

'Genomics and the future direction of health research'



AWMGS

All Wales Medical Genomics Service

Sian Morgan

Consultant Clinical Scientist,

Head of The All Wales Genomic Service

The UK's investment and expertise in genomics means that it now has an unparalleled opportunity to use genomic research assets to drive the next generation of Life Sciences discoveries, deliver genomics-enabled clinical trials and support the growth and R&D of innovative genomics-focused companies.

This will be done through:

- **Continuing to support and enhance our Genomic research infrastructure –** The combination of world class 'omics assets contained in longitudinal cohorts, such as UK Biobank, Our Future Health, NIHR BioResource and Genomics England, alongside a clear route to patient impact is globally unique and continues to be strongly supported by industry. These will continue to be used to enhance our research cohort genomic infrastructure – with a joined-up “front door” and interoperable research environments bringing scale benefits to researchers and industry.
- **Evaluating variants and their role in prediction and public health –** The availability of polygenic risk scores from the UK Biobank cohort will allow these tools to be used to better predict most common and some rare diseases. Combining novel arrays with these prevention tools will allow for large pilot studies in the NHS and in Our Future Health, which can then be applied more widely to define and address individual risks.
- **Utilising new genomic tools to improve prediction and early diagnosis capabilities –** As seen with the partnership between NHS England and GRAIL to undertake GRAIL's pivotal studies of asymptomatic cancer detection in the UK. Future expansion of the prediction and early diagnosis agenda, such as the new-born sequencing pilots that are currently in public dialogue, will bring more sequencing capacity to the UK, create a substantial opportunity for novel gene therapies to transform the lives of patients with genetic conditions, and deepen insight into many common and rare disease areas.

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Life Sciences Vision

- **Bringing the best emerging science and technology to bear on cancer diagnosis and treatment.** Alongside early detection and prediction, we have an opportunity to build on early pilots and deploy emerging technologies (such as long read sequencing, methylation, transcriptomics, proteomics and other medtech) to improve diagnosis, stratification of patients, referrals to clinical trials, and personalised therapeutics for patients. Our ambition is to have the closest link between clinical research, iterative innovation and patient care of any country in the world.
- **Delivering a world class offer on Functional Genomics –** There are now thousands of genetic variants known to be implicated in disease pathogenesis. The challenge now is to understand how these variants mediate their effects. A new set of tools including single cell sequencing, dynamic gene expression profiling, and systematic CRISPR screens will, when allied with insights from genomics datasets and advanced imaging and pathology, open up high throughput approaches to understanding the role of



HM Government

GENOME UK
The future of healthcare



Pillar 3: Research – Supporting fundamental and translational research and ensuring a seamless interface between research and healthcare delivery.

- 1: Data-driven innovation and meeting patients' expectations about data use
- 2: Harmonising consent frameworks to maximise participation in research
- 3: Functional analysis of genomic variation
- 4: Informatics
- 5: Equity and genetic diversity
- 6: Opportunities to participate in clinical research
- 7: Translation

Let's prevent disease together



We will use the health information, including genetic data, to calculate disease risk scores for participants in Our Future Health where possible. Based on these risk profiles, it might be possible to better target individuals who are at higher risk of developing certain diseases. This will provide an opportunity to test the potential of new diagnostic tests or treatments as they are discovered and to see how effective they could be for people at higher risk of certain diseases. This will also mean Our Future Health can facilitate research addressing important questions about the potential uses of new 'genetic risk scores' in health care.

Our Future Health will be the UK's largest ever health research programme, bringing people together to develop new ways to detect, prevent and treat diseases.

Cancer: Blood test for 50 types to be trialled by NHS

27 November 2020 | Comments



GETTY IMAGES

A blood test designed to detect more than 50 types of cancer at an early stage will be trialled by the NHS.

NHS to pilot potentially revolutionary blood test that detects more than 50 cancers

27 November 2020

Cancer

An innovative blood test that may spot more than 50 types of cancer will be piloted by the NHS in a world-leading programme, chief executive Sir Simon Stevens announced today.

The Galleri blood test, developed by GRAIL, can detect early stage cancers through a simple blood test, and will be piloted with 165,000 patients in a world-first deal struck by NHS England.

Genomics for Precision Medicine Strategy 2017

Co-production

Demonstrate a commitment to work in an open and transparent manner with patients and the public in Wales, using their collective experiences to shape and add value to the work of the Genomics Partnership and future genomics services in Wales

Clinical and Laboratory Services

Develop internationally-recognised medical and public health genomics services with strong collaboration across NHS and academia to ensure equity of access to the best genomics healthcare for the citizens of Wales

Research and Innovation

Establish an internationally competitive genomics research environment through investment in genomic research technologies and Precision Medicine platforms, collaborative infrastructures and ambitious training portfolios

Workforce

Nurture an enthused and highly skilled workforce that can serve as ambassadors for genomics within the NHS, ensuring that our services evolve at pace and remain progressive, equitable and reliable

Strategic Partnerships

Establish Wales as an outward-looking, collaborative and reputable home for business development, promoting the genomic services in Wales to attract the best partnership opportunities

Genomics service developments in Wales

Sgrinio Cyn Geni Cymru
Antenatal Screening Wales



Prenatal services

April 2018: NIPT introduced within antenatal screening programme – 1st in the UK



Precision medicine

June 2020: NTRK gene fusion testing commissioned service for all patients in Wales

