WELCOME TO

Understanding Genomics in the NHS Conference 2022

Check Out Our Agenda Here...

Tuesday 19th November 2022- 10:50am – 15:00pm – GoTo Webinar

Conference hosted by Convenzis Group Limited

Understanding Genomics in the NHS Conference 2022

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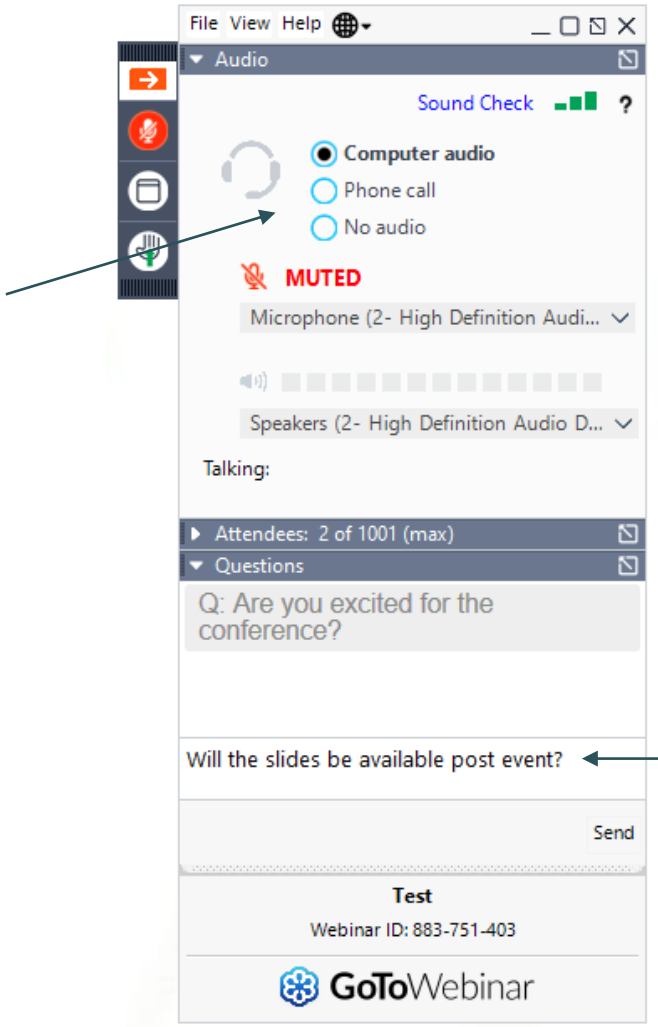

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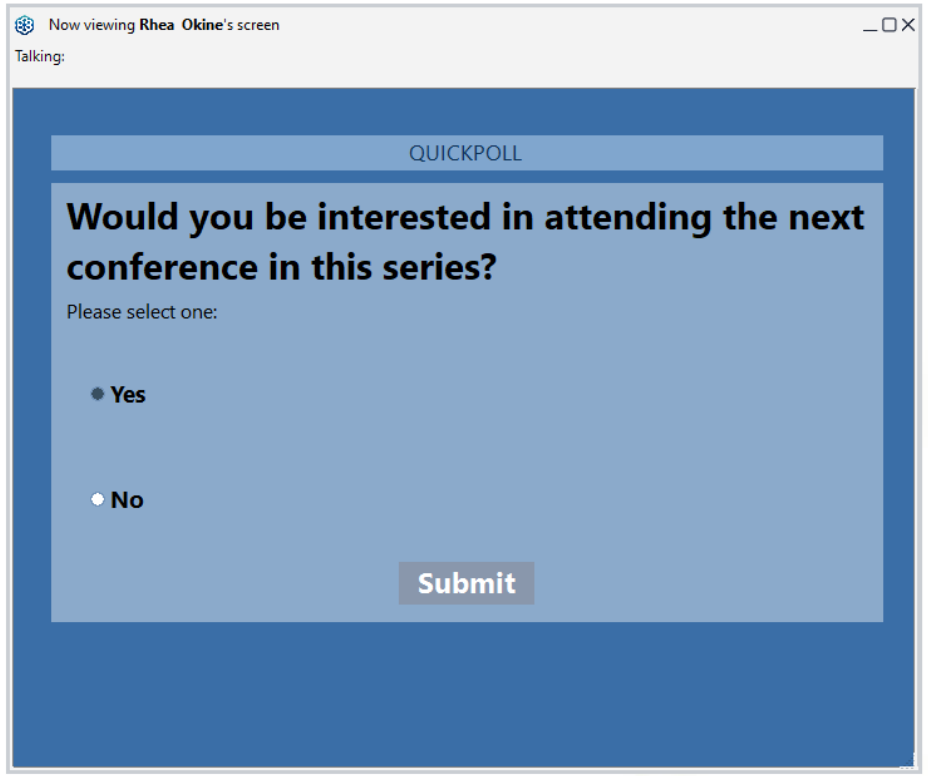

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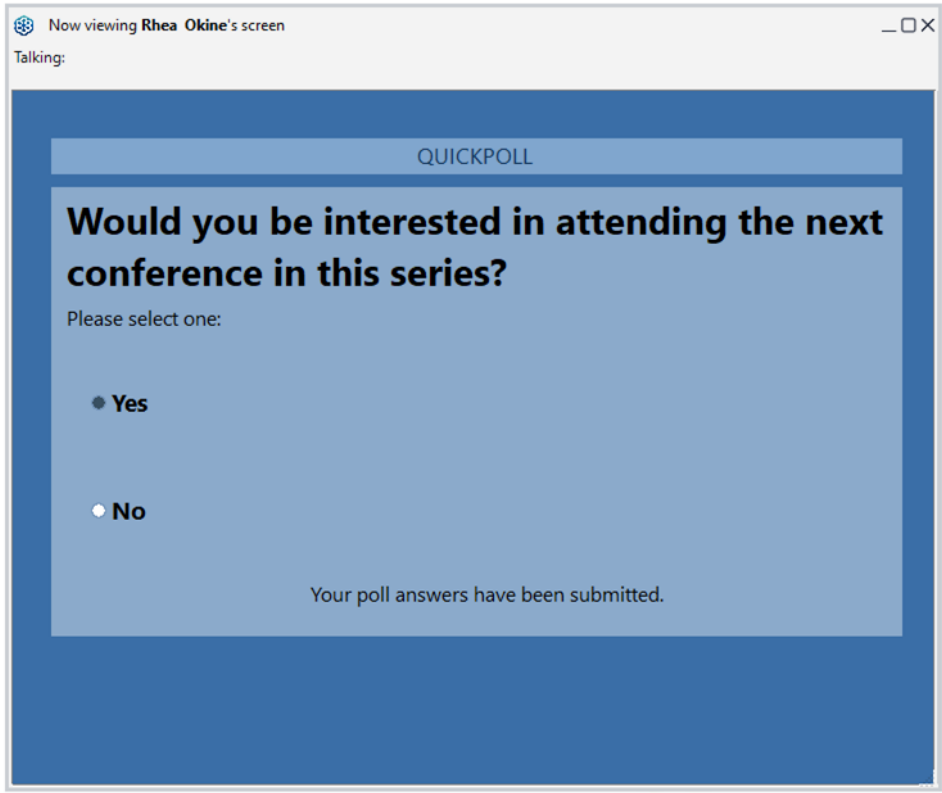

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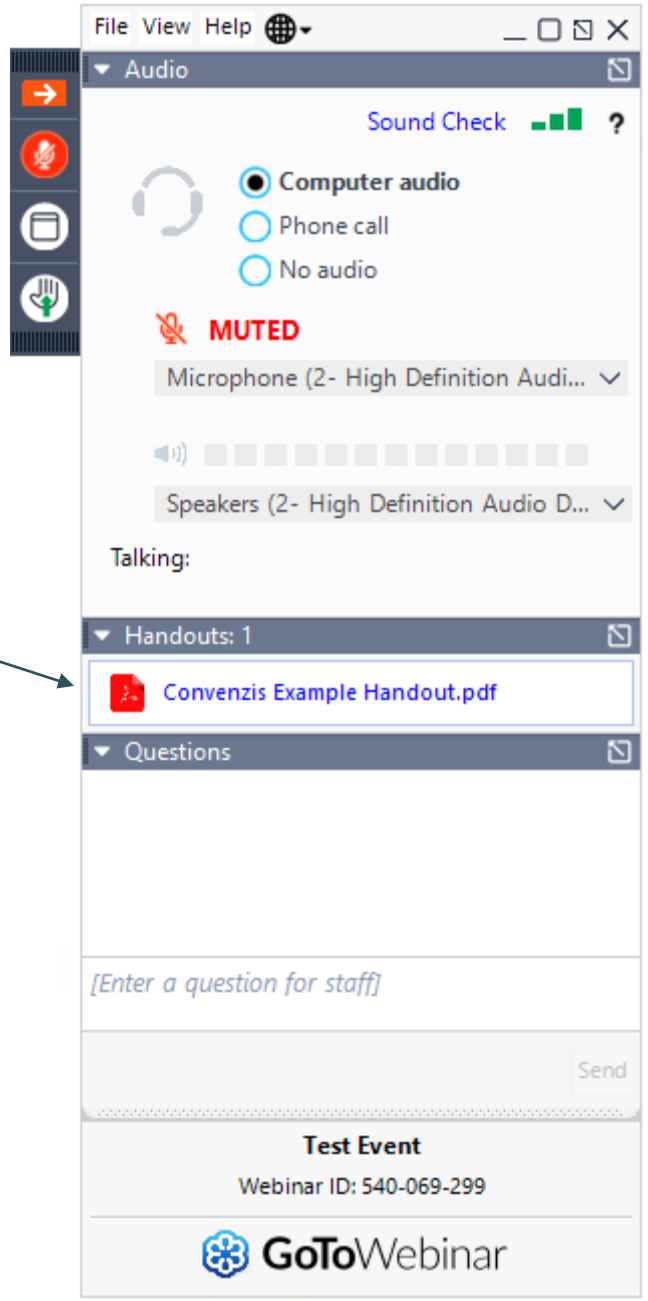


Understanding Genomics in the NHS Conference 2022

SPEAKING NOW

Kate Tatton-Brown

Professor in clinical genetics and genomic education; clinical director & head of the Genomic Education Programme within Health Education England; consultant clinical geneticist - Health Education England / St George's University Hospitals NHS Foundation Trust

I will be discussing…

"The Genomics Education Programme: Upskilling the Healthcare Workforce"

Genomics Education Programme

NHS
Health Education England

The Genomics Education Programme




Professor Kate Tatton-Brown

Clinical Director and head of the Genomics Education Programme

Health Education England

Background

Video courtesy of Dr Katie Snape

The genomics revolution

Prevention

Diagnosis

Treatment

The genomics revolution

Prevention

E.g:
Polygenic risk scores
Newborn WGS screening
Cell free tumour DNA

Diagnosis

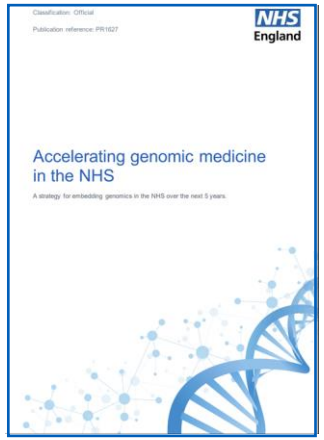
E.g:
Rare Disease
Somatic testing in cancer

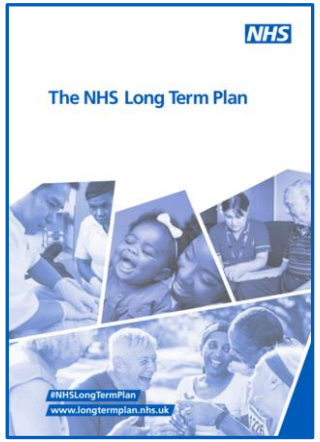
Treatment

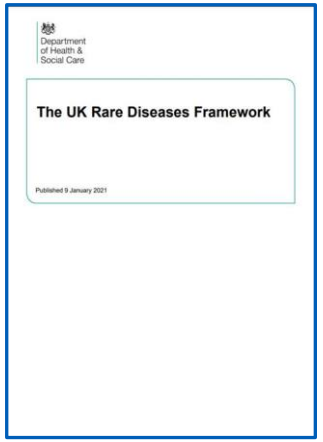
E.g:
Gene–directed therapies
Pharmacogenomics

The Genomics Education Programme

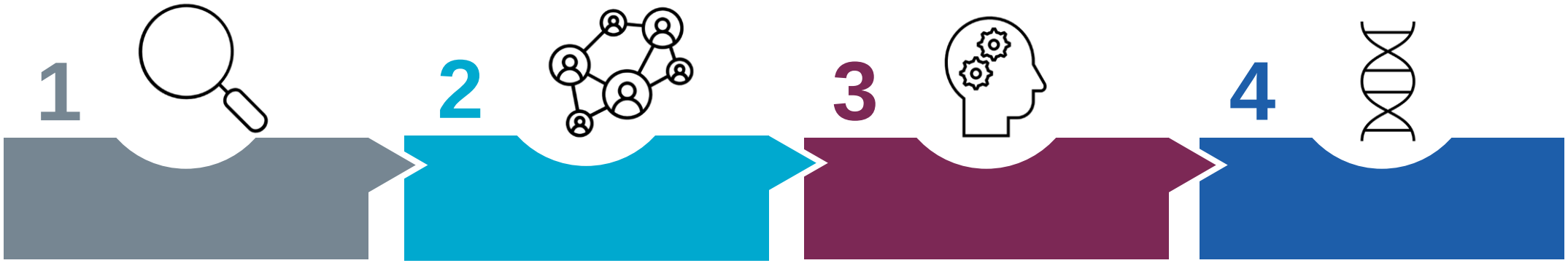
To upskill at scale and pace the multi-professional, multi-specialty and multi-regional 1.3 million healthcare workers to adopt and utilise genomic medicine for the diagnosis and management of patients







The GEP workstreams



Identify NHS workforce needs

…and build and join networks across the country

…to help educate and develop the NHS workforce

….and increase awareness of genomics across healthcare

1. Identify workforce needs

- Workforce surveys: medical and pharmacy
- Community feedback

1. Identify workforce needs: CPI

- **C**linical **P**athway **I**nitiative
- Method of scoping workforce requirements, mapped to patient pathways
- Competency based
- Avoids duplication, shares best practice

	Identify at-risk individuals	Assess individual genetic risk	Assess family history	Explain test and consent	Arrange genetic testing
Identify learning needs	1. Understand what familial hypercholesterolaemia (FH) is and recognise its associated clinical features 2. Recognise clinical signs that could indicate FH	1. Understand what FH is and recognise its associated clinical features 2. Be able to assess individual risk of FH	1. Understand what FH is and recognise its associated clinical features 2. Be able to take and draw a family history 3. Be able to identify autosomal dominant inheritance pattern based on family history	1. Able to explain genetic testing in accessible language 2. Understand implications of positive and negative results for the family 3. Understand what variants of uncertain significance are	1. Understand the processes needed to send off a genetic test 2. Understand the GMSA/GLH structure
Identify resources	FH factsheet (1, 2)	FH factsheet (1) Genetic risk assessment tool and allied learning (2)	FH factsheet (1) Family history tool and supporting resources (2) Taking and Drawing a Genetic Family History course (2) Autosomal dominant inheritance animation (3)	Talking Genomics: Tips and Tools for Communicating with Patients course (1) Let's Talk About Genetic Testing film series (1) Discussing Diagnostic Germline Tests course (2, 3)	Local/regional guidelines (1, 2)
Workforce identified					

2. Build and join networks:

"Do once and share"

- Facilitate flow of information: national to local, local to national
- Share expertise/good practice
- Avoid duplication

- Work with devolved nations
- Primary care SIG
- Pharmacy round table
- Education and training lead group
- Workforce steering group

3: Educate and develop the workforce

- Reactive learning
- Proactive learning
- Genomic Training Academy

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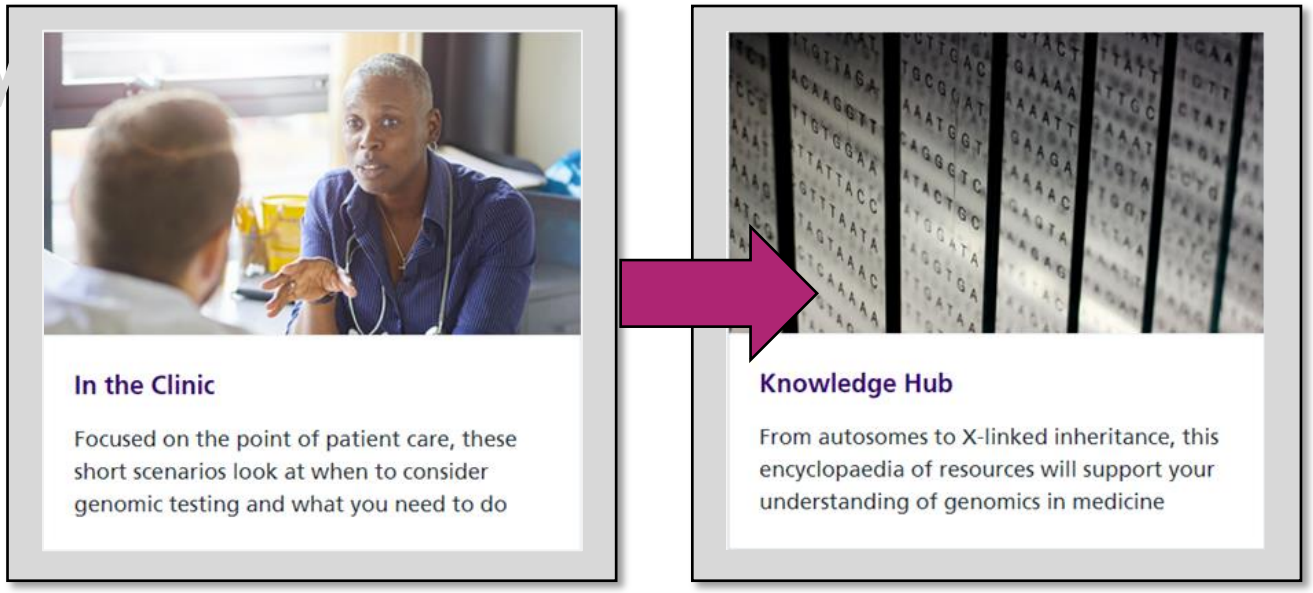
- Reactive learning
- Proactive learning
- Genomic Training Academy

