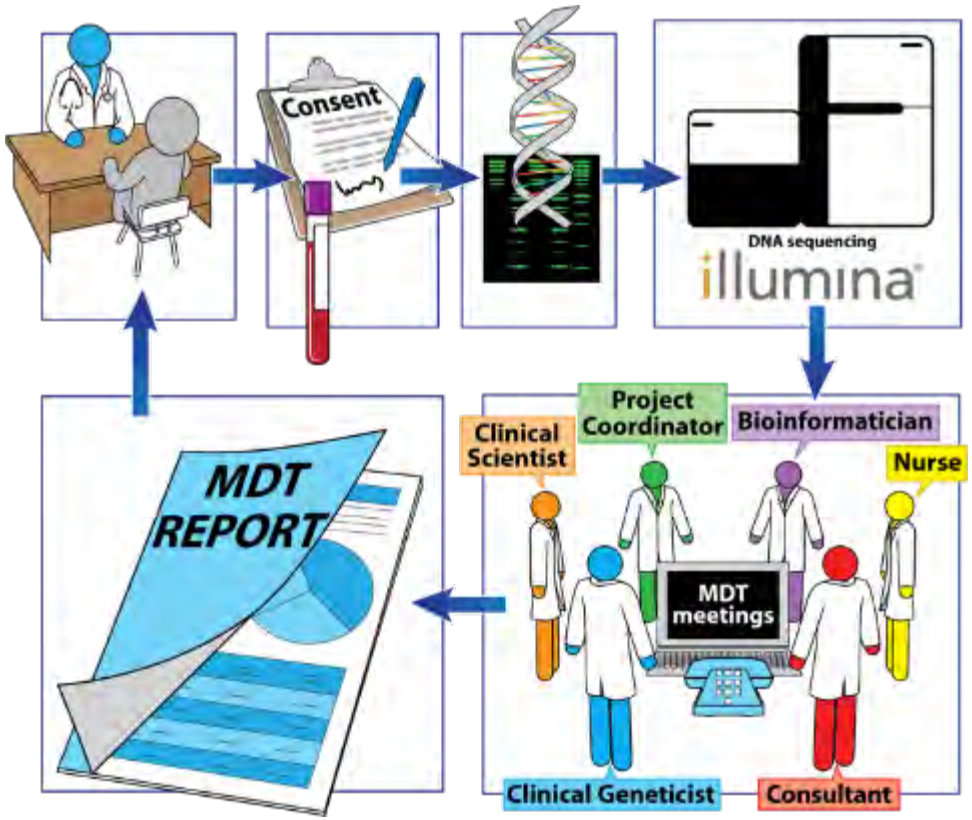
with ~1000 novel variants per individual genome



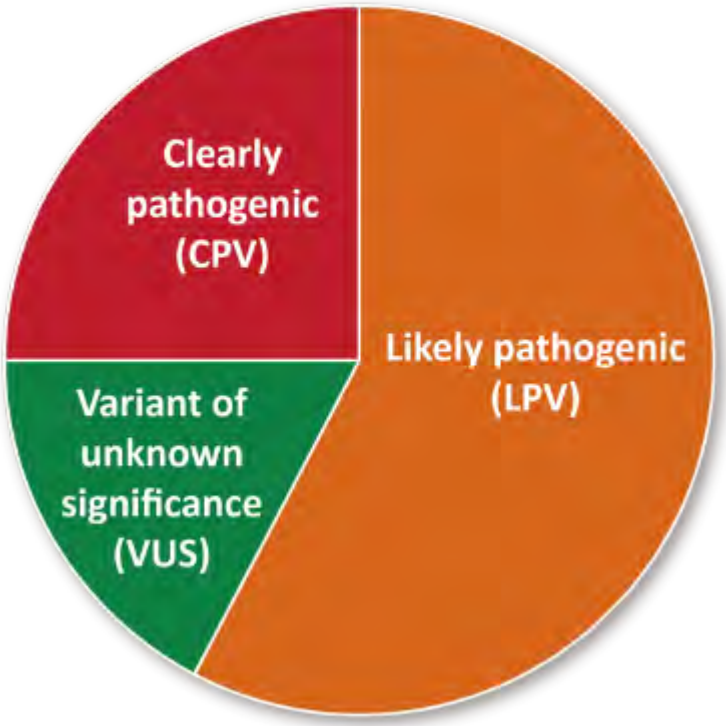
NIHR BioResource, Nature (in review)