August 2021: CYmru Service for Genomic Oncology Diagnoses - flagship genomic service



Pharmacogenetics

June 2020: DPYD gene testing launched across Wales – first in the UK



Specialist Rare Disease services

April 2020: WINGS testing launched – only service in the NHS using whole genome sequencing

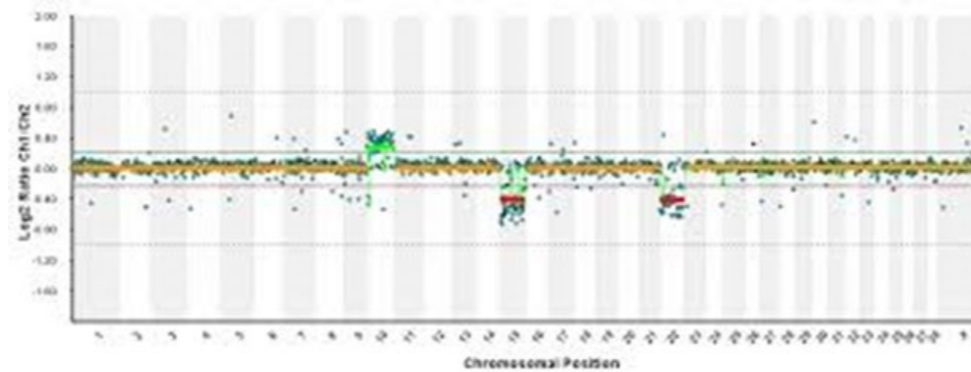


Infectious diseases



Co-location of human and pathogen genomics clinical service with Wales Gene Park, Consent models, Data sharing, Collaborative research

Genomic Technologies and Detection Of A Rare Disease Diagnosis



NHS WALES GIG CYMRU **All Wales Genetics Laboratory**

Severe Infantile Epilepsy 36 Gene Panel

Background
This panel of 36 genes is designed to assist in the diagnosis of genetic forms of severe infantile epilepsy. Epileptic encephalopathies are characterized by recurrent intractable seizures and persistent abnormality of cortical function which results in impaired cognitive, sensory and motor development. In the majority of patients, the epilepsy is caused by structural brain malformations, acquired brain insults or inborn errors of metabolism. However, a proportion of cases have a genetic cause. Identification of a causative mutation provides information on prognosis, avoids unnecessary investigations, informs treatment and is useful for genetic counselling.