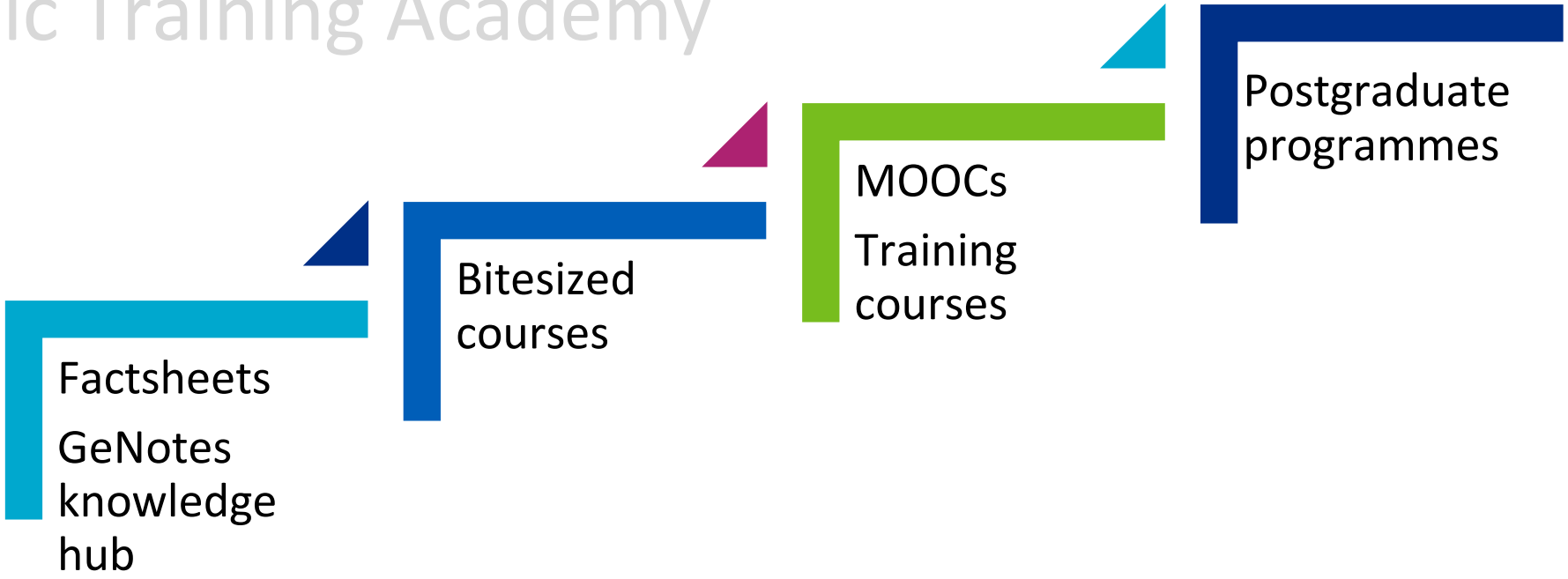
Genomics Education Programme

GeNotes
Genomic notes for clinicians



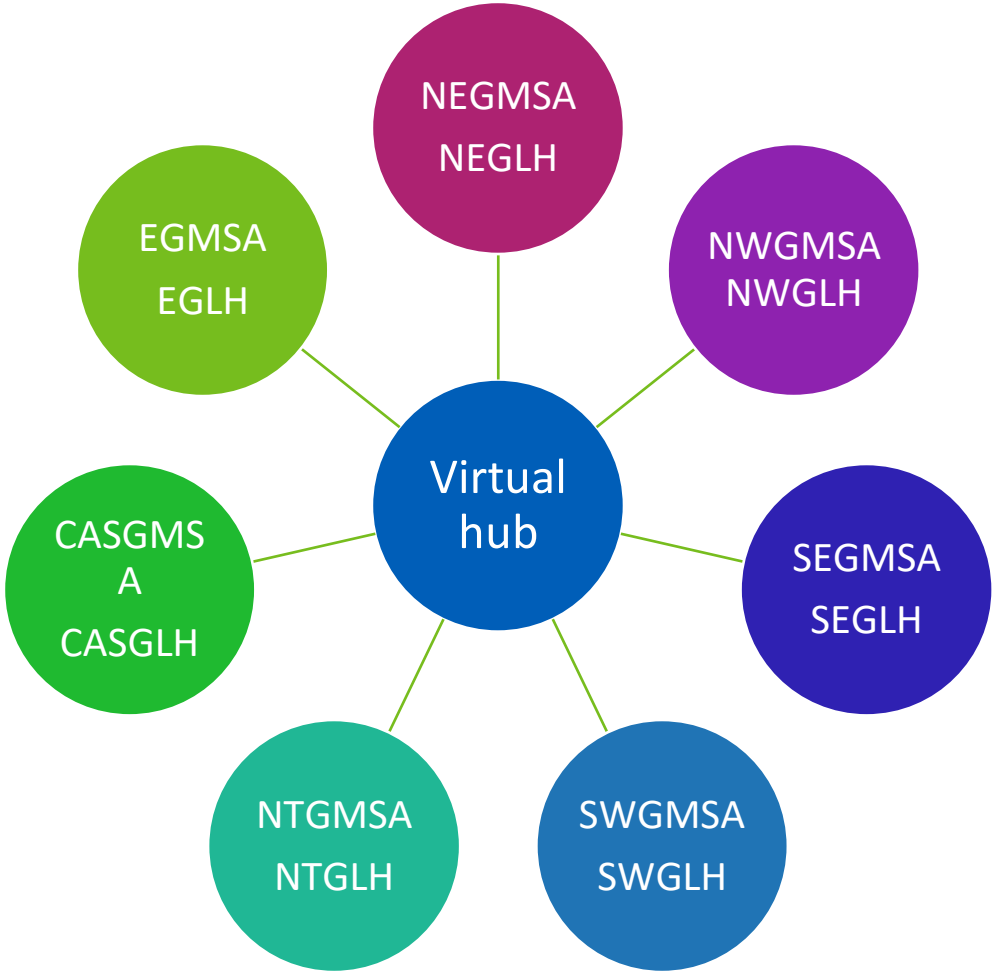
3: Educate and develop the workforce

- Reactive learning
- Proactive learning
- Genomic Training Academy



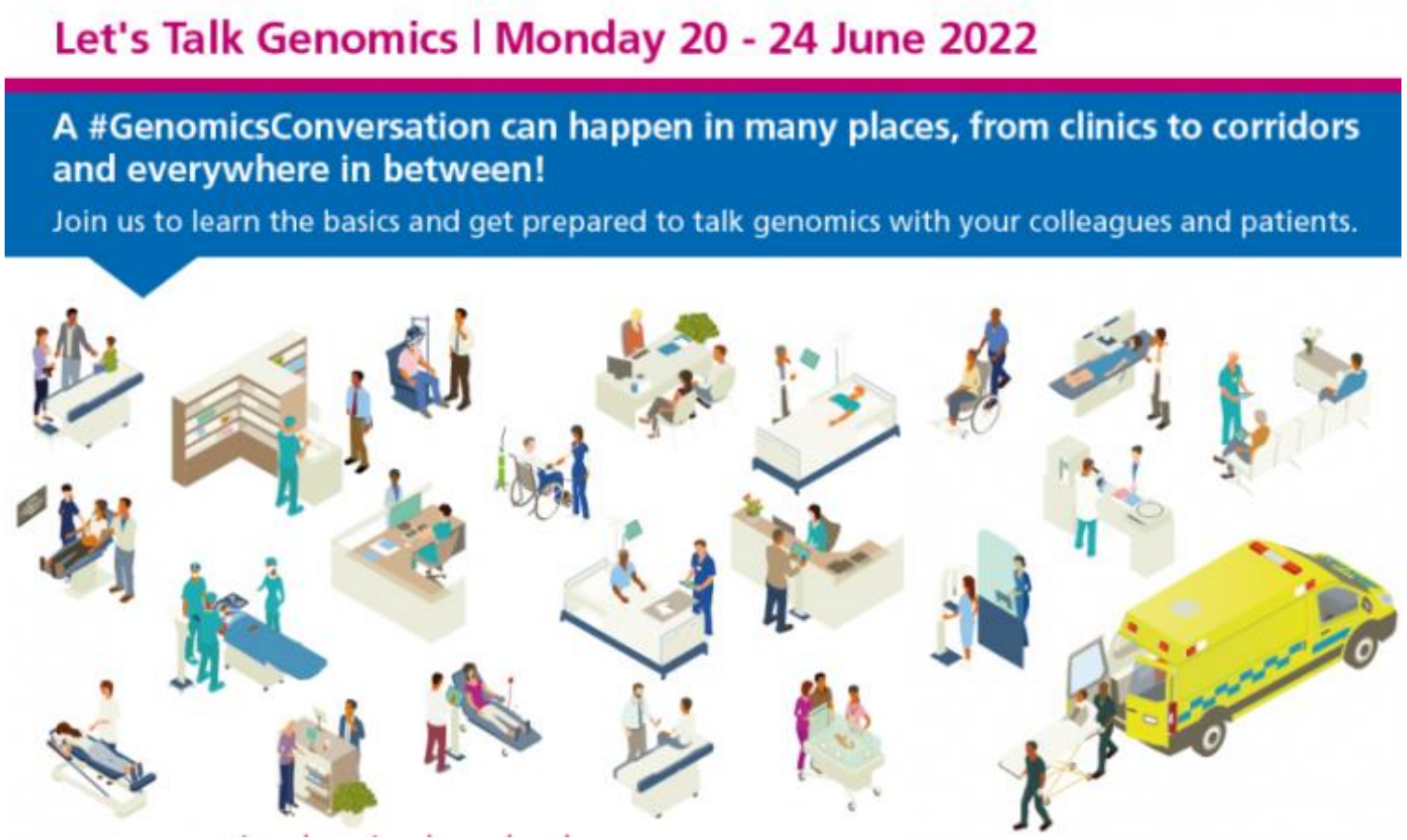
3: Educate and develop the workforce

- Reactive learning
- Proactive learning
- Genomic Training Academy

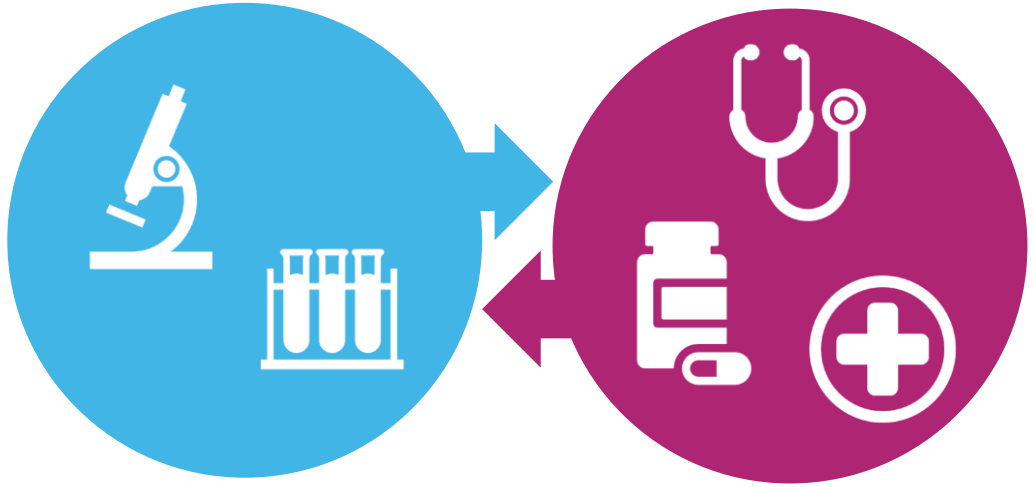


4. Increase awareness of genomics

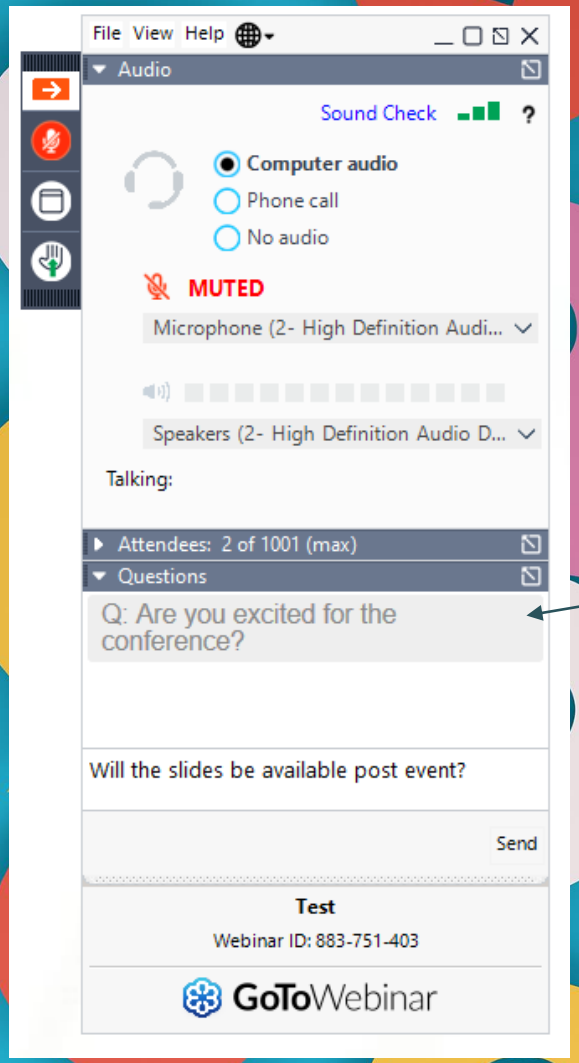
- Week of action
- Month of genomics
- Blogs



Summary



- The last decade has witnessed the emergence of new genomic technologies;
- These are transforming healthcare;
- It is essential that healthcare workers are appropriately trained and educated to use genomic data and understand rare disease;
- Genomic education and training must be prioritised.



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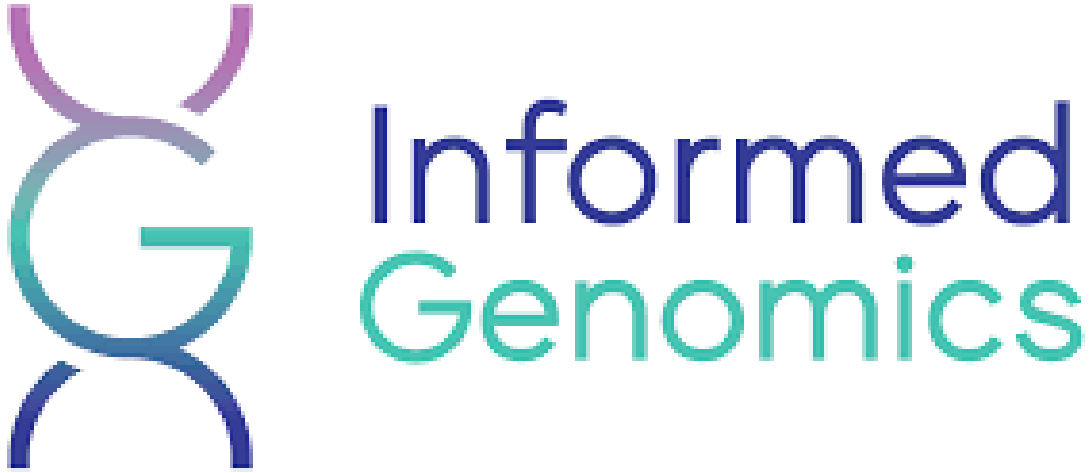
UP NEXT...



Understanding Genomics in the NHS Conference 2022

SPEAKING NOW

Ian Cook

Commercial Director
Informed Genomics Ltd

I will be discussing…

"Informed Genomics, an industry partner to deliver Genomics Healthcare Services"


Informed
Genomics

Informed Genomics

An Industry Partner to Deliver Genomic Healthcare Services

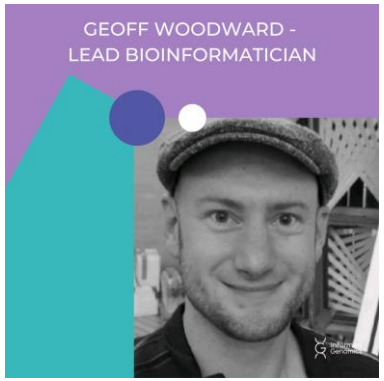
Informed Genomics an Introduction

- UK Genomics Services Company, based in Birmingham
- ISO 15189:2012 accredited laboratory
- Quality and patient-focussed
- Small but rapidly growing
- Moving into new, custom built laboratories in 2023
- Mission:
    - To provide accessible genomic testing in cancer, enabling earlier diagnosis, personalised treatments and improved patient outcomes.

The IGL Core Team

Previously Principal Clinical Scientist within the West Midlands Regional Genomics Lab, huge experience of managing within a clinical genomics lab.

Dr Louise Harewood joined the company from her previous role as Genomics Scientific Lead at the Precision Medicine Centre of Excellence in Belfast.



HCPC-registered Clinical Bioinformatician with experience of working within both the NHS and industry.

Former Principal Clinical Scientist for the Molecular Pathology Diagnostic Service, Birmingham, vast experience of managing NGS services in oncology.

Extensive experience working within a Clinical Laboratory environment in Quality Management. Vital for maintaining ISO 15189:2012 standards.

Hereditary Cancer Screening - Why Test?

- 50% of people in the UK will be diagnosed with cancer in their lifetime
- Whilst the majority are sporadic, 5-10% are linked to a hereditary genetic variant
- The presence of genetic variants in certain genes can increase the risk of different types of cancer.
- By understanding your hereditary cancer risk, you can take proactive steps and preventative measures which may reduce your likelihood of developing cancer or allow for earlier detection through access to screening programmes.
- As these variants are hereditary it gives the knowledge to inform other family members of their possible cancer risks and they too can make positive lifestyle choices.

Half of germline pathogenic and likely pathogenic variants found on panel tests do not fulfil NHS testing criteria

Tala Andoni, Jennifer Wiggins, Rachel Robinson, Ruth Charlton, Michael Sandberg & Rosalind Eeles

Scientific Reports **12**, Article number: 2507 (2022) | Cite this article

Abstract

Genetic testing for cancer predisposition has been curtailed by the cost of sequencing, and testing has been restricted by eligibility criteria. As the cost of sequencing decreases, the question of expanding multi-gene cancer panels to a broader population arises. We evaluated how many additional actionable genetic variants are returned by unrestricted panel

Why test with IGL?