Robust variant reporting in virtual MDTs

bringing together experts across the UK to improve the care of NHS patients



Variant classification based on ACMG guidelines

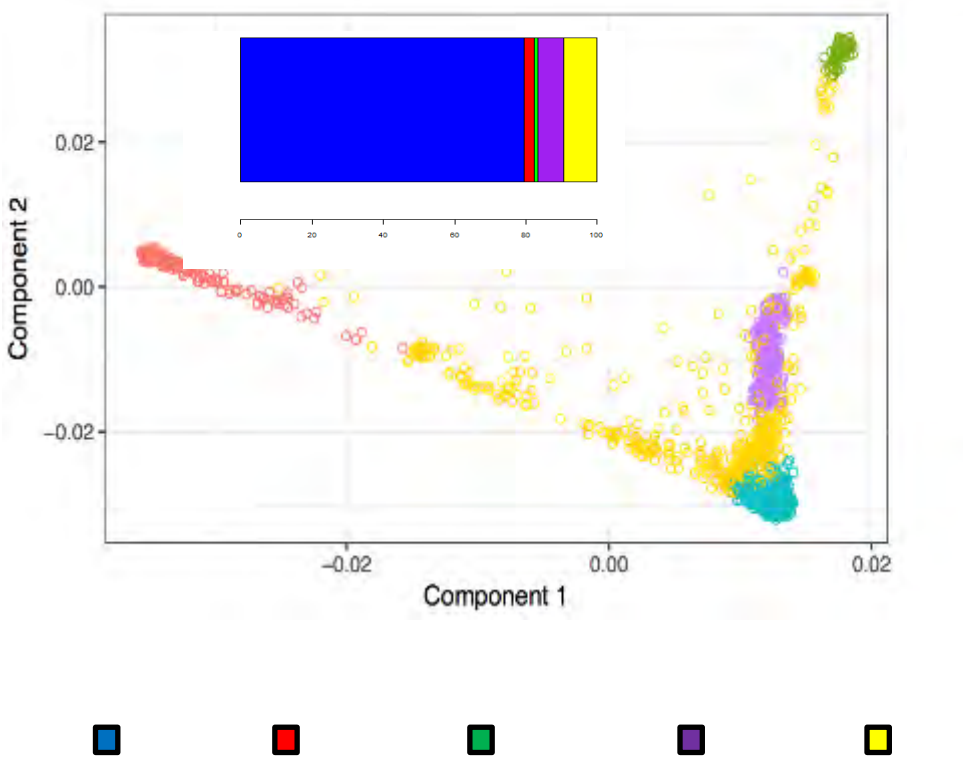


CONGENICA
GENOME BASED MEDICINE

Richards *et al*, ACMG standards and guidelines, Genetics in Medicine 2015

Inference of ethnicity and relatedness

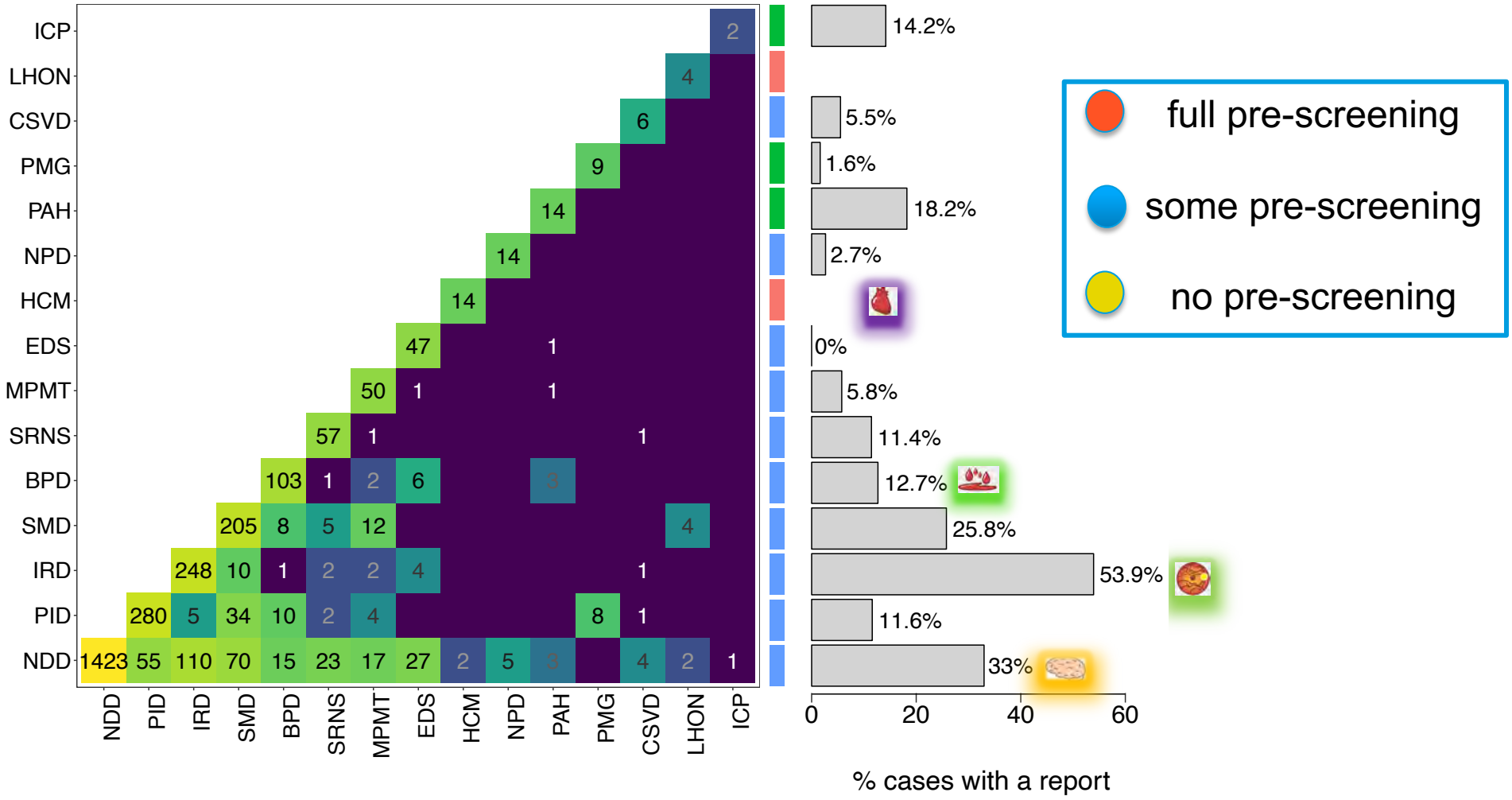
is essential for the clinical reporting of Likely Pathogenic and Pathogenic variants



NIHR BioResource, Nature (in review)

Diagnosis rates after MDT review

1,107 diagnostic reports in 304 genes (27% of the affected participants)



At least 1 in 20 patients would **not have received a diagnosis** if whole exome sequencing had been used instead of whole genome sequencing

Leadership by the CMO in transforming clinical genomics

patient are rightly expecting rapid delivery of genomic precision medicine

Professor Dame Sally C. Davies, Chief Medical Officer for England

Genomics is not tomorrow. Its here today.