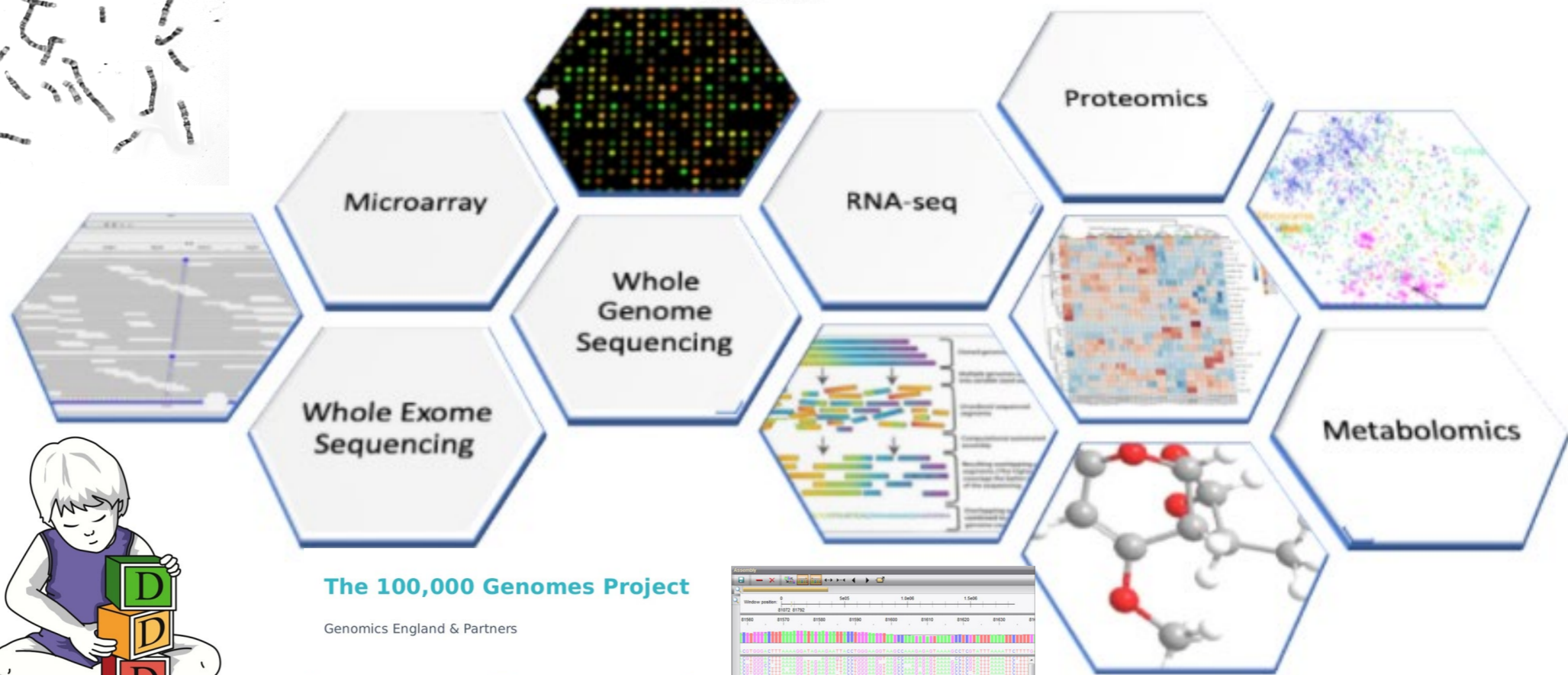
Genes

ALDH7A1	CHD2	GLUD1	MECP2	PNKP	SCN8A	SPTAN1	ZEB2
ARHGGEF9	CNTNAP2	GRIN2B	MEF2C	PNPO	SCN9A	STXBP1	
ARX	FOXP1	HCN1	NRXN1	POLG	SLC25A22	SYNGAP1	
BTD	GABRB3	KCNQ2	PCDH19	SCN1A	SLC2A1	TCF4	
CDKL5	GABRG2	MAPK10	PLCB1	SCN2A	SLC9A6	UBE3A	

If required, Sanger sequencing is available on request for those genes in **bold** – see over for more details

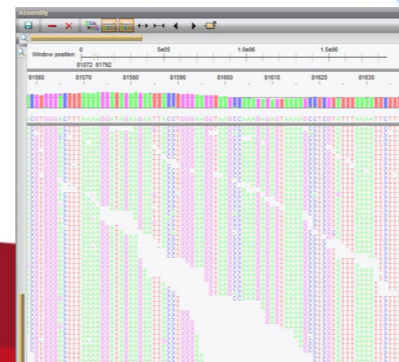
Recommended Clinical Referral Criteria

- Patients with epileptic encephalopathy but without an apparent aetiology on the basis of clinical evaluation, normal neuro-imaging and negative results on metabolic screening.



The 100,000 Genomes Project

Genomics England & Partners



Wales Infants' and children's Genome Service (WINGS)

- For patients being cared for in the neonatal or paediatric intensive care units who have a combination of serious health problems.
- The AWMGS WINGS test is designed to reduce the child's diagnostic journey by searching through their whole genome data to find a genetic cause of their clinical features.
- Diagnostic yield ~45%
- TAT 14 calendar days, so far mean reporting time ~10 calendar days



2021 UK Advancing Healthcare awards

One in 17 people are affected by a rare disease, and more than 30% of children with a rare disease die before their fifth birthday. A key priority of the UK Strategy for Rare Diseases is to identify and improve the pathway for patients with unknown or delayed diagnosis - "The Diagnostic Odyssey". Until recently, targeted gene testing was adopted with patients waiting years (sometimes up to 20) for their diagnosis. WINGS, launched in April 2020, uses whole genome sequencing (WGS) to deliver a rapid genetic diagnosis for critically ill infants and children. This means that the whole genome is tested at the same time, within 1-2 weeks, therefore increasing the possibility of a diagnosis in a clinically actionable timeframe. International medical systems and UK research that have adopted a rapid WGS approach have increased their diagnostic rate, demonstrated substantial reductions in healthcare spending due to fewer days in hospital and avoiding unnecessary surgeries and other invasive procedures as well as preventing future, avoidable harm. Although rapid genomic sequencing is increasingly being adopted internationally, the WINGS service is the first commissioned NHS diagnostic WGS service within the UK.

“This is a fantastic project, said the judges, which was potentially transformative in terms of patient pathways, with a clear impact on patient care. There were clear patient benefits but there were also benefits in developing the workforce and creating infrastructure to support innovation.”

I'm a **WINNER!**

Viapath award for innovation in healthcare science



THE VIAPATH AWARD FOR INNOVATION IN HEALTHCARE

WINNER

Wales Infants' and children's Genome Service (WINGS)

Sian Corrin and Jana Jezkova, Clinical Scientists.