- Testing based on saliva sample (can also process blood)
- All testing, analysis and interpretation is performed at our own ISO 15189:2012 accredited genomics laboratory in the UK.
- All results are interpreted by our team of HCPC-registered clinical scientists.
- IGL place quality at the heart of all we do – all of our scientists are NHS-trained.
- Our panels have been designed, based on solid clinical evidence, to ensure that the genes tested can provide meaningful, actionable results.
- Our service includes access to a GCRB-registered genetic counsellor with 20+ years experience both within and outside of the NHS.
- Fast TAT – result within 10 - 15 working days of receiving sample at laboratory
  - Reduced anxiety for the customer
- Modular service available

Clinical Report

Informed Genomics
Birmingham Research Park
97 Vincent Drive
Birmingham

Contact XXX XXXX
XXXXX@XXXXXXX

Hereditary Cancer Susceptibility Report

Status - FINAL

IGL ID:
Patient Name: Michelle Doe
Date of Birth: 14/05/1992
Gender:

Requested By:
Referral Centre:
Your lab ref:

Specimen:
Collection: 09/08/2022
Received: 18/08/2022
Report date:

Result Summary: Evidence of a pathogenic variant detected

A pathogenic variant associated with Hereditary cancer susceptibility was detected in the BRCA2 gene. The identification of this variant significantly increases the risk of developing cancer during your lifetime.

Variant Details

Gene	Transcript	Genotype	Protein Change	Exon	Zygosity	^Classification
BRCA2	NM_000059.4	c.7978T>G g.32363180T>G	p.(Tyr2660Asp)	18	Heterozygous	Pathogenic

^See Evidence for pathogenicity section for details on the evidence used to define pathogenicity. Refer to basis of test for classification guidelines.

Variant Impact

A pathogenic heterozygous variant has been detected in this sample in the BRCA2 gene. BRCA2 is a TS gene is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis.

Heterozygous BRCA2 pathogenic variants cause cancer susceptibility (OMIM:604370 and 614320) and the presence of this variant increases the risk of developing cancer in particular Breast or ovarian cancer although BRCA2 mutations can also result in other cancers.

Implications

Since genetic changes are often shared within families, any offspring will be at a 50% risk of inheriting this variant and disorder. Other relatives, particularly females are at increased risk of this disorder as there is a chance that they too have inherited this variant.

BRCA2 mutations do not have a 100% penetrance which means that not everyone with a variant will develop cancer therefore this result does not mean you have cancer or that you will develop cancer in your lifetime.

Clinical Assurance

- Interpretations based on ACMG, ACGS and CanVar specifications
- Weekly updated clinical decision support software provides our HCPC-registered Clinical Scientists with the latest evidence for determining the pathogenicity of variants
- Genetic report fully compliant to best practice guidelines
- Only pathogenic and likely pathogenic variants are reported as standard
- Complete test has been thoroughly validated and submitted for UKAS accreditation.
- IGL operates a robust QMS that adheres to the standards of ISO 15189:2012 accreditation

.

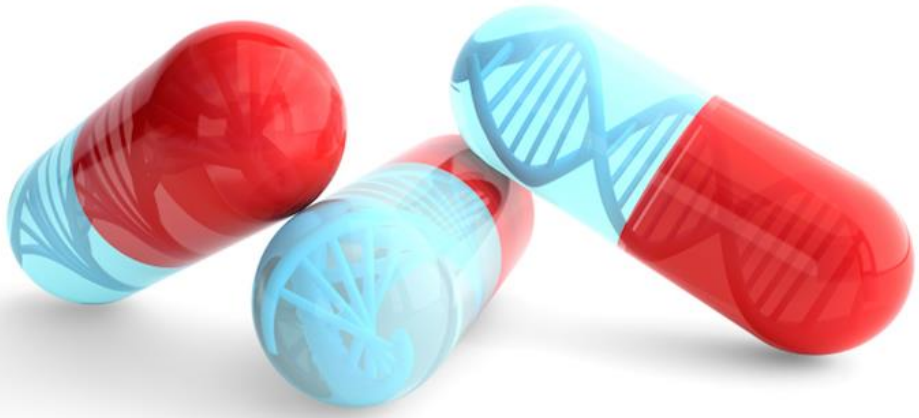
Pharmacogenomic Testing

"The aim of pharmacogenomics is **to make sure patients get the right drug, at the right dose, at the right time to be able to improve their outcomes, treat their symptoms, cure their disease and prevent side-effects**."

- Majority of commonly-prescribed drugs (such as antidepressants) only work in 30-50% of people for whom they are prescribed.
- Adverse reactions to medications account for 6.5% of UK hospital admissions
- 15% of hospital inpatients have an adverse reaction to a medication during their stay in hospital.
- Together, these result in around 8,000 overnight stays in hospital beds each year, costing the taxpayer £1 billion.

Pharmacogenomic Testing

- Some pharmacogenomic testing is already available within the NHS (e.g. DPYD testing for patients planned to receive fluoropyrimidine treatment).
- Testing is limited.
- Some of this work is already outsourced outside of the UK.
- Improved testing can have a massive impact on not multiple care pathways e.g. oncology, psychiatry, cardiology, pain management etc.

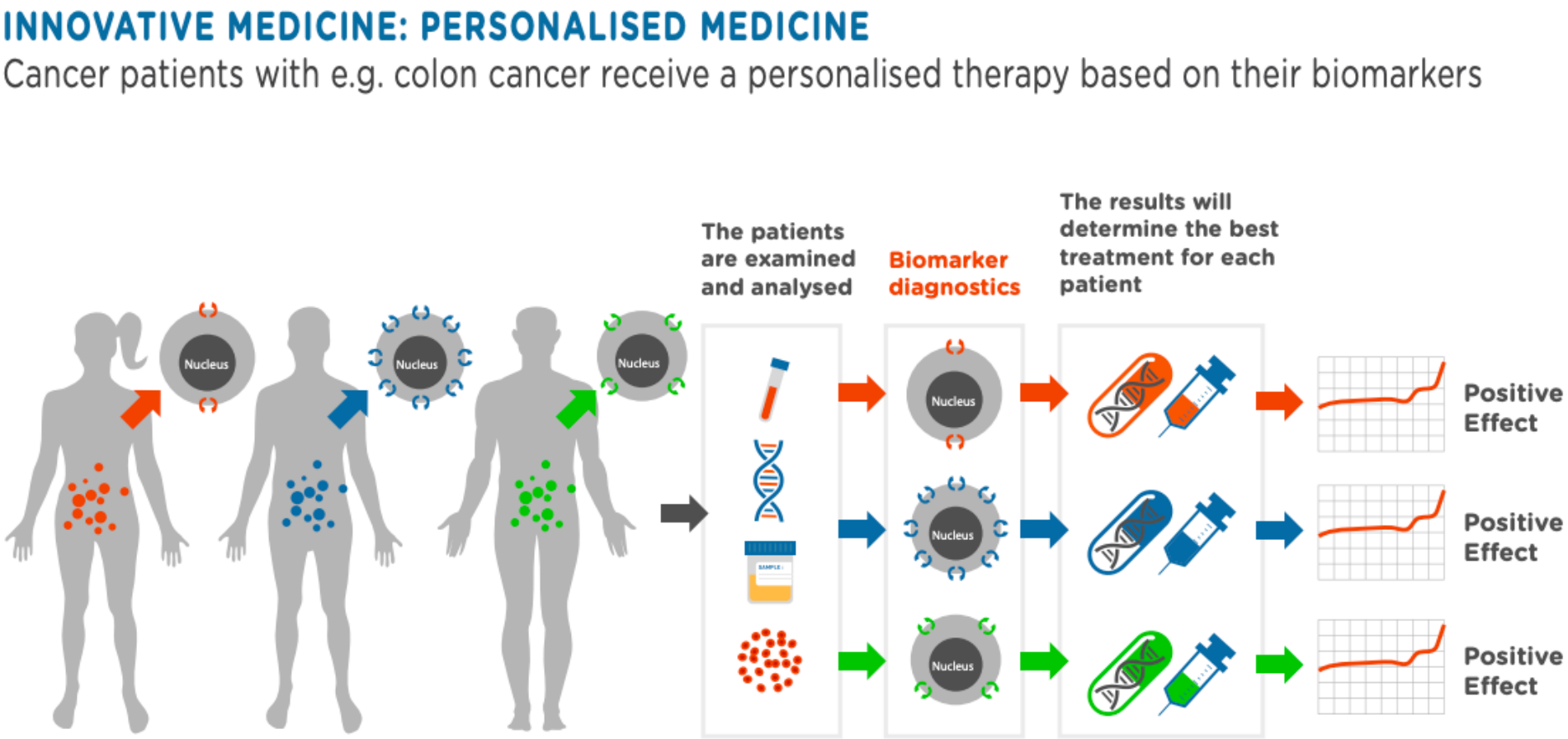


Pharmacogenomic Testing

- Informed Genomics will offer an extensive panel of pharmacogenomic hotspots with a known association with drug metabolism.
- Aid in treatment selection and dosing
- Comprehensive, actionable report on drugs used in a wide array of different medical specialities.
- Simple sampling – saliva/blood
- Short TAT – important for patients experiencing adverse affects or where a treatment decision needs to be made.
- Affordable
- Potential to save NHS millions £ in mis-prescribed drugs

Solid Tumour Genomic Tests

- Personalised medicine has been a buzz word for over a decade

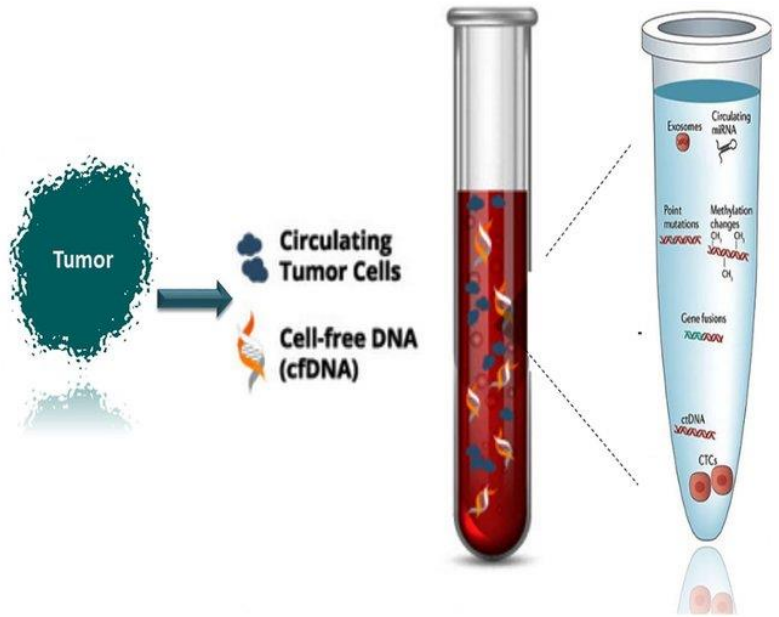


Solid Tumour Genomic Tests

- Personalised medicine has been a buzz word for over a decade
- Several individual tests are offered routinely to patients e.g. small targeted gene panels for colorectal carcinoma.
- Testing useful but sometimes limited genomic information for treatment of disease.
- Generally performed on FFPE tissue – can present issues such as:
  - Limited amount of material to test
  - Degraded DNA
  - Formalin induced DNA artefacts
- Limited ability to monitor treatment efficacy, residual disease and disease progression.
- Access to more comprehensive tumour profiling and liquid biopsy testing limited by high costs.

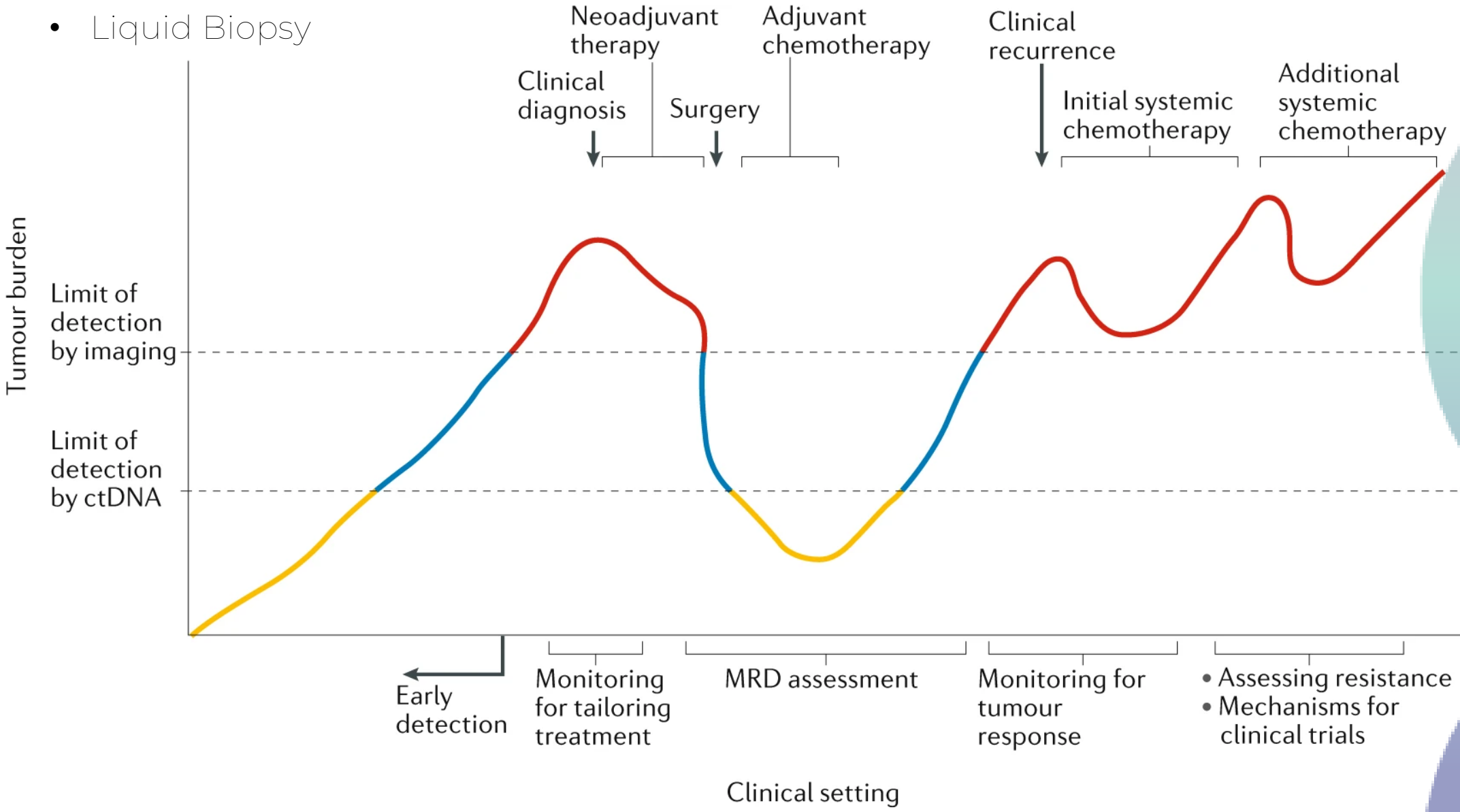
Solid Tumour Genomic Tests

- Benefits of liquid biopsy:
  - Easy sampling – blood sample versus tumour biopsy.
  - Faster TAT from sampling to result.
  - One sample can provide both tumour material and normal germline material to serve as control.
  - Can detect genetic variants at lower levels –
    - Detection of rare genetic events
    - Monitoring of MRD
    - Assessment of disease progression
    - Early detection of resistance to therapy



Solid Tumour Genomic Tests

- Liquid Biopsy

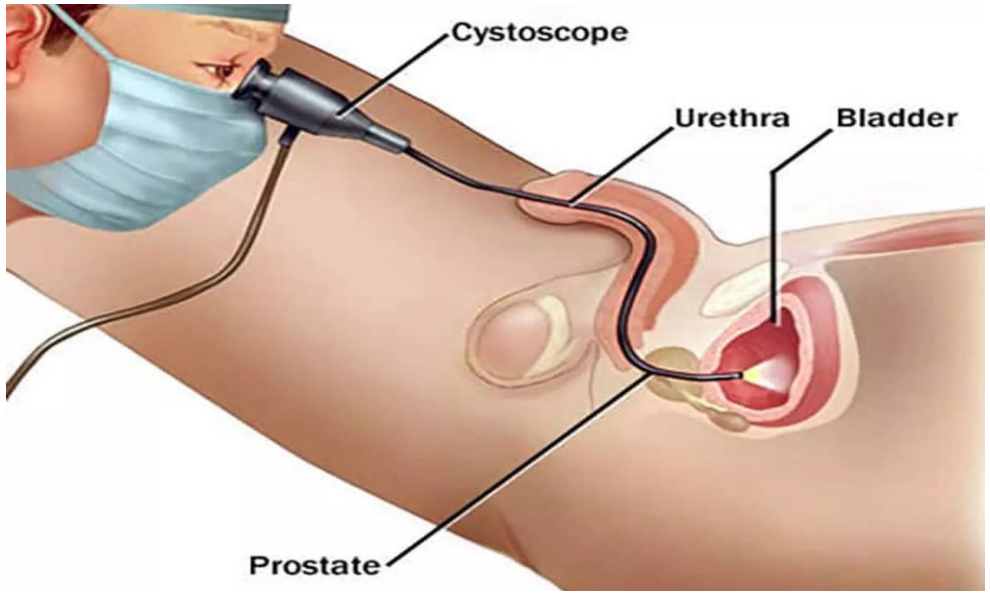


Solid Tumour Genomic Tests

- IGL aim to introduce comprehensive tumour profiling at an affordable price within the UK.
- Available for both traditional biopsy (FFPE) and also liquid biopsy.
- Will detect different variants that can be important in driving disease but are also critical for determining the most effective treatment strategy
  - SNVs, indels, rearrangements, CNVs, MSI and TMB.
- Will contain relevant genes for the majority of solid tumour types.
- Smaller, disease specific panels also available.
- Following primary tumour analysis, personalised STAT assays can be designed to allow for more cost-effective regular monitoring through blood sampling.