I believe genomic services should be available to more patients, whilst being a cost-effective service in the NHS. This is exciting science with the potential for fantastic improvements in prevention, health protection and patient outcomes.

Now we need to welcome the genomic era and deliver the genomic dream!

Personalised or Precision Health Care

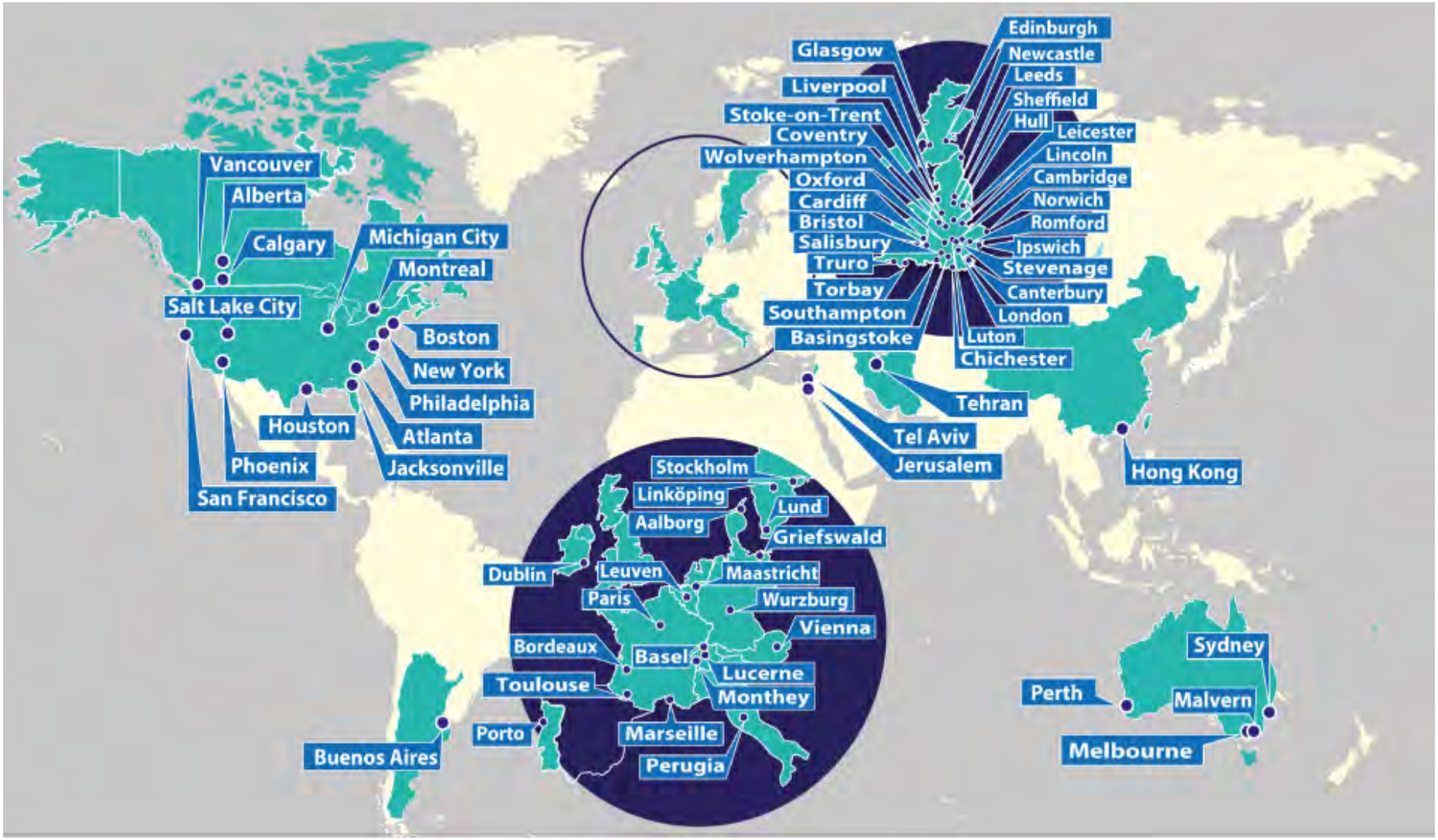
- Different rare diseases require different treatments
- Treatment needs to be tailored to the individual patient
- In many instances the best way to treat the disease may not be known