All Wales Medical Genomics Service



FIND OUT MORE

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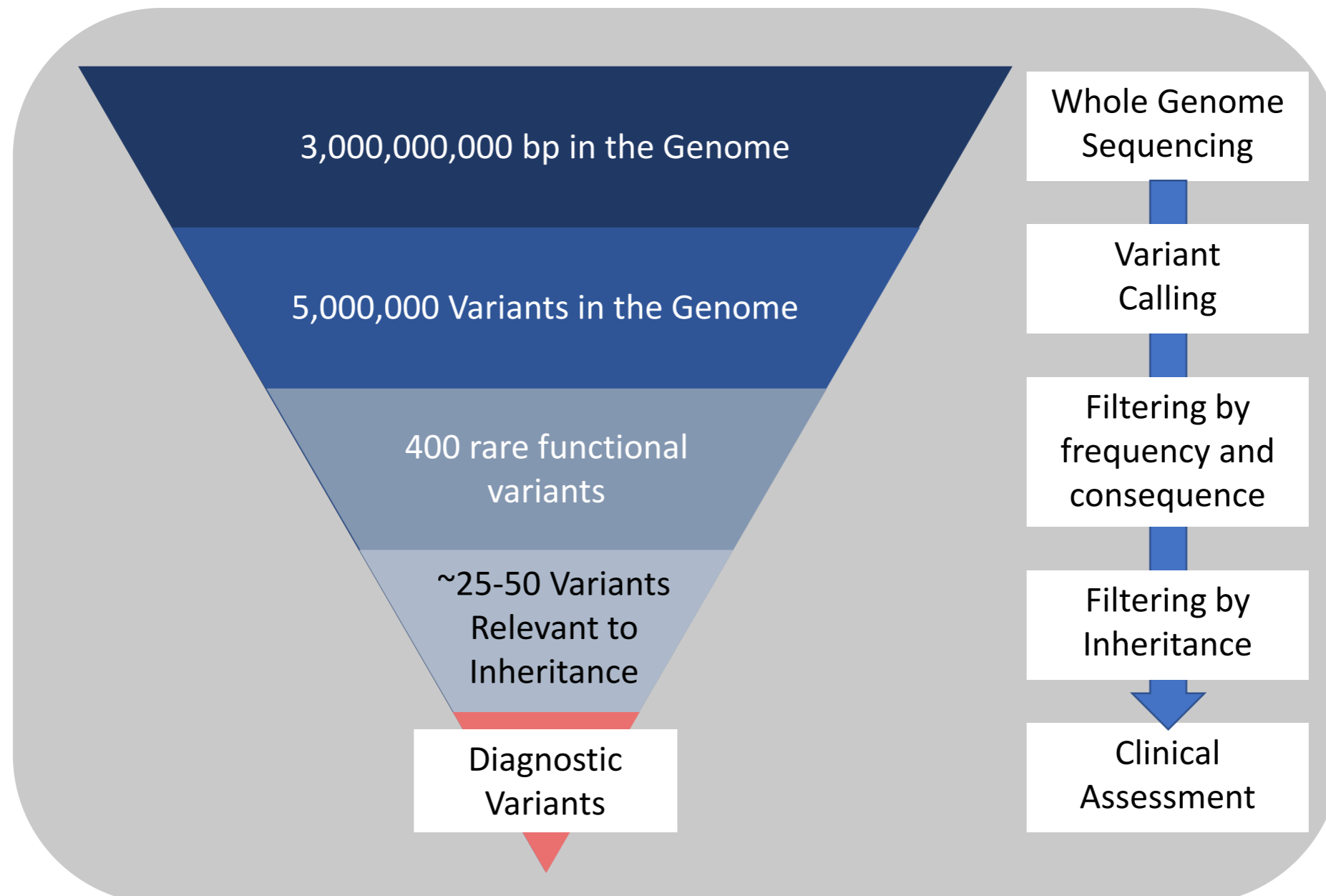
WINGS

Wales Infants' & Children's Genome Service



Analysis and Filtering of data

- A diagnosis must occur quickly to be relevant for clinical decision-making
- To facilitate rapid analysis, strict filters are applied to prioritize variants
- This balance is struck to find diagnoses quickly without being overwhelmed by the large amount of data

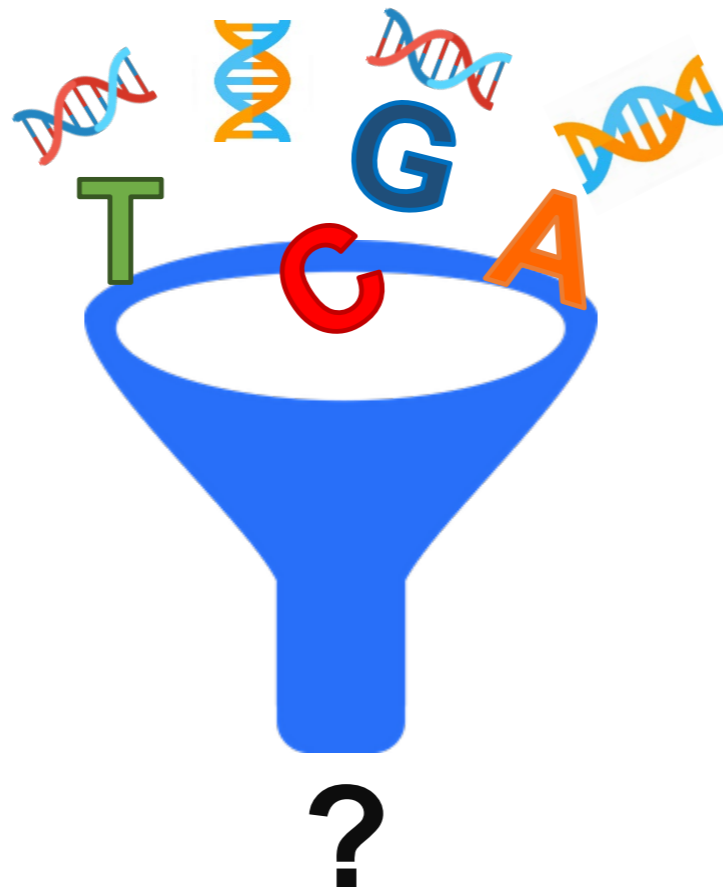


- If a change is not found, it remains possible there is a genetic cause for the child's condition.
- This is because rWGS uses strict filters to improve speed and because some genetic causes need to be discovered.
- However, genetic knowledge and analysis tools are continually being updated.
- **Diagnostic yield can be improved by ~10% after re-analysis of the existing data in a research setting¹.**



Child too young to manifest key features of disease

Filters too strict



Gene discovery



200 new genetic disorders every year²

1. Wright et al. *Genet.Med.* (2018)
2. Boycott et al. *Am.J.Hum.Genet.* (2017)

RCBC research re-analysis of data



Research questions:

Can more diagnoses can be achieved using advanced analysis and different approaches that cannot be used during routine diagnostic testing?