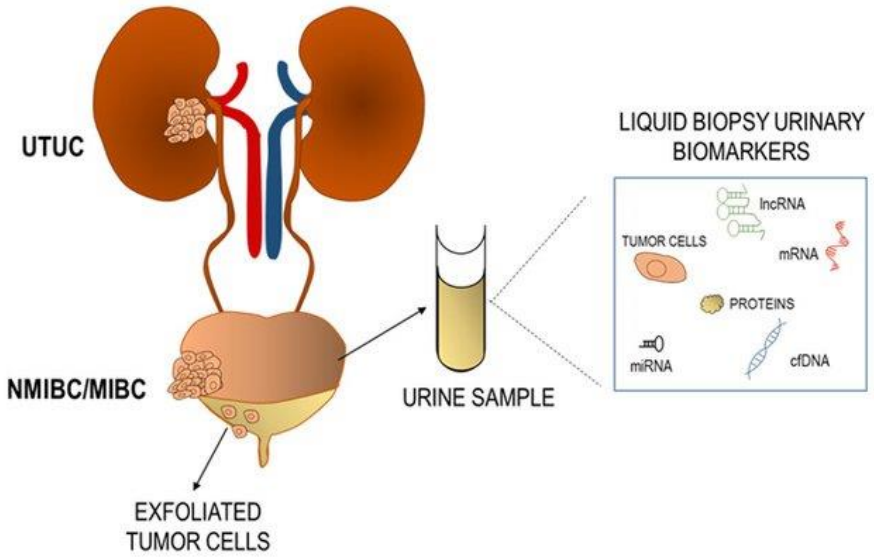
Bladder Cancer

- 10,000 new cases diagnosed each year in the UK
- 11th most common cancer
- Blood in urine is most common symptom
- Traditional follow up is flexible cystoscopy – uncomfortable and expensive
- 110,000 cystoscopies performed per year in UK
- Cost of £55M to NHS



Bladder Cancer

- IGL to offer a non-invasive, urine based genomic screen.
- Detection of genomic variants in cancer cells and cfDNA within urine
- Can eliminate the need for flexible cystoscopy in 88% of cases.
- Simple sampling – urine sample can be provided at home or in clinic.
- Short TAT to eliminate anxiety.
- Affordable test – obvious potential to save the NHS £Millions.
- Clinical Trial to start early 2023.

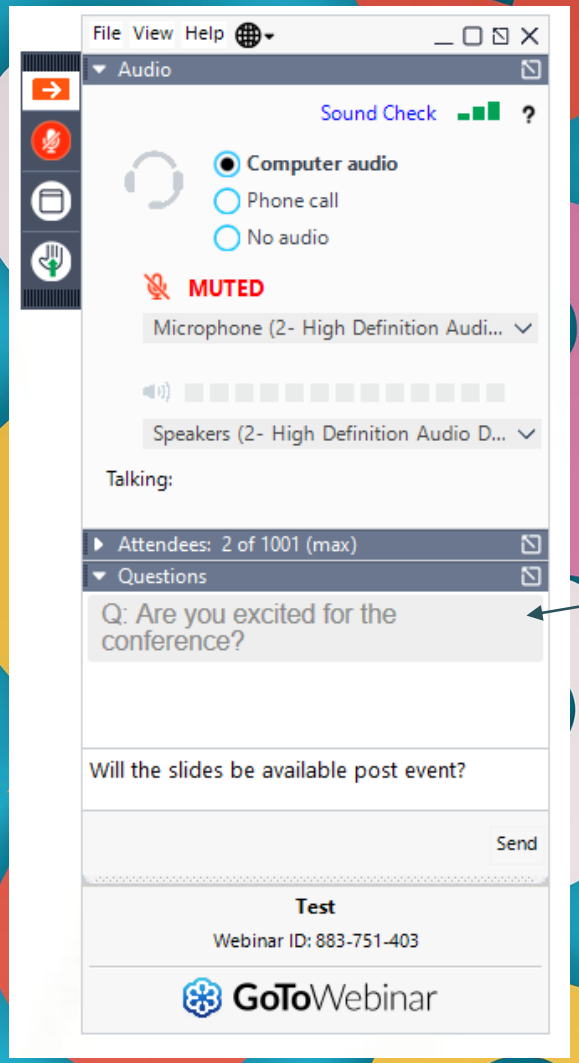


Summary

- Informed Genomics is a perfect outsourcing partner for the NHS in Genomic Healthcare.
- ISO 15189:2012 Accredited lab within the UK.
- All clinical service will be submitted for UKAS accreditation.
- Strong team of HCPC-registered Clinical Scientists.
- Mission is to provide highest quality services at affordable prices, making genomic testing more accessible.
- Able to provide short TATs for time sensitive tests.
- Focussed on actionable genomic testing, mainly in the oncology pathway.
- Also able to provide RUO sequencing services for research projects/development

Informed Genomics


Informed
Genomics



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Understanding Genomics in the NHS Conference 2022

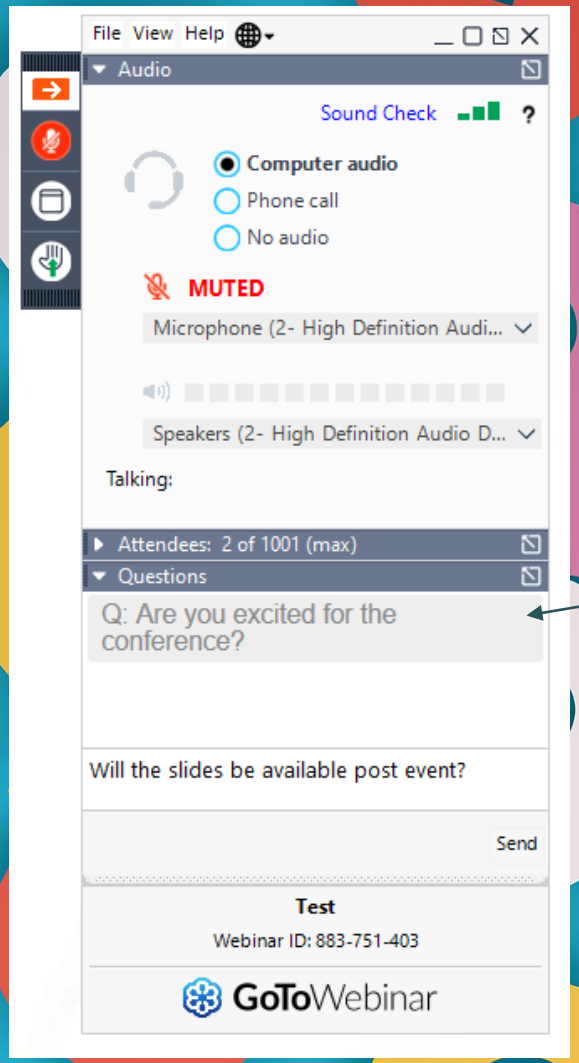
SPEAKING NOW

Richard Scott

Chief Medical Director
Genomics England

I will be discussing…

"Genomics England's mission is to continue refining, scaling, and evolving our ability to enable other to deliver genomic healthcare and conduct genomic research"



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Understanding Genomics in the NHS Conference 2022

UP NEXT...

Understanding Genomics in the NHS Conference 2022

SPEAKING NOW

Tonya McSherry

VP Sales EMEA
Oxford Nanopore Technologies plc

I will be discussing…

"Transforming the future of Healthcare"

Transforming the future of healthcare

Tonya McSherry
VP Sales, EMEA

Understanding Genomics in the NHS
29 November 2022

Oxford NANOPORE Technologies

Many of the world's problems today can be improved with better access to biological information

Food security

- How can I grow a more efficient crop?
- How can I stop food spoilage?
- How can I quality assure this product?

Health

- How can I catch illness earlier?
- How can I understand and treat it better?
- How can I live a better, longer life?

Environment

- Is this species endangered and how can I stop that?
- How is this ocean microbiome changing?
- What is in this water? Is it safe?

Until recently…we haven't had the full picture

"The National Institutes of Health (NIH) will host researchers from the Telomere-to-Telomere (T2T) consortium, who have now sequenced the remaining 8% of DNA that was unable to be sequenced by the Human Genome Project and has eluded researchers for nearly two decades."
March 31, 2022 - https://www.genome.gov/news

Oxford NANOPORE Technologies

Towards our goal of the analysis of anything, by anyone, anywhere

Today

Reshaping biological research

Continuous disruption & innovation

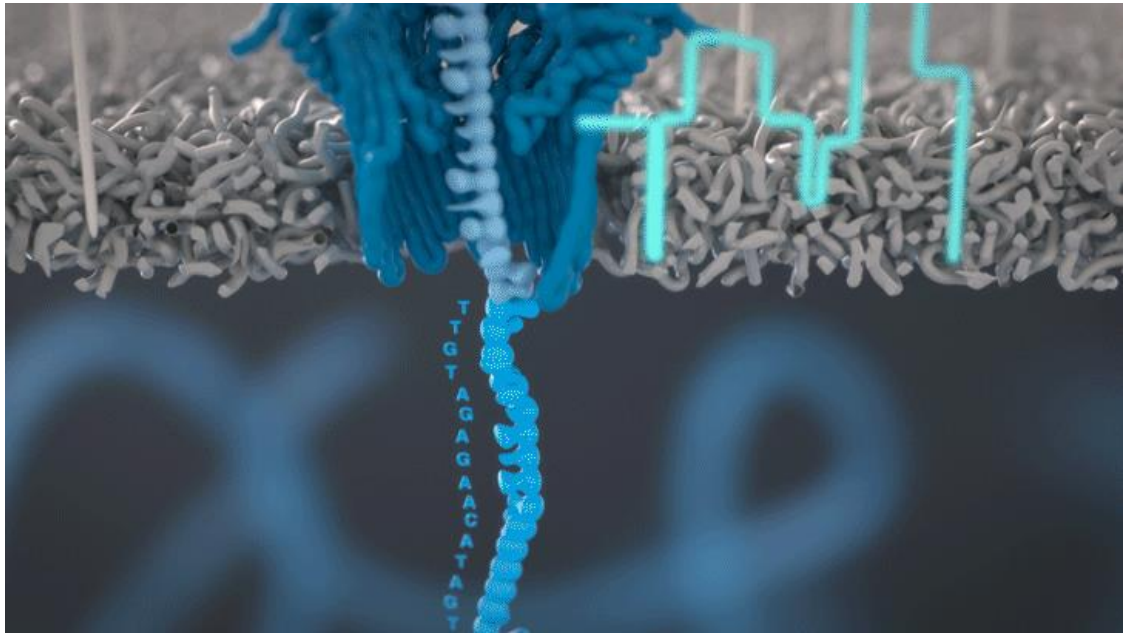
Improved translational applications

Unlocking applied capabilities

Broad opportunities from health, agriculture, supply to environment

ONE sequencing platform

The power of native sequencing



- Retain all the biological information, including methylation
- Simplify chemistry and hardware with no labels or optics required
- No GC bias, access the whole genome
- Read any fragment size

Oxford NANOPORE Technologies

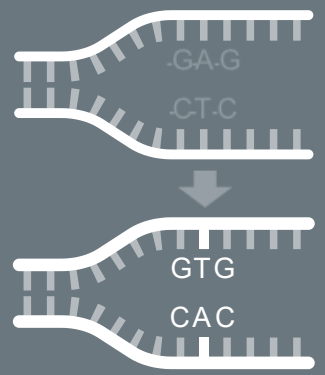
More comprehensive genomic insights

Traditional short-read SBS is limited to SNVs and indels

Nanopore provides this same information…

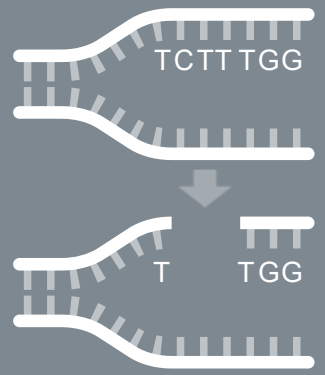
…with added features including any-length fragments and PCR-free DNA sequencing

1 SINGLE NUCLEOTIDE VARIANTS



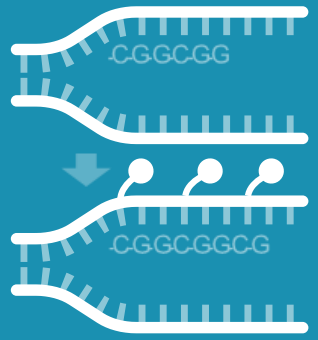
e.g. sickle cell disease

2 INSERTION / DELETIONS



e.g. cystic fibrosis

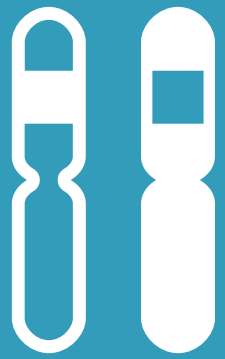
3 METHYLATION IN REAL TIME



e.g. fragile x syndrome

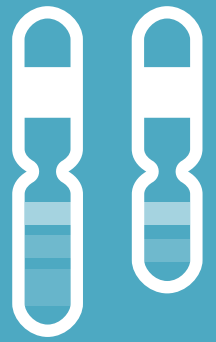
DNA methylation patterns are globally disrupted in cancer

4 STRUCTURAL VARIATION



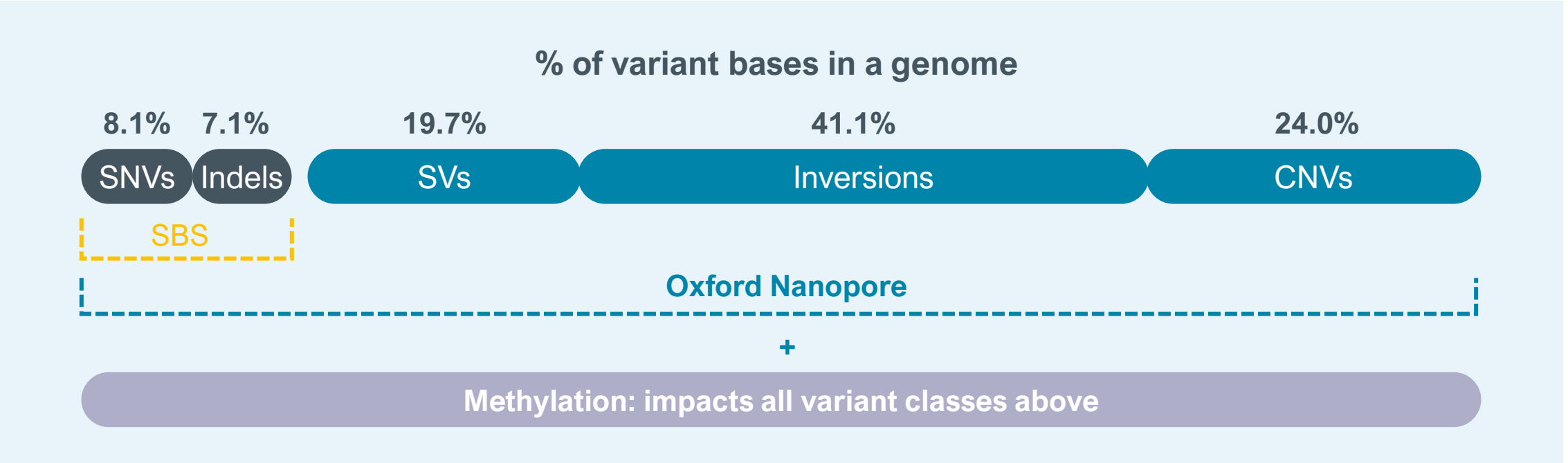
e.g. Alzheimer's, Parkinson's, Prader-Willi syndrome

5 COPY NUMBER VARIATION



e.g. autism, schizophrenia, ADHD

Variants characterised by Oxford Nanopore Technologies capture a much larger proportion of genomic variation than short-read technology



Adapted from E. Eichler. 2019. NEJM. 381:64-74.

>84% more variation + methylation — discover significant disease impact

Personalized medicine starts with the complete picture

MAYO CLINIC

8% Genome missed by SBS technologies

https://genomebiology.biomedcentral.com/articles/10.1186/s13059-019-1707-2

Children's Hospital of Philadelphia

"~ 19% of the human genome is inaccessible to conventional short-read sequencing technologies to find variants reliably"

Ahsan, M.U., Liu, Q., Fang, L. et al. Genome Biol 22, 261 (2021)

deCODE genetics

Study shows that short-reads miss 40% of all structural variation

https://www.decode.com/rounding-off-the-human-genome/; https://vimeo.com/546557078

UNIVERSITY OF EXETER

<3% of all CpG sites covered by standard genotyping approaches

Hum Mol Genet. 2022 Sep 10;31(18):3181-3190. doi: 10.1093/hmg/ddac112

UNIVERSITY OF WASHINGTON 1861

"34% of all disease-causing variation is made up of variants that are larger than a single base-pair substitution"

"Large structural variants are more than 30x as likely to affect the expression of a gene"

Evan Eichler, New England Journal of Medicine, 2019

As a result, today

Seattle Children's HOSPITAL · RESEARCH · FOUNDATION

"…approximately half of individuals with a suspected Mendelian condition remain undiagnosed"

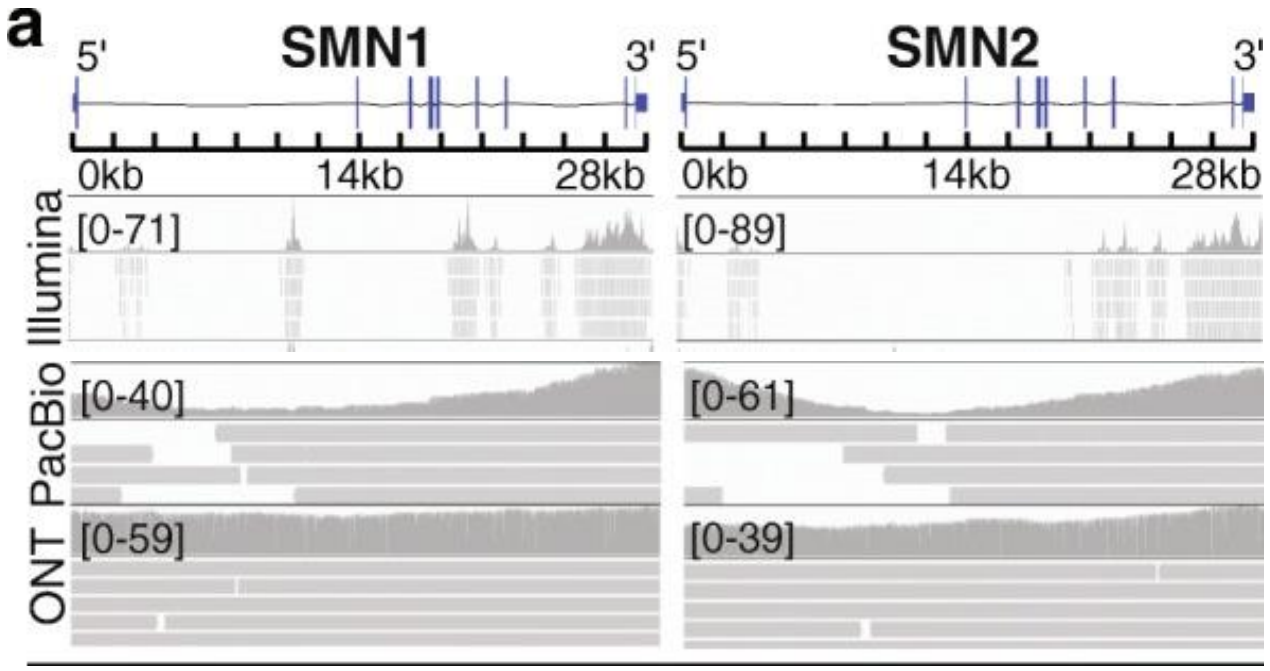
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8387463/

Oxford NANOPORE Technologies

Access “dark” regions of the human genome with nanopore technology

- 8% genome missed by SBS
- 90.4% dark regions identified by ONT data
- Nanopore fully unmasks key genes e.g. *SMN1, SMN2, CR1*

“Comparing linked- and long-read sequencing… the ONT platform performed best, both when assessing entire gene bodies, and when considering only CDS regions.”