Platelets

- 150 – 400 x $10^{9}/L$
- Circulate as discoid cells

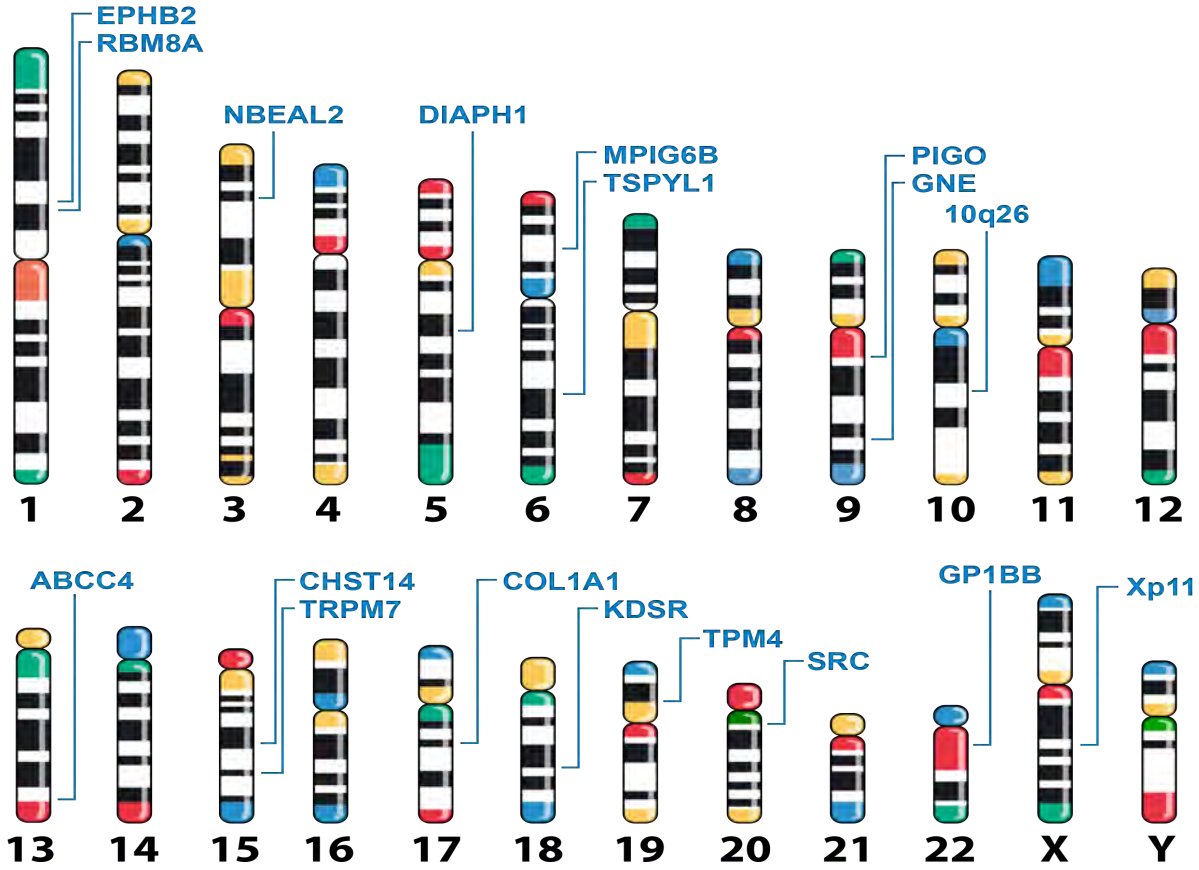
An international collaboration with shared data use

with the aims being gene discovery and bringing genomics to the frontline of care



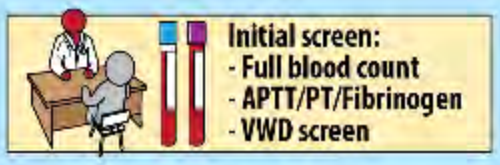
18 new genes for Bleeding, thrombotic and Platelet Disorders

increases diagnostic accuracy and informs more precise treatment



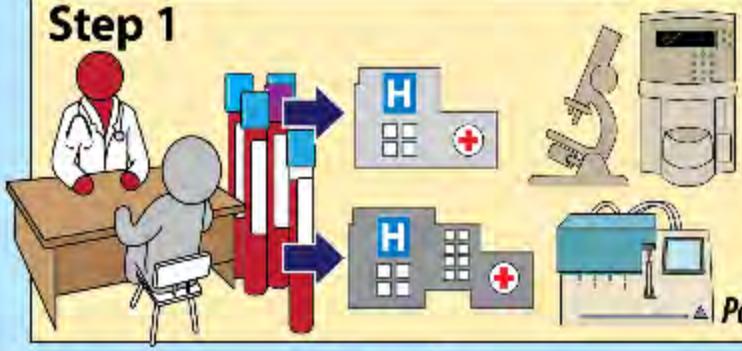
Albers *et al*, Nat Genetics 2011; Albers *et al*, Nat Genetics 2012; Cvejic *et al*, Nat Genetics 2013; Chen *et al*, Science 2014; Westbury *et al*, Genome Medicine 2015*;* Green *et al,* AJHG 2016; Stritt *et al*, Nat Comm 2016; Turro *et al,* Science Transl Med 2016; Stritt *et al*, Blood 2016; Simeoni *et al*, Blood 2016; Lentaigne e*t al*, Blood 2016; Poggi *et al,* Haematologica 2016; Bariana *et al*, BJH 2017; Sivapalaratnam *et al,* Blood 2017; Pleines *et al*, JCI 2017; Greene *et al*, AJHG 2017; Westbury *et al,* Blood 2017; Sivapalaratnam *et al,* BJH 2017; Morren *et al,* Orphanet 2017*; Freson et al,* JTH 2017; Sowerby *et al,* JCI 2017; Mayer *et al*, Blood 2018; Revel-Vilk *et al,* Blood 2018; Berrou *et al*, Blood 2018; Hofman *et al*, Blood 2018; Bariana *et al,* Haematologica 2018; Westbury *et al,* Blood Advances 2018; Downes *et al*, Blood 2019; Lentagine *et al*, Blood 2019; Megy *et al,* JTH 2019; Chan *et al*, Circ Research (in review)