Use RNA-Seq to confirm change in protein expression therefore increasing diagnostic yield

Use of 'long read' sequencing to increase diagnostic yield



Building Research Capacity for Nursing & Allied Health Professionals and Pharmacists

Cynyddu Gwaith Ymchwil ar gyfer Nyrsio a Gweithwyr Proffesiynol Cysylltiedig a Fferyllwyr

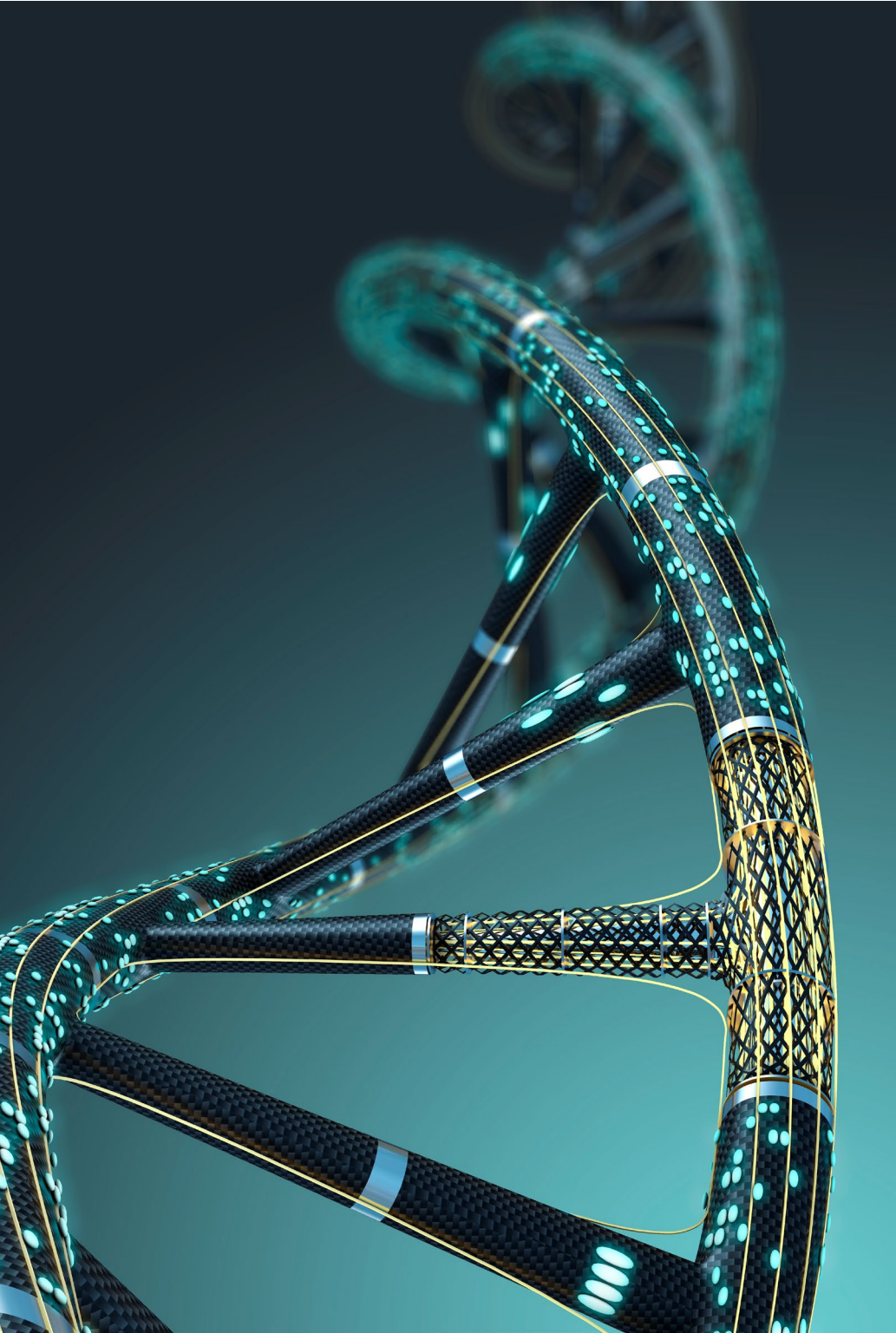


Llywodraeth Cynulliad Cymru
Welsh Assembly Government



Ymchwil Iechyd
a Gofal Cymru
Health and Care
Research Wales

**Research Capacity Building
Collaboration Wales
RCBCWales**



Welsh Strategy to Integrate Liquid Biopsy Services within NHS Wales for All Cancer Patients

Sian Morgan, Rhian White, Rachel Dodds, Erik Waskiewicz - All Wales Medical Genomics Service

Magda Meissner - CRUK Clinical Trial Fellow, Centre for Trials Research, Cardiff University

Richard Adams - Director Centre for Trials Research - Cancer Division, Director Wales Cancer Bank, Professor and Honorary Consultant Clinical Oncologist, Cardiff University and Velindre Cancer Centre

Robert Jones - Specialty Lead for Cancer in Wales Phase 1 trials lead in Wales, Clinical Director of R&D Velindre University NHS Trust, Reader and Medical Oncology Consultant, Cardiff University and Velindre Cancer Centre

Paul Shaw - Consultant Clinical Oncologist, Lead for Early Phase Drug RT, Velindre Cancer Centre, Honorary Senior Lecturer, School of Bioscience, Cardiff University

Olivier Ottmann - Professor and Head of Haematology, Division of Cancer and Genetics, Cardiff University

Samantha Cox - Clinical Oncologist Consultant, Chair of All Wales Genetics Oncology Group(AWGOG), Velindre Cancer Centre

Mark Davies - Medical Oncology Consultant, South West Wales Cancer Centre (SWWCC) in Swansea and Honorary Associate Professor at Swansea University Medical School



GIG
CYMRU
NHS
WALES

Bwrdd Iechyd Prifysgol
Caerdydd a'r Fro
Cardiff and Vale
University Health Board

Why AWMGS?