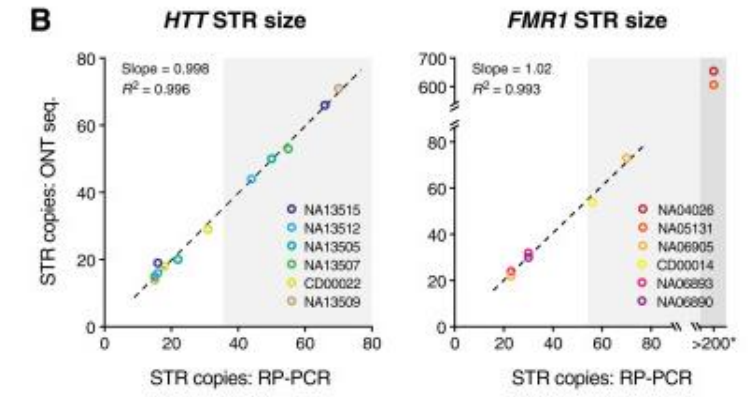
Ebbert *et al.*, Genome Biology (2019), https://doi.org/10.1186/s13059-019-1707-2

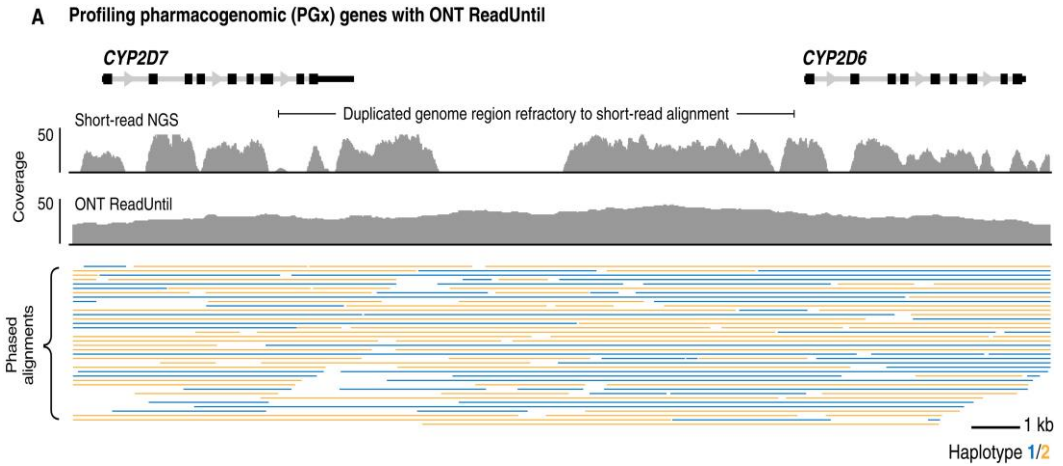
Accurately profile STR lengths in repeat expansion disorders

1
Test
50
Diseases
Adap tive
Technology
Rapid & Comprehensive Answers

Research Aims & Outcome

- Interrogation of unusually, long repetitive DNA sequences, STR expansions
- Programmable for quick target gene analysis, including pharmacogenomics – informing care
- Ending 10 years, diagnostic odyssey for one patent with CANVAS



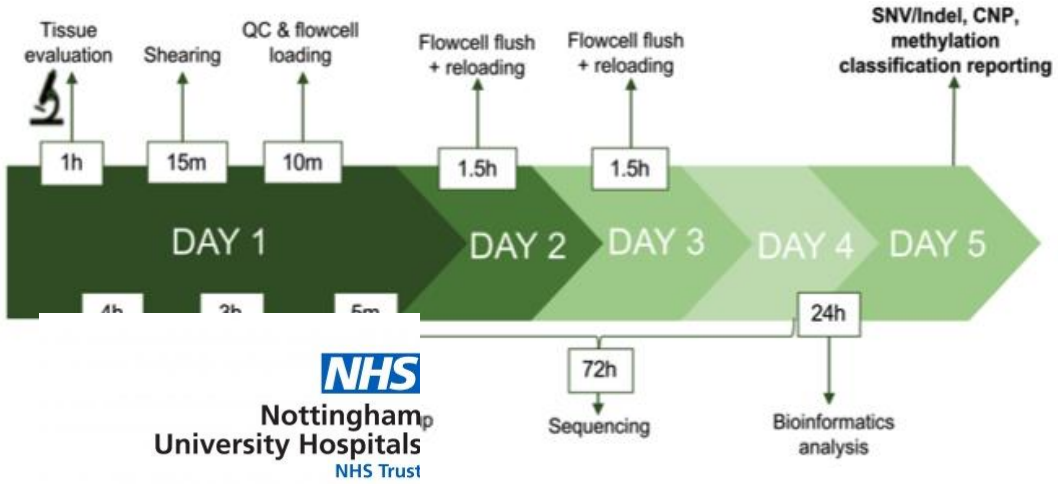


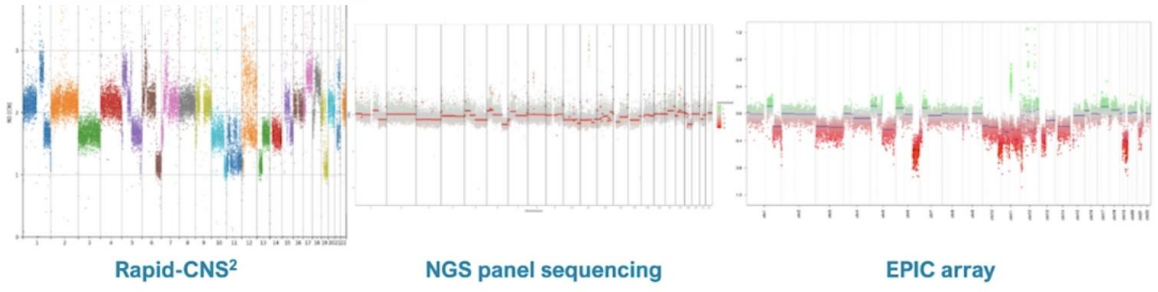
Stevanovski *et al.*, Science Advances (2022). https://doi.org/10.1126/sciadv.abm5386

Oxford NANOPORE Technologies

Rapid, comprehensive adaptive nanopore sequencing for CNS classification

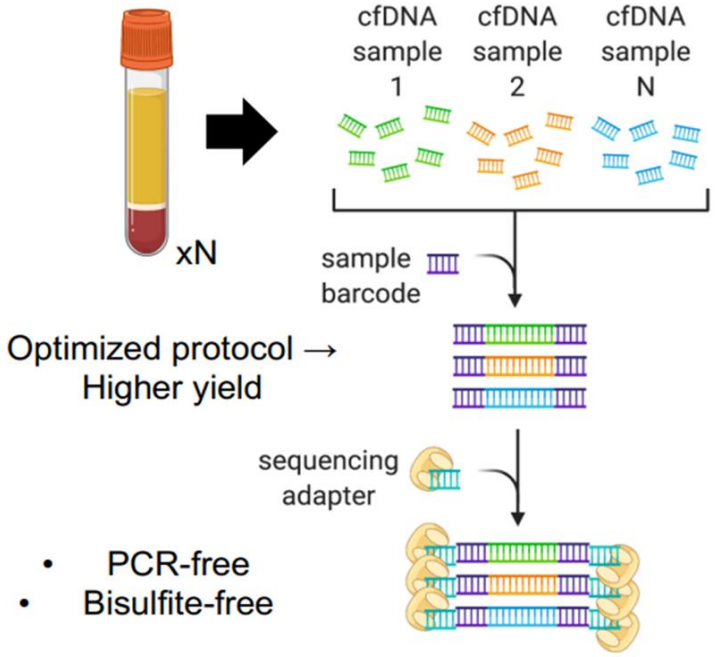
- Classification of central nervous system (CNS) tumors includes multiple molecular markers and patterns
- RAPID-CNS^2 enables:
  - Comprehensive mutational, methylation and copy number profiling of CNS tumors
  - A single, cost-effective sequencing assay.
  - Rapid turnaround time (no batching required), highly flexible target selection.

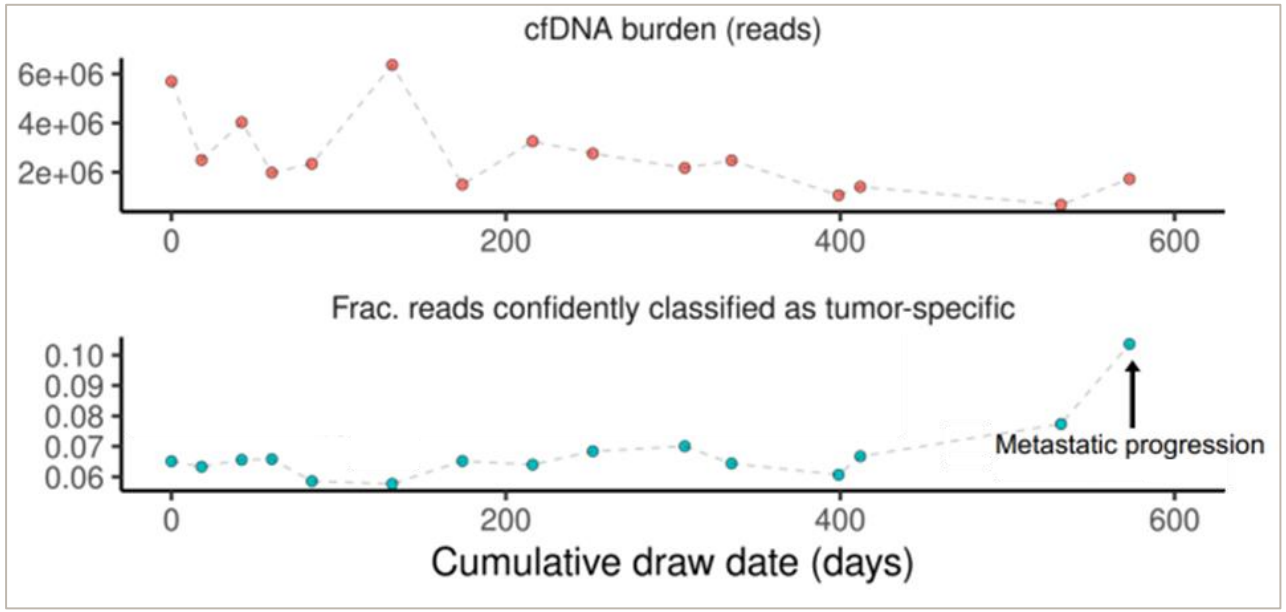




Patel *et al,* Acta Neuropathologica (2022). https://doi.org/10.1007/s00401-022-02415-6

Single molecule methylation profiles of cell-free DNA in cancer

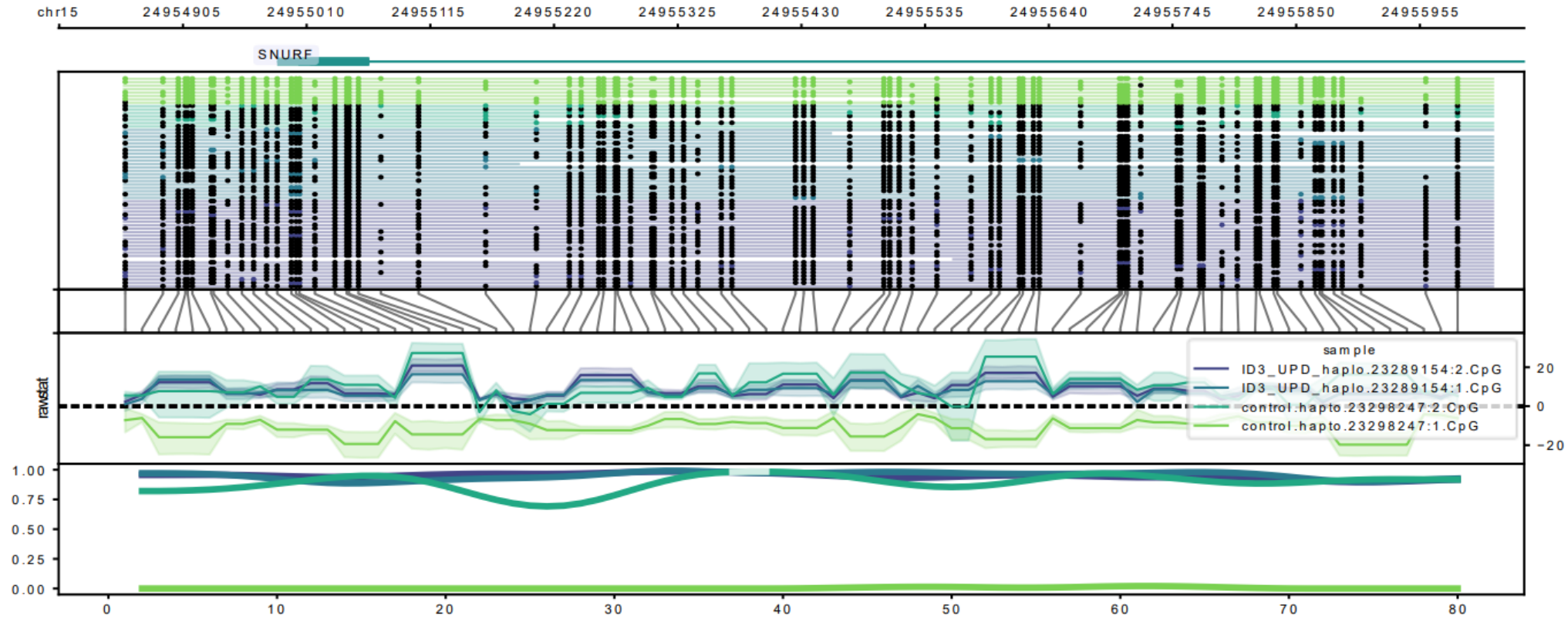




- PCR-free process generates sequencing libraries from nanogram amounts or less of cfDNA per sample

Lau *et al.*, BioRxiv (2022)., https://doi.org/10.1101/2022.06.22.497080

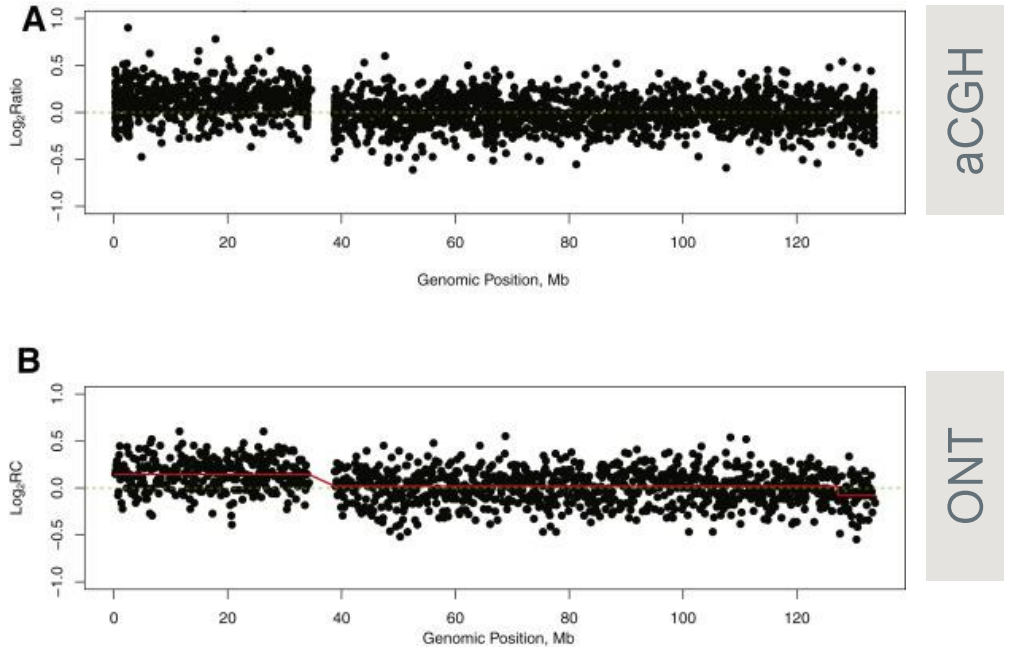
Novel common SVs in Prader-Willi Syndrome and associated psychosis



Deest M *et al*. medRxiv (2022). https://doi.org/10.1101/2022.07.18.22277235

Third-generation cytogenetic analysis – hallmark for genetic disease analysis

- Traditional approaches are time consuming, labor intensive with diagnostic times from 3-15 days
- 7 patient study showed 100% concordance to array CGH – with large chromosomal anomalies identified in 30 minutes, CNVs <500kb after 30 hours
- Higher resolution of mosaic CNVs for diseases such as Pallister-Killian syndrome



Magini P *et al*, J Molecular Diagnostics (2022) https://doi.org/10.1016/j.jmoldx.2022.03.013

Ultra-rapid structural variant detection in acute myeloid leukemia

- Proof of concept for rapid diagnosis using probe–based enrichment
- Reduced TAT with no batching
- Identification of:
  - ✓ Precise genomic breakpoint
  - ✓ Novel translocations in one-third of the tested samples
    - 80% of which involve known oncogenes.