Investigation of inherited BPDs



Stepwise investigation of platelet disorders

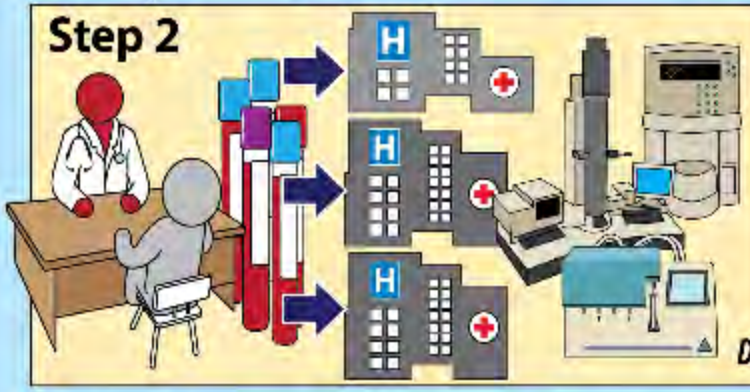
Step 1



Blood smear
Light Transmission Aggregometry (LTA)
Flow cytometry (FC)
Granule release

Potential diagnostic yield 40%

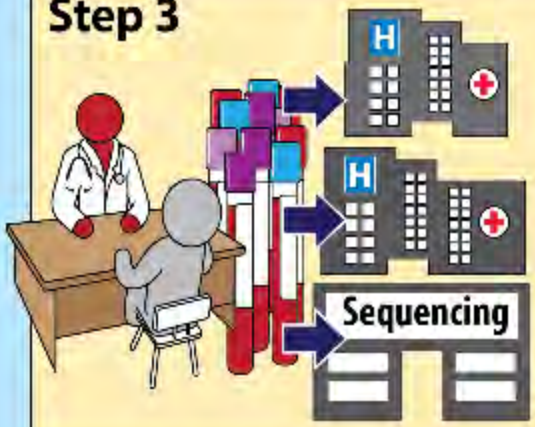
Step 2



Extended LTA
Extended Flow cytometry
Granule content
Mixing tests (LTA/flow)
Serum TxB2
Clot retraction
Electron microscopy

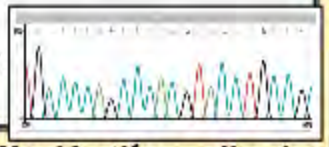
Diagnosis of further 7% cases

Step 3



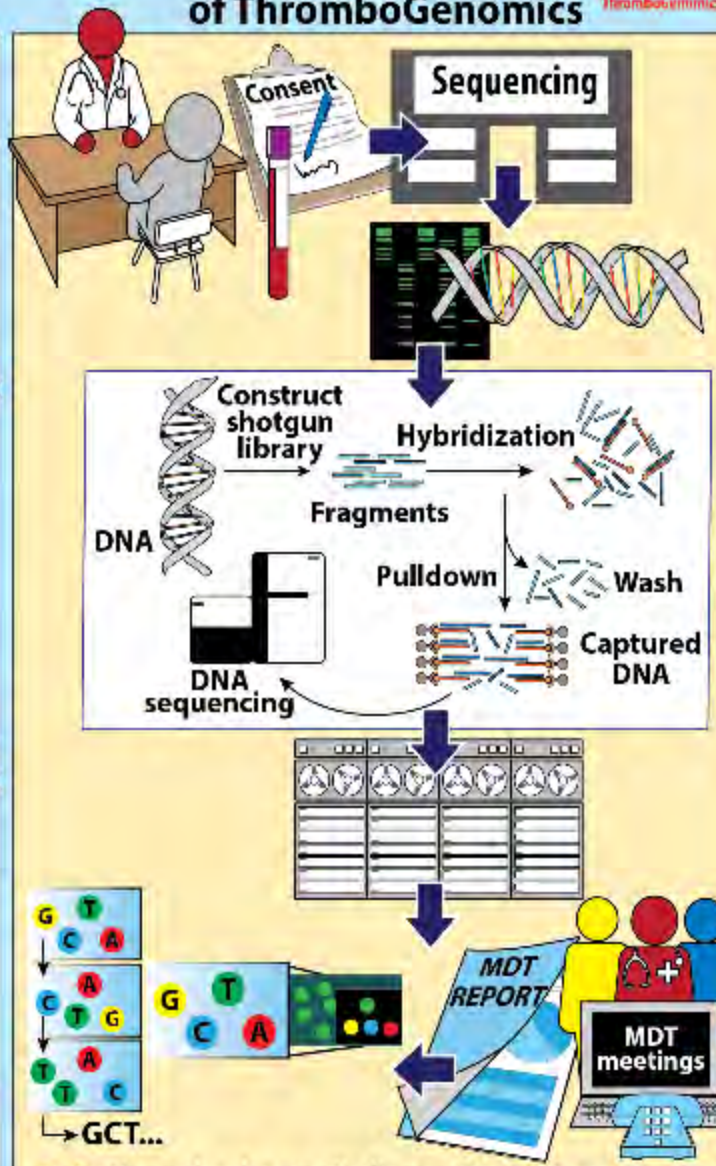
Biochemical studies:
- Surface glycoproteins (WB); spreading assay
- Adhesion and thrombus formation under flow conditions
- Protein phosphorylation (WB, FC)
- Second messengers (Ca2+, IP3, cAMP...)
- Receptor binding studies
- MYH10 (WB)