Diagnostic hub and clinical hub have functioned effectively and efficiently

A UK leader in SMP2 trial

Wales as a devolved NHS has had significant opportunity to develop single cancer pathway more effectively, including rapid diagnostic centres (cancer direct referral from primary care)

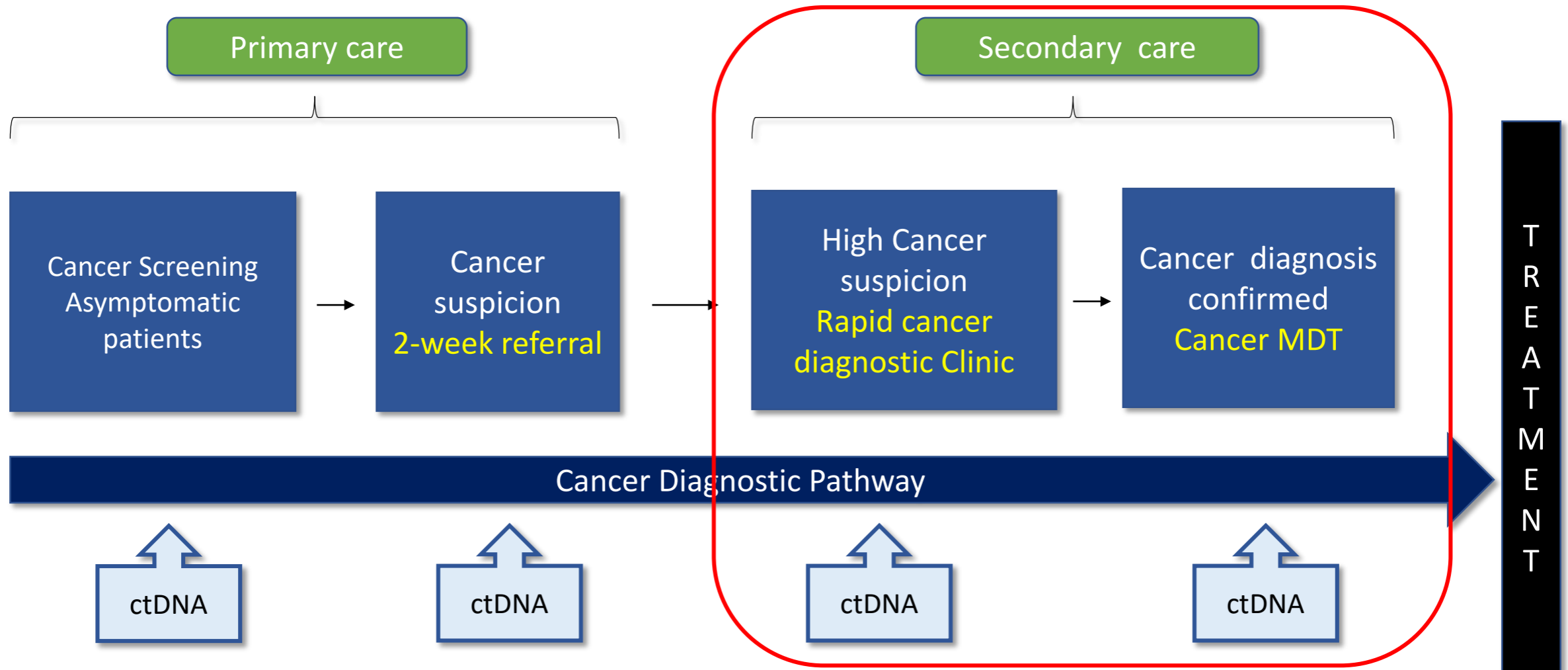
Wales is an early developer and adopter of ctDNA as an NHS diagnostic service

AWMGS - a rapid adopter of Illumina TruSight Oncology 500 HT DNA/RNA panel, the CYmru Service for Genomic Oncology Diagnoses (CYSGODI)

TruSight Oncology 500 HT DNA panel and the TruSight Oncology 500 ctDNA panel offers opportunities for integrated research structures