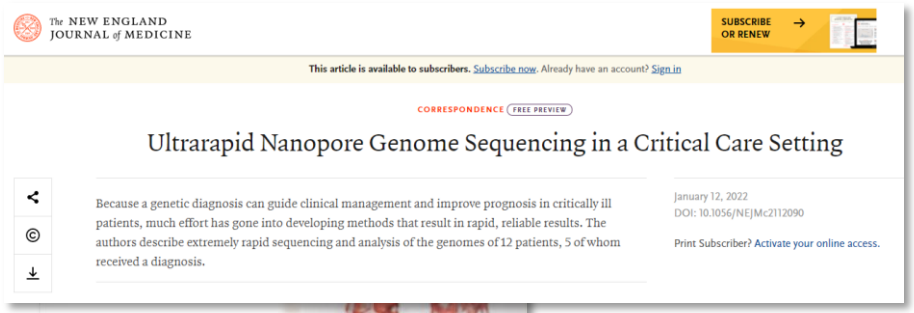
Ali R. Awan *et al.* The Journal of Molecular Diagnostics (2022); https://doi.org/10.1016/ j.jmoldx.2022.09.006)

The impact in the clinic

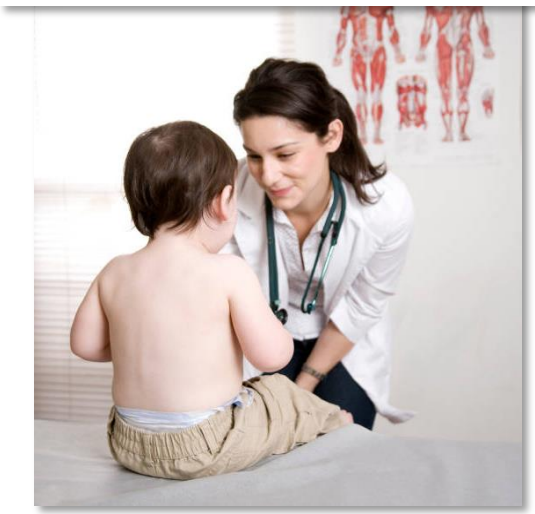
Oxford NANOPORE Technologies

Actionable & accurate information in real-time

Nanopore demonstrates the future potential to have a positive impact on critical care using ultrarapid WGS



"Our workflow combines streamlined preparation of commercial nanopore sequencing, distributed Cloud based bioinformatics, and a custom variant-prioritization approach."



"We would have been in the dark for many weeks."

Nanopore sequencing identified disease causing variant missed by standard of care, in rapid time

- 3-month old with epileptic seizures, MRI normal
- **Pathogenic variant identified in 8 hours**; definite identification of Poirier-Bienvenu neurodevelopmental syndrome
- Further testing stopped & disease management actioned
- Standard of care results returned 2 weeks later, only variants of unknown significance identified

12% more disease causing variants with comparable SNP accuracy to standard care

https://med.stanford.edu/news/all-news/2022/01/dna-sequencing-technique.html

Oxford NANOPORE Technologies

3-hour genome sequencing and targeted variant analysis in a newborn

Demonstration of ultra-rapid assessment of risk variant inheritance

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Ruling out the presence of known variants after birth

- Older sibling affected by a single gene disorder
  - Prior genetic information shared: specific gene and pathogenic variant known; adaptive sampling of region revealed another of interest
- Newborn genome sequenced:
  - Optimized workflow to reduce blood input – compatible with heel stick
  - 20 flow cells ran in parallel
  - Analysis accelerated with known genes of interest
- Confirmed newborn was not affected (nor a carrier)

Answer in < 3 hours from birth

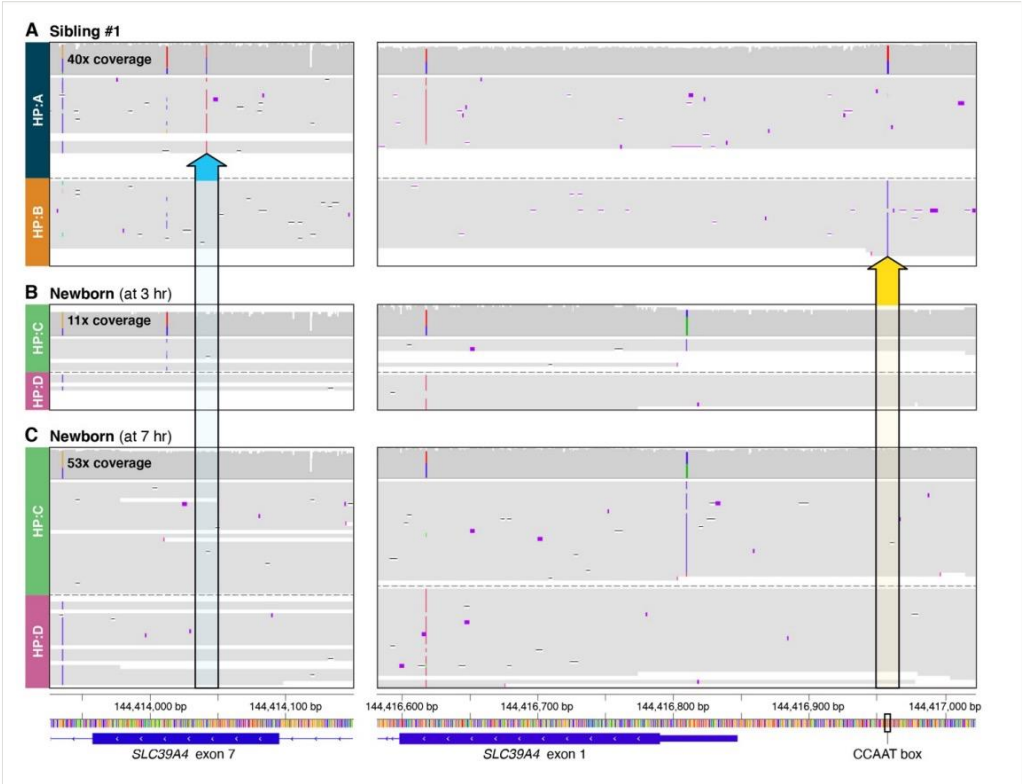


Figure: IGV screenshot demonstrating *SLC39A4* variants (blue and yellow arrows) found in affected sibling but absent from newborn research sample at 3h of life, confirmed at 7h.

Galey et al. medRxiv. DOI: https://doi.org/10.1101/2022.09.09.22279746 (Sep 2022)

Oxford NANOPORE Technologies

Case study: infectious disease

Metagenomic pathogen identification and resistance profiling in ≤6 hours

Disease overview

Lower respiratory infections (LRIs) cause >3 million deaths per year worldwide. Current culture-based analysis techniques lack sensitivity and are too slow to guide early, targeted antimicrobial therapy.

Case study

Charalampous *et al.* developed a nanopore-based metagenomics assay that enables rapid identification of LRIs, including hospital-acquired and ventilator-associated pneumonia.

- Rapid bacterial/fungal ID and AMR — ≤6 hours sample to result
- Results support earlier targeted antibiotic therapeutics
- Improves overall antibiotic stewardship
- Supports tracking of nosocomial infections

Impact

Future clinical adoption could reduce LRI mortality through earlier implementation of appropriate antimicrobial therapy, and reduce overuse of broad-spectrum antibiotics.

"Pathogens and antibiotic resistance genes can be identified in 6h. With additional sequencing time (up to 48h), it provides sufficient data for public health and infection control applications."

Charalampous et al. Nat Biotechnol. 37(7):783-792 (2019).

Benefits identified in 80% of cases at Guy's and St Thomas' Trust

Case study: deceased donor HLA typing

Sample to HLA results ~4 hours

Disease overview

High-resolution HLA typing is critical for successful solid organ transplant. In deceased donor transplantation, there is a very narrow window of opportunity for transplantation, so rapid typing of donors is paramount.

Case study

De Santis *et al.* developed a rapid, high-resolution HLA typing workflow for the low-cost Oxford Nanopore Flongle device (~$90).

- Two-field typing of 11 HLA loci
- Validated on 42 patient samples
- Compete concordance with existing typing methods
- Sample to HLA results ~4 hours

Impact

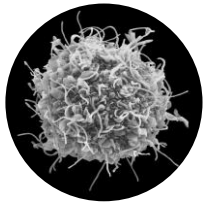
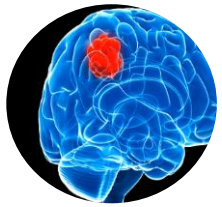
Increase in higher quality organ matches and improved transplant survival from deceased donors

"The ability to perform high-resolution typing at all HLA loci for deceased organ donor allocation prior to transplantation would have major clinical benefits, in particular for highly sensitised recipients."

De Santis et al. HLA. 96(2):141-162 (2020)

Oxford Nanopore has the potential to impact many areas of health

Combining genomic accuracy with real-time results to transform human health

Fast to market with HLA for transplant Dx TB presence/absence and drug resistance		Rapid cytogenetic tests in specialist markets		Global infection Dx and genetic screening	
					
Deceased donor Routine and registry HLA typing	**TB**	**Preimplantation (and prenatal) genomic screening**	**Cancer testing**	**Respiratory metagenomics**	**Thalassaemia screening: newborn and preconception**
Increase in higher quality organ matches and improved transplant survival from deceased donors	Improve access to rapid presence/absence and drug resistance TB	Improve reproductive choice and outcomes, and reduce costs, for couples having IVF or high risk pregnancies	Reducing delay and improving accuracy in cancer diagnosis to increase access to new therapies targeted to genetic abnormalities	Enable precise and effective treatment, contributing to better outcomes for patients for antimicrobial stewardship and for infection control	Increase global access to precision screening, enabling life saving treatments and greater reproductive choice
De Santis et al. HLA. 96(2):141-162 (2020)		Zev Williams, M.D., Ph.D. N engl j med 387;7 nejm.org August 18, 2022		Charalampous et al. Nat Biotechnol. 37(7):783-792 (2019).	Burns et al. BMC Genomics. 22(1):902 (2021)

omicon GENDX

Oxford NANOPORE Technologies

Adding valuing with new insights

Oxford NANOPORE Technologies

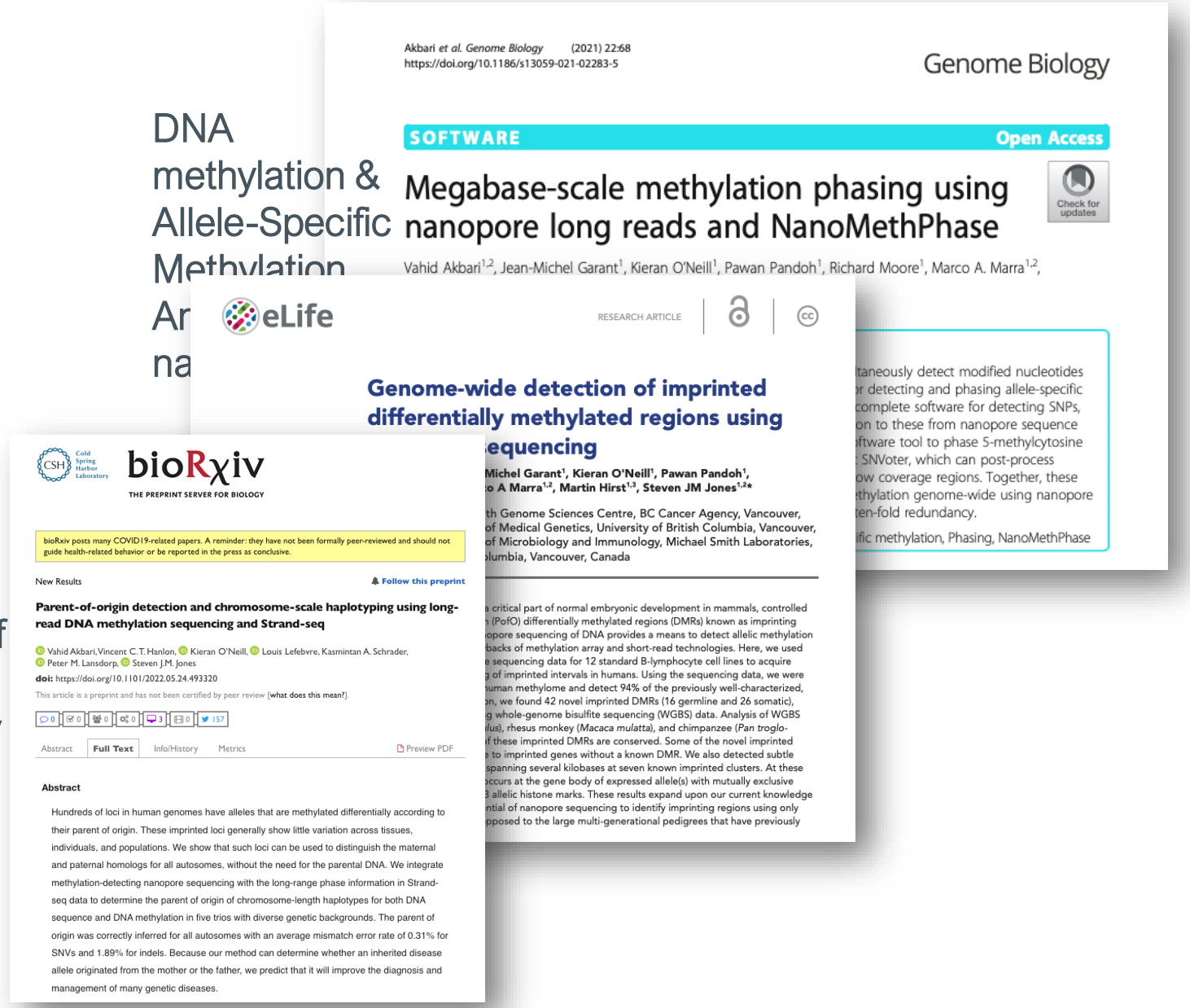
Epigenetics is evolving but critical

Novel methylation markers will uncover new functions of disease

Aging | Metabolic | Cancer | Neuro | Mental

DNA methylation & Allele-Specific Methylation Ar na

Parent of origin correctly inferred for all variants



Akbari *et al. Genome Biology* (2021) 22:68
https://doi.org/10.1186/s13059-021-02283-5

Genome Biology

SOFTWARE Open Access

Megabase-scale methylation phasing using nanopore long reads and NanoMethPhase

Vahid Akbari[1,2], Jean-Michel Garant[1], Kieran O'Neill[1], Pawan Pandoh[1], Richard Moore[1], Marco A. Marra[1,2],

taneously detect modified nucleotides
r detecting and phasing allele-specific
complete software for detecting SNPs,
on to these from nanopore sequence
ftware tool to phase 5-methylcytosine
SNVoter, which can post-process
ow coverage regions. Together, these
thylation genome-wide using nanopore
ten-fold redundancy.

ific methylation, Phasing, NanoMethPhase

eLife

RESEARCH ARTICLE

Genome-wide detection of imprinted differentially methylated regions using
equencing

Michel Garant[1], Kieran O'Neill[1], Pawan Pandoh[1],
o A Marra[1,2], Martin Hirst[1,3], Steven JM Jones[1,2]*

th Genome Sciences Centre, BC Cancer Agency, Vancouver,
of Medical Genetics, University of British Columbia, Vancouver,
of Microbiology and Immunology, Michael Smith Laboratories,
olumbia, Vancouver, Canada

a critical part of normal embryonic development in mammals, controlled
(PofO) differentially methylated regions (DMRs) known as imprinting
opore sequencing of DNA provides a means to detect allelic methylation
backs of methylation array and short-read technologies. Here, we used
e sequencing data for 12 standard B-lymphocyte cell lines to acquire
g of imprinted intervals in humans. Using the sequencing data, we were
uman methylome and detect 94% of the previously well-characterized,
n, we found 42 novel imprinted DMRs (16 germline and 26 somatic),
g whole-genome bisulfite sequencing (WGBS) data. Analysis of WGBS
ilus), rhesus monkey (*Macaca mulatta*), and chimpanzee (*Pan troglo-*
f these imprinted DMRs are conserved. Some of the novel imprinted
to imprinted genes without a known DMR. We also detected subtle
spanning several kilobases at seven known imprinted clusters. At these
ccurs at the gene body of expressed allele(s) with mutually exclusive
3 allelic histone marks. These results expand upon our current knowledge
ntial of nanopore sequencing to identify imprinting regions using only
pposed to the large multi-generational pedigrees that have previously

CSH Cold Spring Harbor Laboratory bioRxiv THE PREPRINT SERVER FOR BIOLOGY

bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

New Results Follow this preprint

Parent-of-origin detection and chromosome-scale haplotyping using long-read DNA methylation sequencing and Strand-seq

Vahid Akbari, Vincent C.T. Hanlon, Kieran O'Neill, Louis Lefebvre, Kasmintan A. Schrader, Peter M. Lansdorp, Steven J.M. Jones

doi: https://doi.org/10.1101/2022.05.24.493320

This article is a preprint and has not been certified by peer review [what does this mean?].