Molecular genetic diagnosis

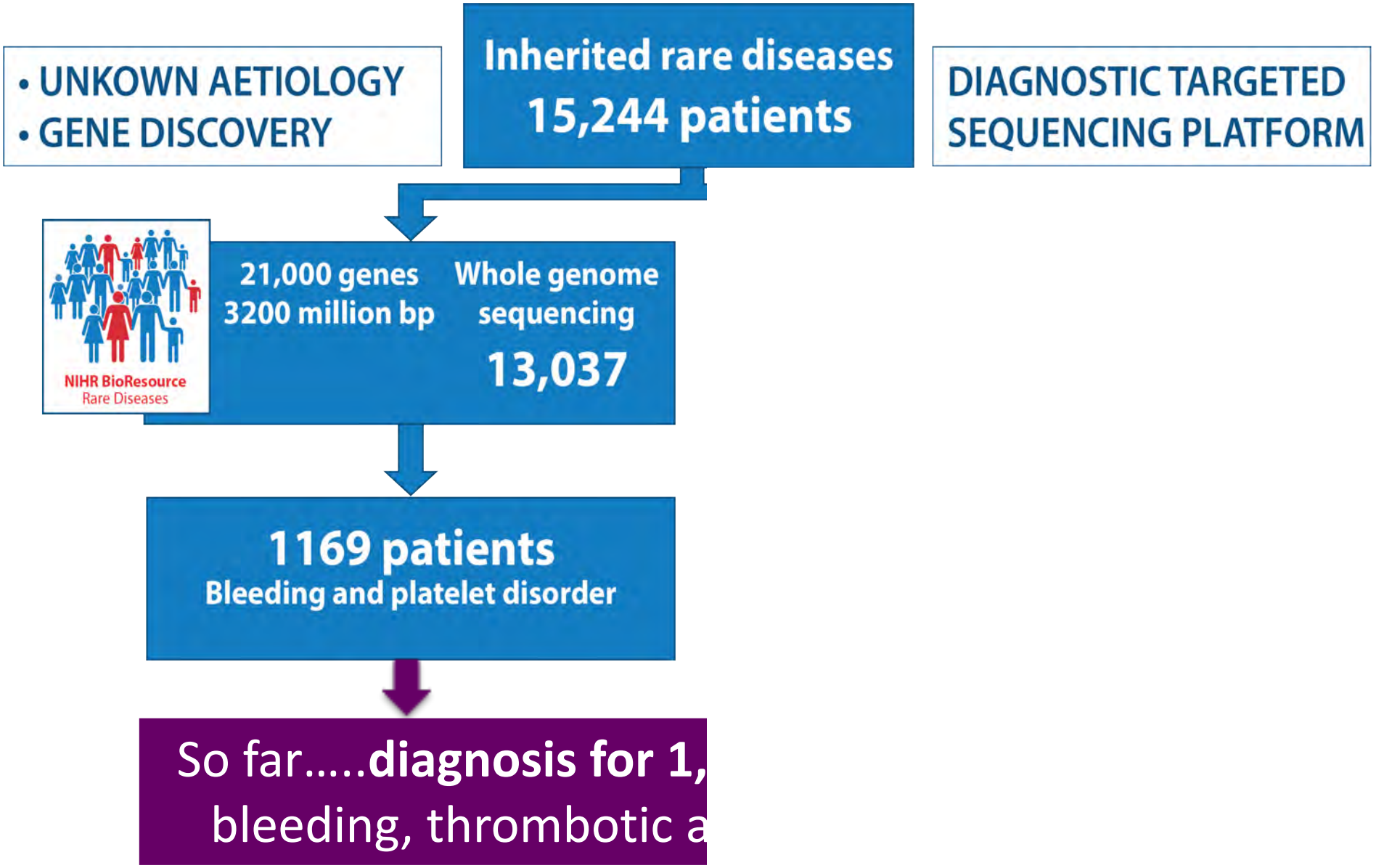


May identify rare disorders

Early incorporation of ThromboGenomics



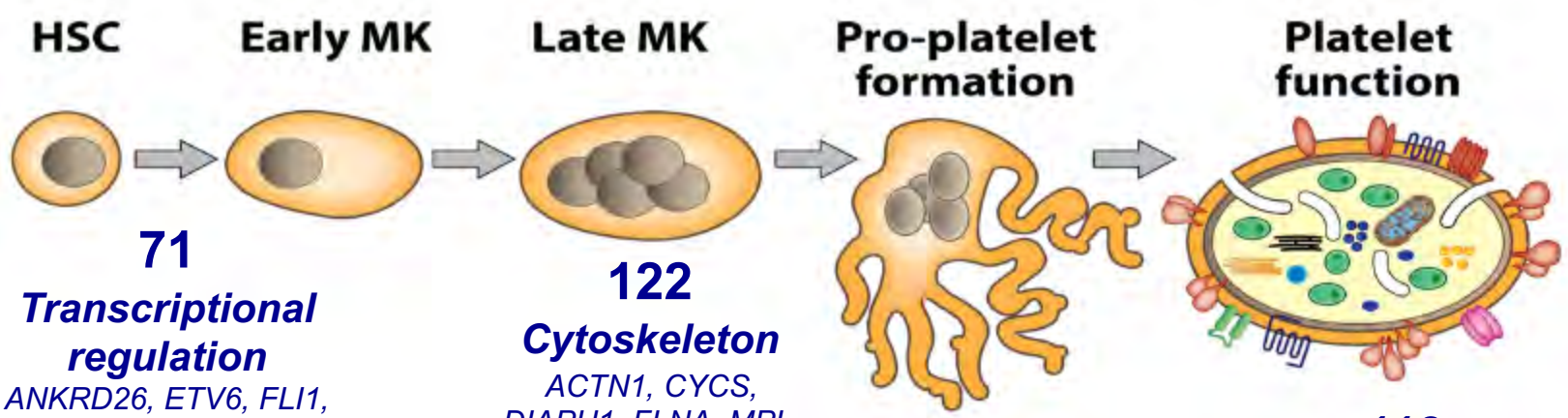
Definitive molecular genetic diagnosis in ~50% cases analysed for the 77 genes associated with inherited BPDs