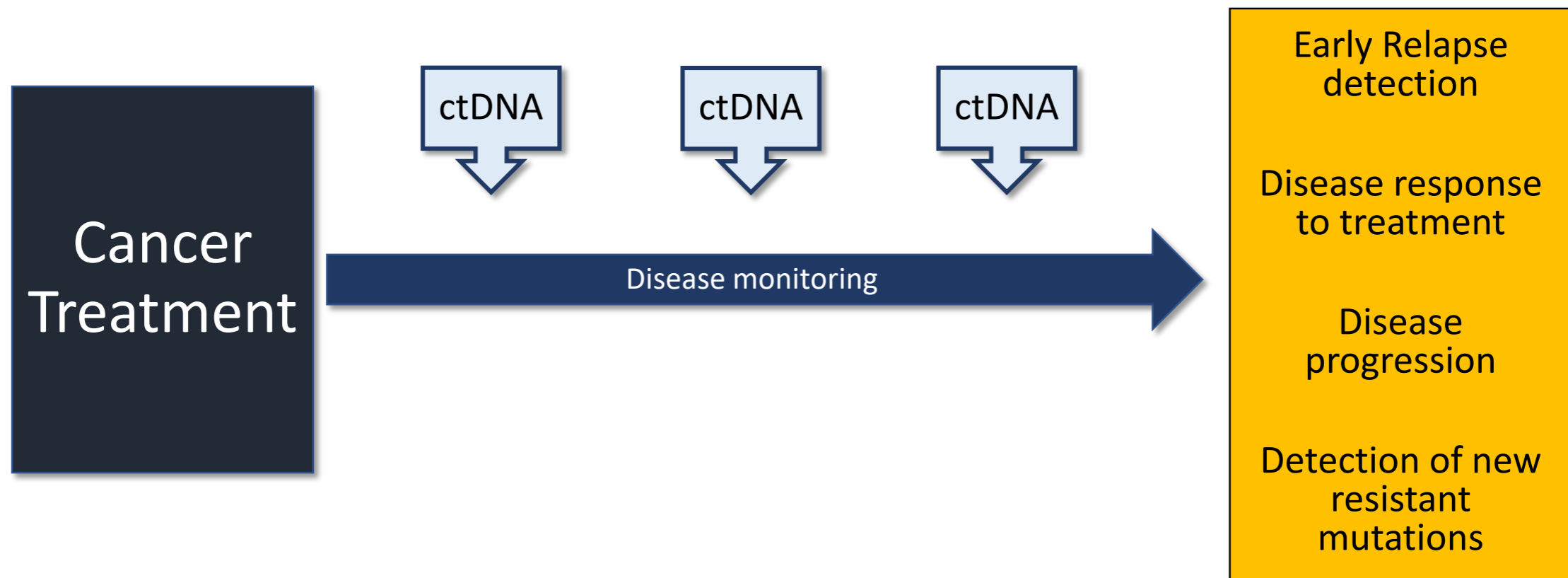
Disruptive approaches for cancer care using liquid biopsy

CtDNA role in diagnostic cancer pathway



Disruptive approaches for cancer care using liquid biopsy

Liquid biopsy role in cancer monitoring during and after anti-cancer treatment



Adverse drug reactions (ADRs)

- Contribute to 6.5% of hospital admissions
- Estimated to cost the NHS (across the UK) £1bn annually
- Up to 20%-30% of ADRs could be prevented by pharmacogenetic testing

ROYAL
PHARMACEUTICAL
SOCIETY
Scotland

**Pharmacy 2030:
a vision for community
pharmacy**

2.1.2 Using data for decisions

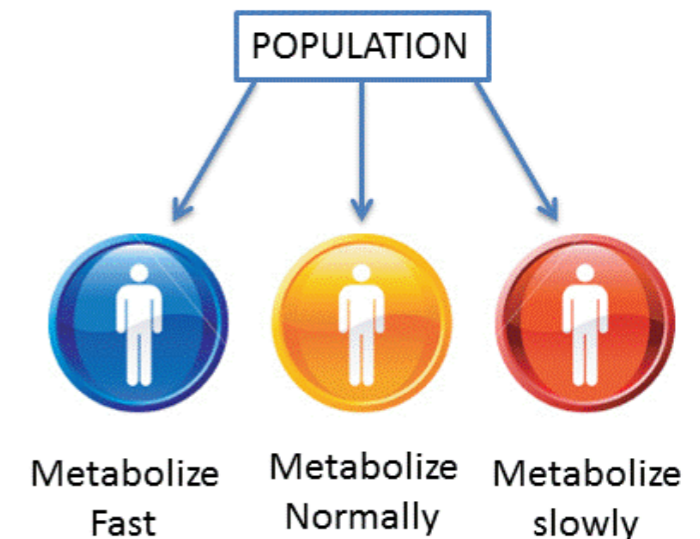
By 2030, community pharmacists will use data routinely to provide personalised care and medicines for patients. This will include both prescribing data and population health data.

Pharmacogenomics is a fast expanding area in pharmacy, and by 2030 it will be in use in all community pharmacies. Pharmacogenomic point of care testing kits will enable community pharmacists to personalise an individual's treatment, for example to identify whether they are a fast or slow metaboliser of a medicine they have been prescribed, and then to adjust the dose accordingly using independent prescribing skills.

Pharmacogenetics at Scale: An Analysis of the UK Biobank

Abstract

Pharmacogenetics (PGx) studies the influence of genetic variation on drug response. Clinically actionable associations inform guidelines created by the Clinical Pharmacogenetics Implementation Consortium (CPIC), but the broad impact of genetic variation on entire populations is not well understood. We analyzed PGx allele and phenotype frequencies for 487,409 participants in the UK Biobank, the largest PGx study to date. For 14 CPIC pharmacogenes known to influence human drug response, we find that 99.5% of individuals may have an atypical response to at least 1 drug; on average they may have an atypical response to 10.3 drugs. Nearly 24% of participants have been prescribed a drug for which they are predicted to have an atypical response. Non-European populations carry a greater frequency of variants that are predicted to be functionally deleterious; many of these are not captured by current PGx allele definitions. Strategies for detecting and interpreting rare variation will be critical for enabling broad application of pharmacogenetics.