Abstract | Full Text | Info/History | Metrics | Preview PDF

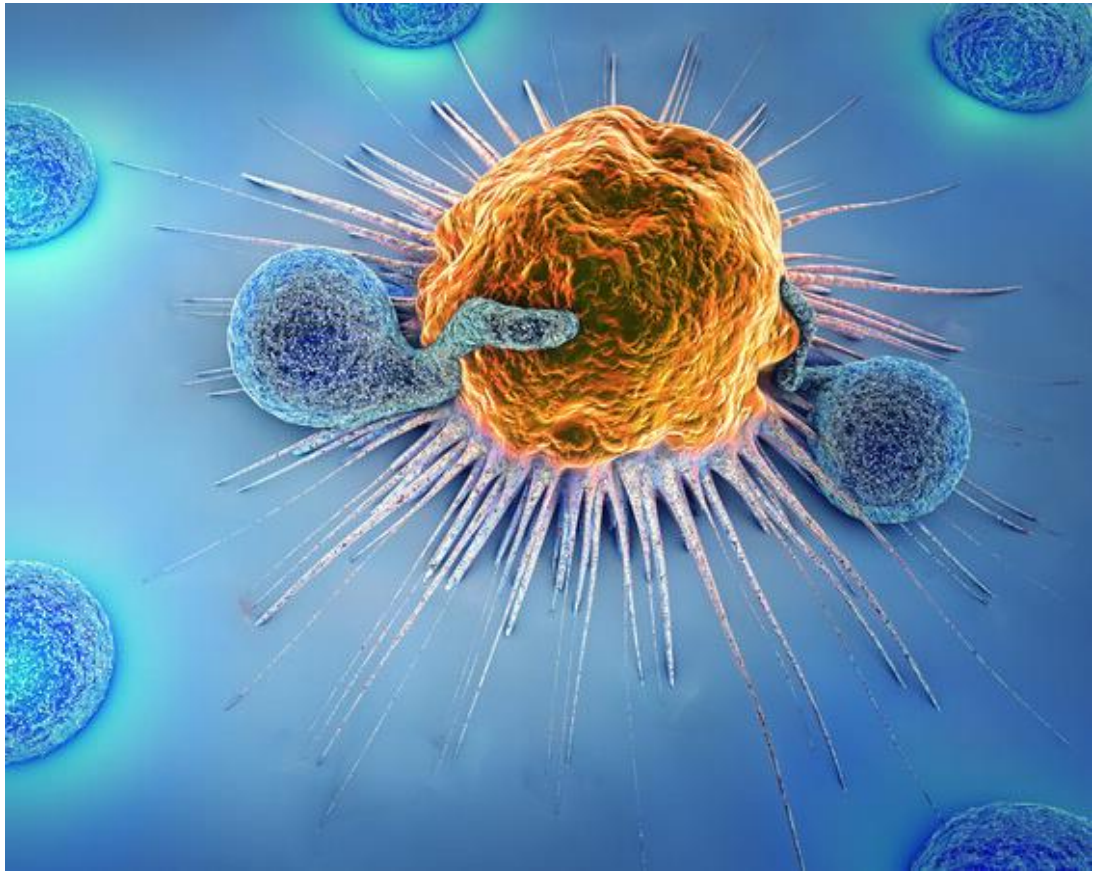
Abstract

Hundreds of loci in human genomes have alleles that are methylated differentially according to their parent of origin. These imprinted loci generally show little variation across tissues, individuals, and populations. We show that such loci can be used to distinguish the maternal and paternal homologs for all autosomes, without the need for the parental DNA. We integrate methylation-detecting nanopore sequencing with the long-range phase information in Strand-seq data to determine the parent of origin of chromosome-length haplotypes for both DNA sequence and DNA methylation in five trios with diverse genetic backgrounds. The parent of origin was correctly inferred for all autosomes with an average mismatch error rate of 0.31% for SNVs and 1.89% for indels. Because our method can determine whether an inherited disease allele originated from the mother or the father, we predict that it will improve the diagnosis and management of many genetic diseases.

Oxford NANOPORE Technologies

Cancer discovery

In partnership with Genomics England



- Increase the diagnostic yield of genomics in cancer by getting the complete picture including dark genome, copy number variation, methylation (5mC, 5hmC), SV and SNP
- Develop the capability to decentralise the assay to local centres of excellence to reduce time to result
- Develop the sample to answer pipeline to lead the industry in cancer

"Oxford Nanopore sequencing and methylation analysis continues to show great promise in cancer.

Genomics England is partnering with ONT and the wider academic community, to validate potential clinical, operational and research benefits of their technology."

Parker Moss, Chief Commercial officer, Genomics England.

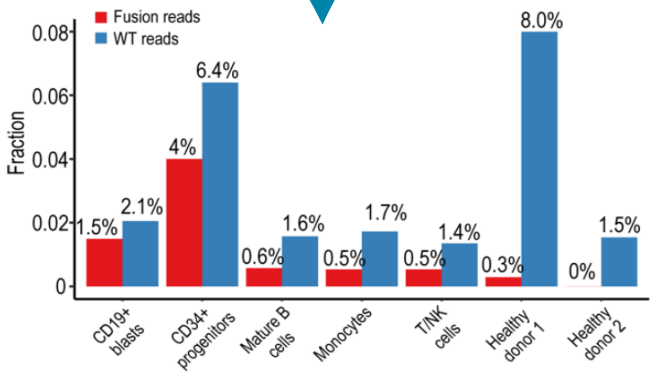
Change the landscape in transcriptomics & single-cell analysis

71,735
Novel isoforms

'The advent of long-read sequencing technologies offers the opportunity to study the role of genetic variation in transcript structure'

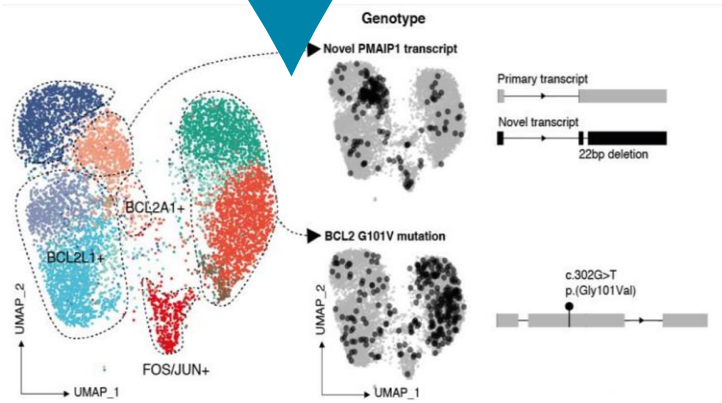
Glinos *et al.*, 2022[1]

Fusion transcripts at the single-cell level



Chen *et al.*, 2020[2]

Explaining resistance for the first time

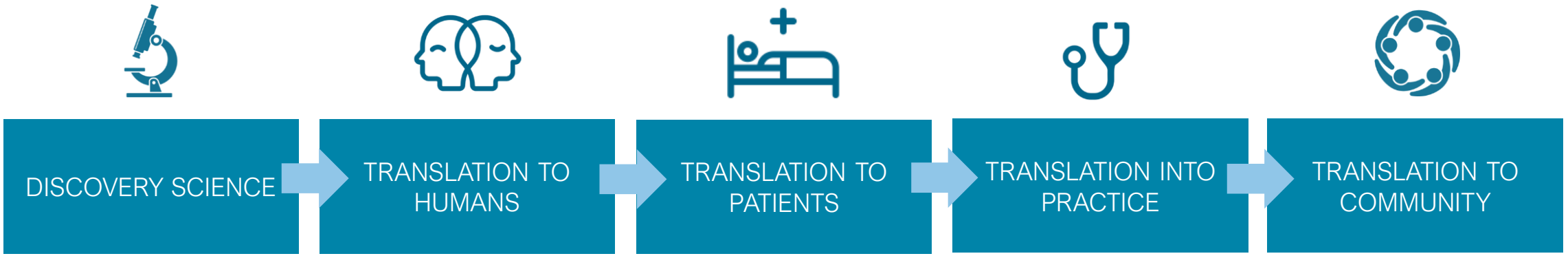


Thijssen *et al.*, 2022[3]

[1]Glinos et al. https://rdcu.be/cSYH6
[2]Chen et al. bioRxiv doi: https://doi.org/10.1101/2020.12.06.413930 (2020).
[3]Thijssen et al. https://doi.org/10.1182/blood.2022016040

Expanding partnership possibilities

Roadmap for deployment of genomic healthcare - Moving from research to community outcomes



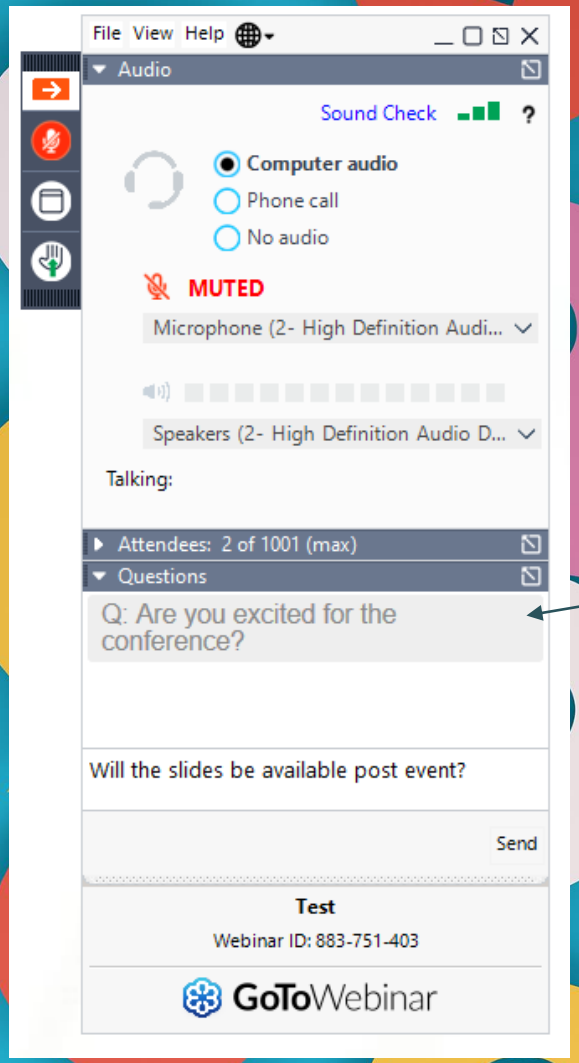
With the same technology…

ONE sequencing platform

- COMPREHENSIVE INSIGHTS
- ANY FRAGMENT LENGTH
- EASE OF USE
- REAL-TIME & RAPID
- SCALABLE
- ECONOMICAL

Oxford NANOPORE Technologies


Thank you
Oxford
NANOPORE
Technologies



If you have any questions or comments for Speakers across the day, please expand the Questions Section on the GoToWebinar panel. You will not be able to see each others questions.

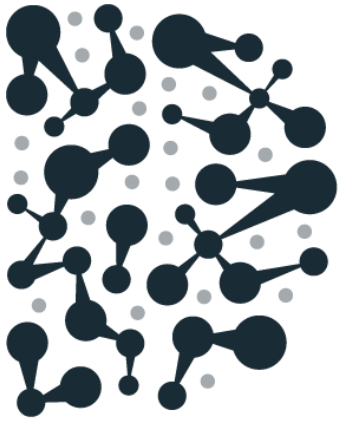
Understanding Genomics in the NHS Conference 2022

COMFORT BREAK

Please remain logged in, we will resume at 12:40pm

Understanding Genomics in the NHS Conference 2022

UP NEXT...



DeepChain

by InstaDeep

Understanding Genomics in the NHS Conference 2022

SPEAKING NOW

Dr Nicholas Lopez Carranza

BioAI Team
InstaDeep

I will be discussing…

"AI-Powered Genomics Research"

Understanding Genomics in the NHS Conference 2022

SPEAKING NOW

Dr Shane McKee

Consultant in Genetic & Genomic Medicine
Belfast Health & Social Care Trust

I will be discussing…

"GenOCEANIC - The Voyage towards an open standards based platform for clinical genomic analysis"

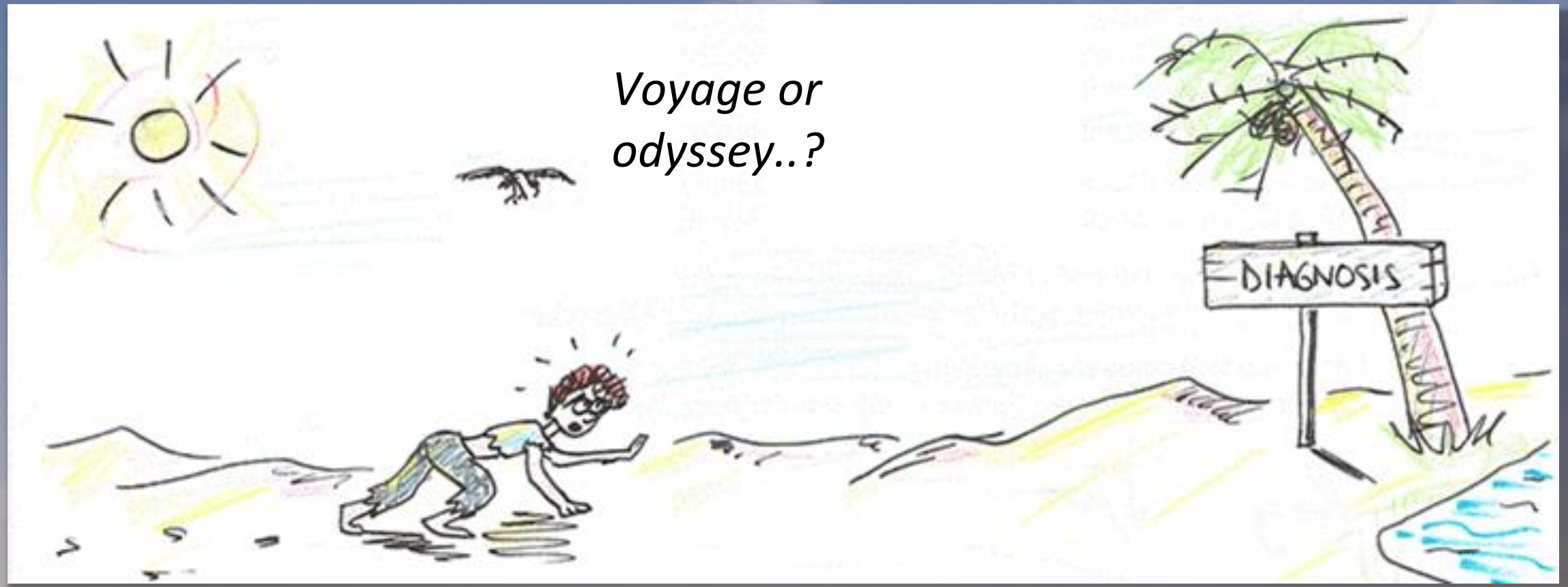
GenOCEANIC – the voyage towards an open standards based platform for clinical genomic analysis

Belfast Health and Social Care Trust
caring supporting improving together

Shane McKee
Consultant in Genetic & Genomic Medicine
Clinical Director NI Regional Molecular Diagnostics Service
Belfast HSC Trust
@shanemuk / @shanemuk@mastodon.ie

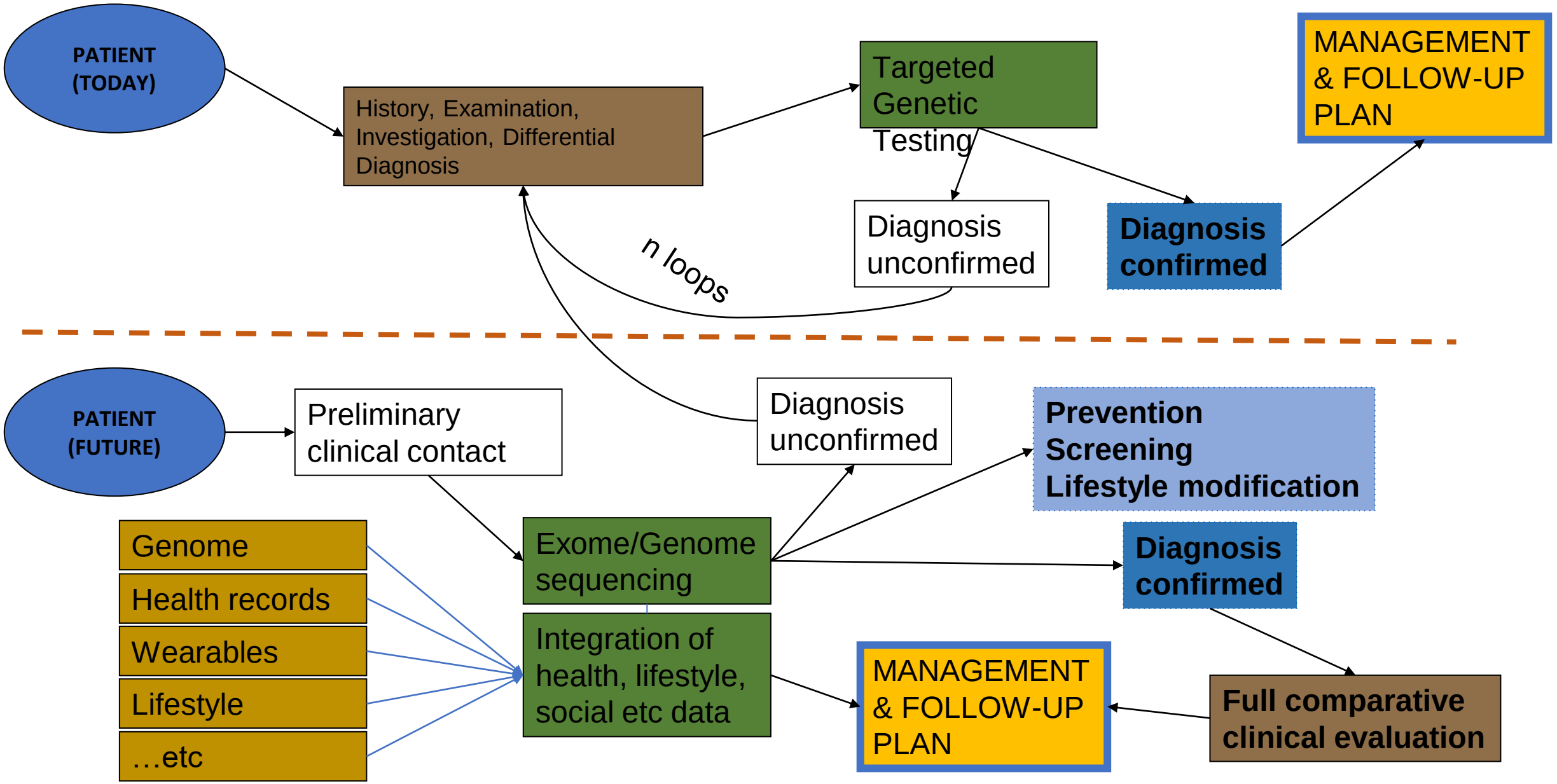

A patient with a problem…
… A clinician with a question
!
?

Voyage or odyssey..?



#NazBike22

Precision medicine for rare diseases?

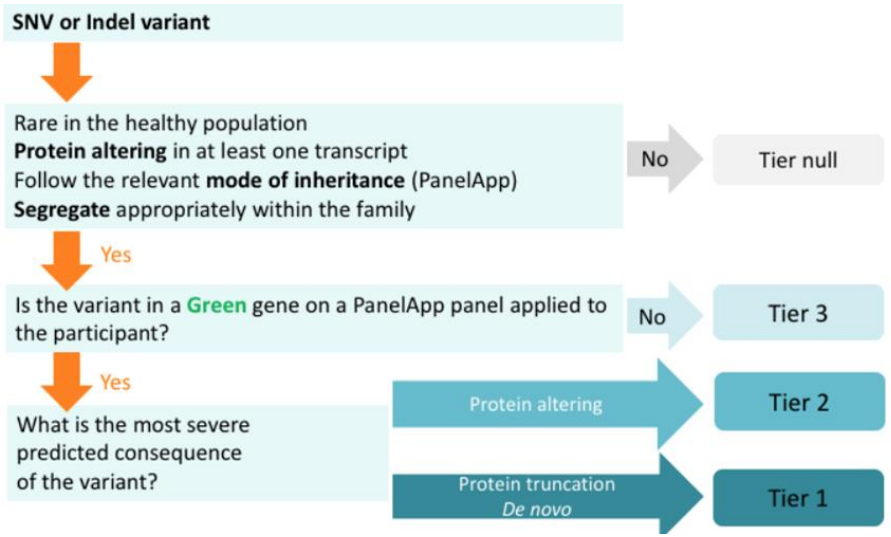


It should be obvious but...