NIHR BioResource, Nature (in review)
Megy *et al*, JTH 2019
Downes *et al*, Blood 2019

Precision diagnosis of inherited thrombocytopenias

informs the clinical management of 382 index patients and affected relatives



71

Transcriptional regulation

ANKRD26, ETV6, FLI1, GATA1, GFI1B, IKZF5, RUNX1

122

Cytoskeleton

ACTN1, CYCS, DIAPH1, FLNA, MPL, MYH9, THPO, TPM4, TUBB1, WAS

76

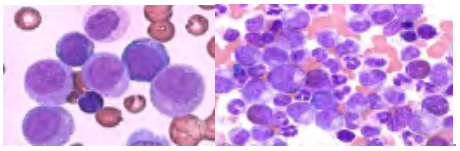
Granules

BLOC1S3, HPS1, 3, 5, 6, KDSR, NBEA, NBEAL2, SLC18A2, SRC

113

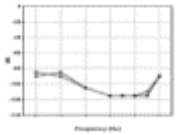
Function disorders

COL5A1, ITGA2B, ITGB3, RASGRP2, GP1BA, GP1BB, GP9, GP6, GNE, P2RY12, PTPN11, TBA2R, THBD

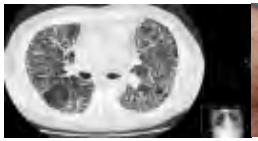


leukaemia

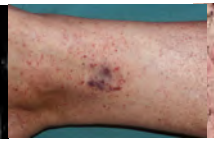
kidney failure



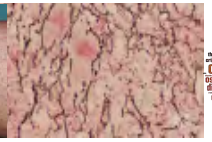
deafness



lymphoma



bleeding



myeolofibrosis

autoimmune disease

autism

Blood transfusion
Genomics Consortium

Extracting transfusion relevant information from WGS

blood supply organisations will need to develop abilities to extract relevant data

THE LANCET
Haematology

Automated typing of red blood cell and platelet antigens: a whole-genome sequencing study

William J Lane*, Connie M Westhoff*, Nicholas S Gleadall*, Maria Aguad, Robin Smeland-Wagman, Sunitha Vege, Daimon P Simmons, Helen H Mah, Matthew S Lebo, Klaudia Walter, Nicole Soranzo, Emanuele Di Angelantonio, John Danesh, David J Roberts, Nick A Watkins, Willem H Ouwehand, Adam S Butterworth, Richard M Kaufman, Heidi L Rehm, Leslie E Silberstein*, Robert C Green*, on behalf of the MedSeq Project†