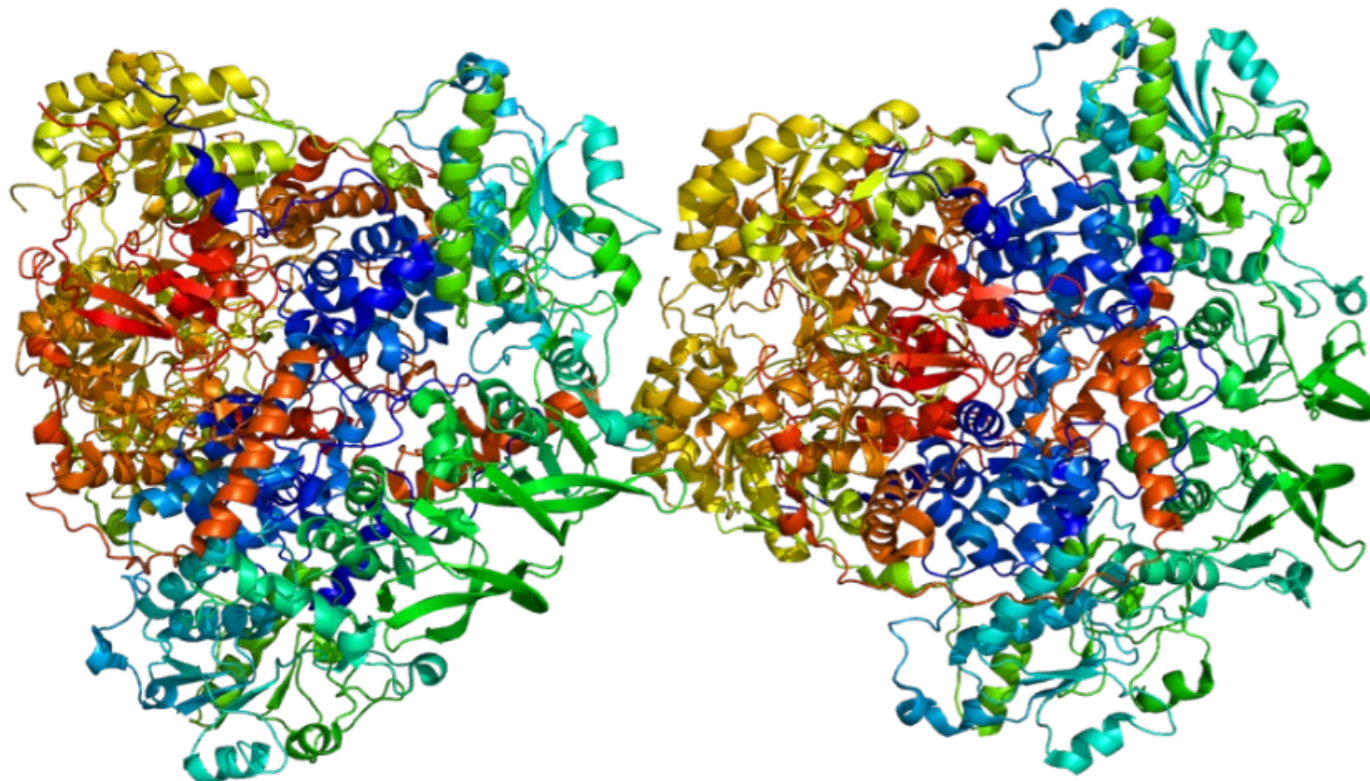
The Pharmacogenetics to Avoid Loss Of Hearing (PALOH) study is a project to assess a point of care genetic test to avoid hearing loss in neonates exposed to the antibiotic gentamicin. 90,000 babies every year in the UK are admitted or assessed on a neonatal intensive care unit (NICU). Most will receive the antibiotic gentamicin to protect against or treat infection. One in 500 babies have a genetic change called m.1555A>G which predisposes to complete irreversible hearing loss when given gentamicin. With colleagues at Genedrive we have developed a rapid test which can tell if babies are susceptible to this drug reaction in less than 30 minutes and so potentially save 200 babies every year in the UK from going deaf. This work, funded by the NIHR i4i program, is currently progressing well and we will trial the tests in Liverpool and Manchester from Summer 2019.



Patients in Wales to receive routine life-saving testing ahead of chemotherapy treatment

📅 Wednesday 7 October 2020

Wales has become the first country in the UK to routinely screen all cancer patients being treated with certain types of chemotherapy, to identify their risk of severe side effects and help prevent this occurring.



- ‘DPYD Health Technology Assessment Service Evaluation’ (VCC, Bangor Uni, AWMGS)
- MRES (AWMGS and Bangor Uni)
Title: CYP2C19 genetic variation and adverse reactions to clopidogrel – A case study for implementation of pharmacogenetic testing service in NHS Wales. Study Start Date April 2021 Study End Date April 2023

Lastly, what is our Precision Medicine Centre of Excellence/Genomic Centre ambition?



A physical centre that will be a major RD&I asset and a focus for public sector and private sector co-production of innovative healthcare platforms that will result in an opportunity for economic growth in the region and in Wales



A AI and data innovation centre that will have excellent digital connectivity with existing clinical data assets such as the national Digital Cellular Pathology programme, NDR, National Imaging Academy and the SAIL databank in Wales