BGC
Blood transfusion Genomics Consortium

bloodTyper

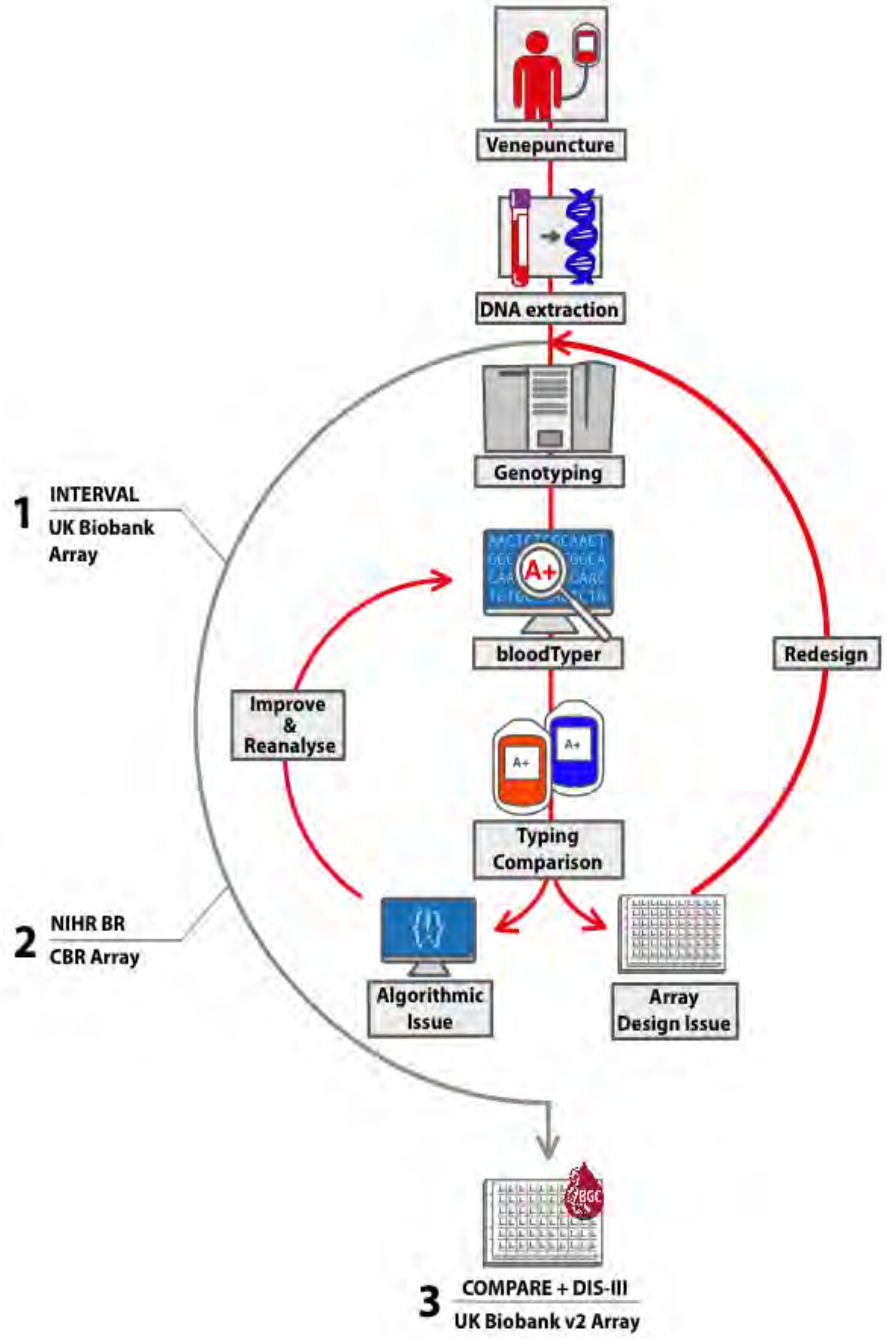
10,027 genomes in 24 hrs

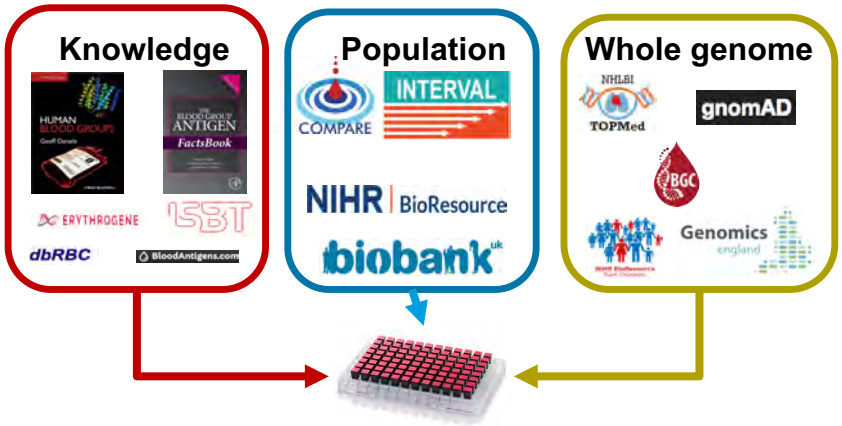
- **Rare red cell antigen negative types**
  - 140 individuals for 18 different antigens
  - U−, Rh26−, CEAG−, Lu13−, Lu(b−), Lu8−, k−, Kp(b−), Js(b−), Yt(a−), Sc1−, Hy−, Jo(a−), Co(a−), Kn(a−), McC(a−), Sl3−, Vel−

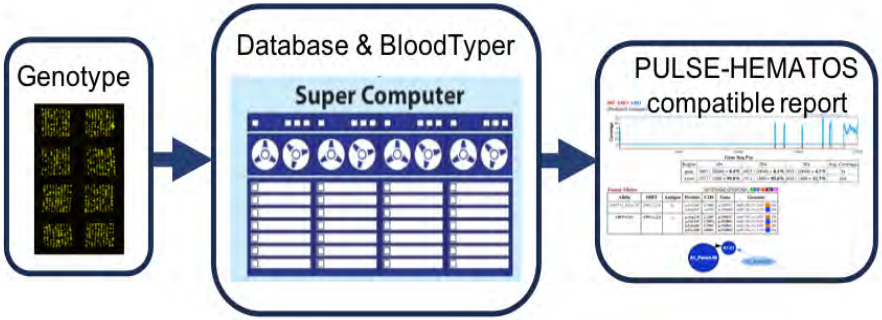
- **Rare platelet antigen negative types**
  - 230 HPA-1b1b

Old way would require 338,000 independent serological tests to find these individuals for at least €500,000

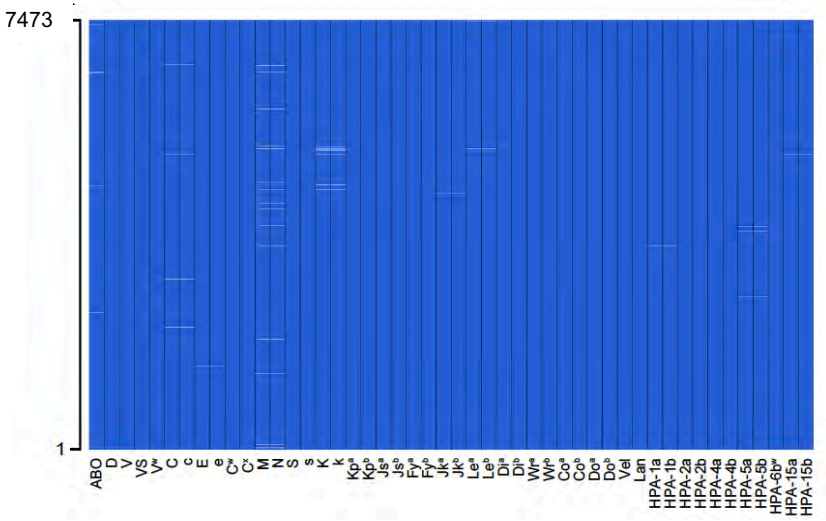
Unpublished data







~1.6 million antigen types



Embracing Genome Medicine

2001	2007	2008	2010	2015	2018	2020	2021	2025
								
Reference genome	**First personal genomes**	**First African genome**	**1K**	**10K**	**100K**	**235K**	**550K**	**500K**

Sanger sequencing → **Next-generation sequencing**

Thank you to the participants and all the teams