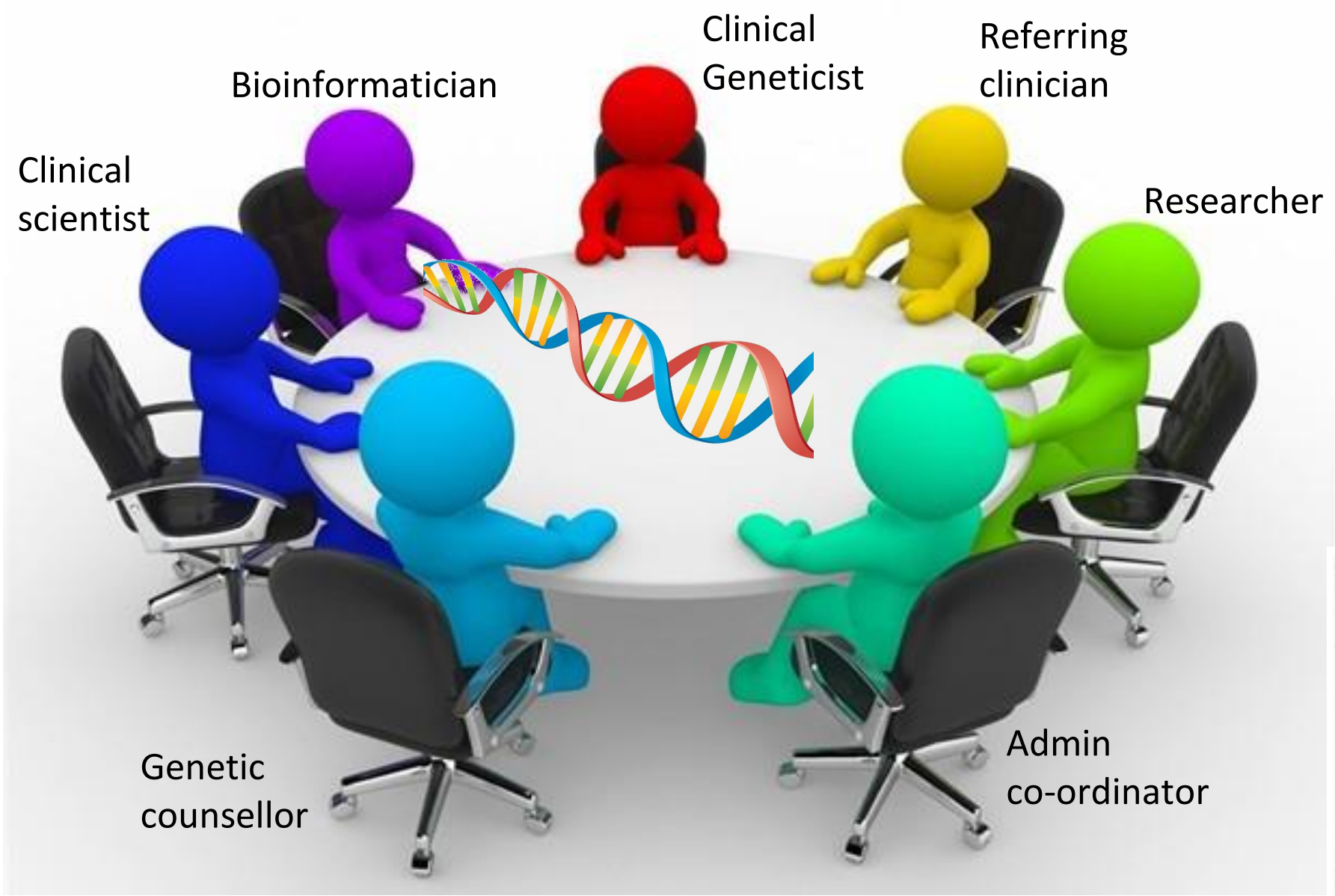
- Precision medicine needs to be precise
- It is not a blunderbuss approach
- Diagnosis is not the end of the process
- "Reading the genome" will not always give us the answer
- Not every rare disorder is "genetic"
- We are likely to need trained professionals for quite some time...

Northern Ireland:
UK 100,000 Genomes Cohorts

- **Cohort 1: 402 probands**
  455 Tier1/Tier2 variants returned
  - 243 selected for classification
  - 22 PATHOGENIC; 37 LIKELY PATHOGENIC (14.7%)
  - (not including Tier3/Untiered)
- **Cohort 2: 39 probands**
  105 variants returned (T1/T2)
  - 56 selected for classification
  - 7 PATHOGENIC; 10 LIKELY PATHOGENIC (43.5%)
- **Current:** “deeper dive” ongoing
  - Pathogenic/Likely Pathogenic: **25%**
- Better phenotyping more diagnoses -
  i.e. better definition of the clinical question

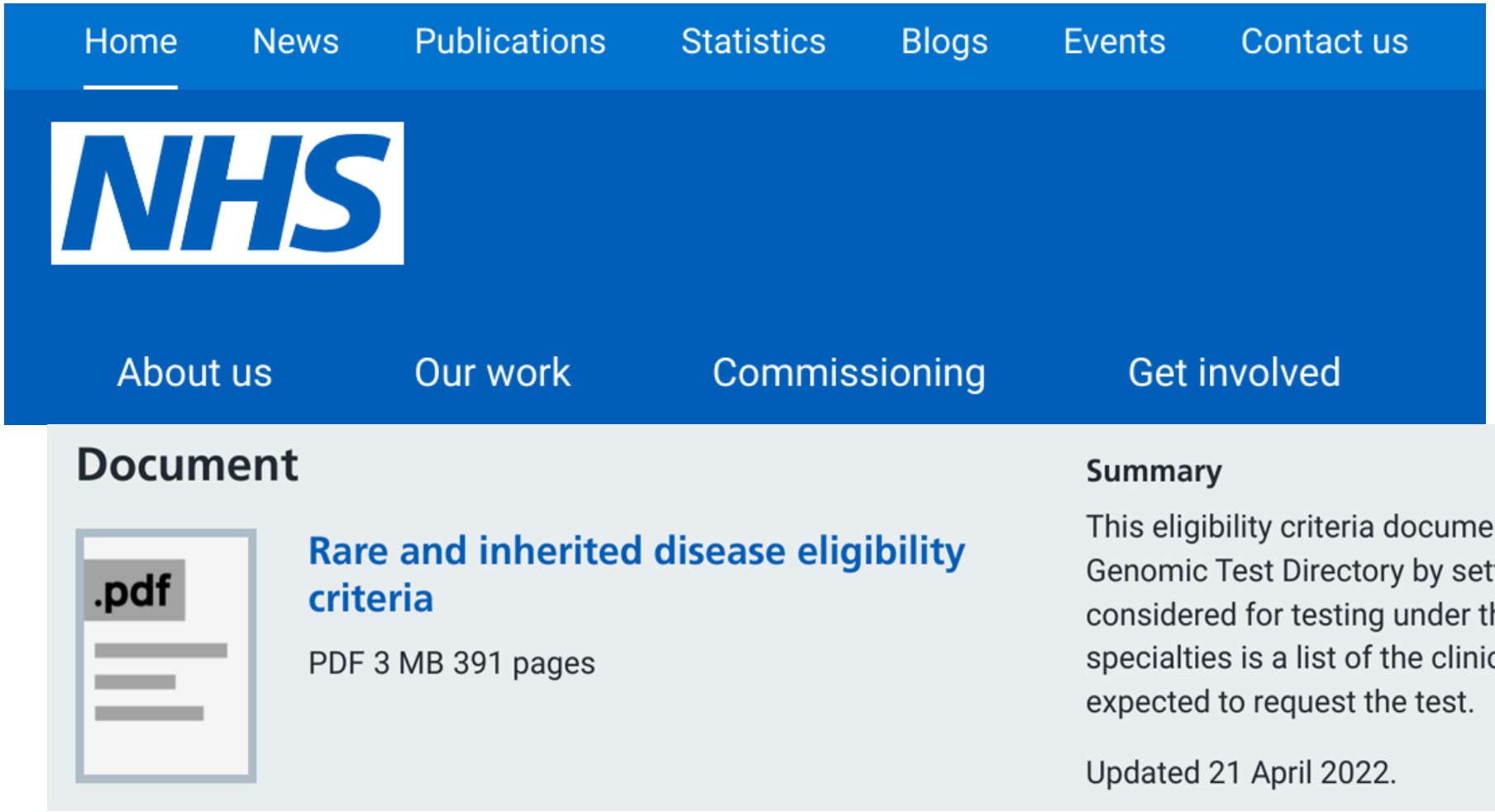


The Genomics Multidisciplinary Team



It takes a village to interpret a genome…

UK National* Test Directory



* England

R60 Adult onset hereditary spastic paraplegia

Testing Criteria

Unexplained spastic paraplegia of likely monogenic aetiology with onset in adulthood

STR testing of spinocerebellar ataxia loci will be included as a component test where spinocerebellar ataxia is considered plausible clinically.

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

At presentation following assessment by a Neurologist or Clinical Geneticist

Requesting Specialties

- Clinical Genetics
- Neurology

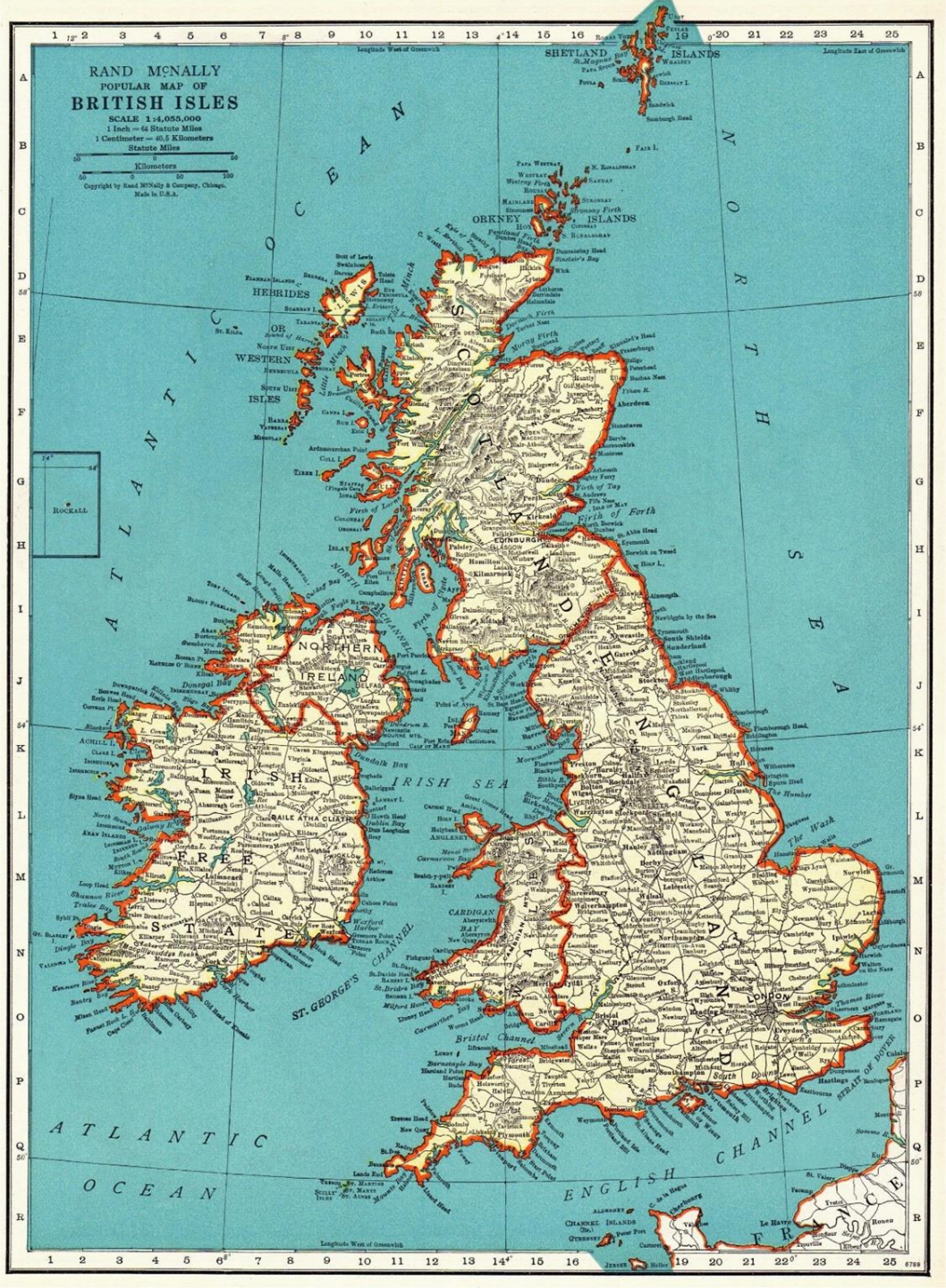
Specialist Service Group

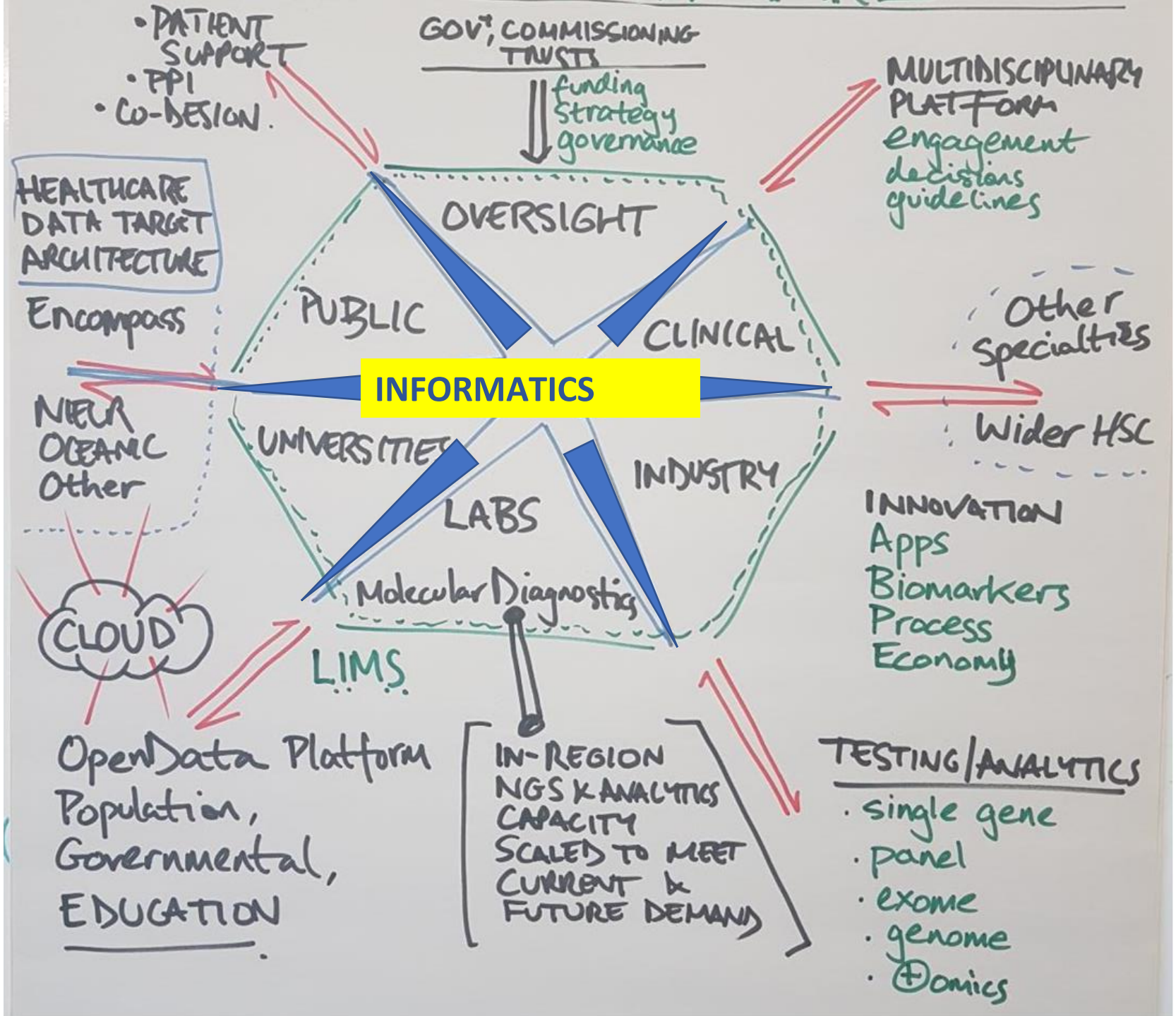
- Neurology

Associated Tests

Please note that initially only WGS testing will be undertaken for R60 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary. Whilst this includes testing of all STRs in the gene panel, analysis is currently not optimal and therefore if a specific STR is suspected this should be stated at referral to prompt additional testing where necessary.

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R60.2	Hereditary spastic paraplegia - adult onset STR testing	Singleton	STRs	Panel of genes or loci	Hereditary spastic paraplegia - adult onset (567)	STR testing
R60.3	Adult onset hereditary spastic paraplegia WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary spastic paraplegia - adult onset (567)	WGS




• PATIENT SUPPORT
• PPI
• CO-DESIGN.
GOV', COMMISSIONING TRUSTS
funding
strategy
governance
MULTIDISCIPLINARY PLATFORM
engagement
decisions
guidelines
HEALTHCARE DATA TARGET ARCHITECTURE
Encompass
OVERSIGHT
PUBLIC
CLINICAL
INFORMATICS
Other Specialties
Wider HSC
NIECR
OCEANIC
Other
UNIVERSITIES
INDUSTRY
LABS
Molecular Diagnostics
INNOVATION
Apps
Biomarkers
Process
Economy
CLOUD
LIMS
OpenData Platform
Population,
Governmental,
EDUCATION
IN-REGION
NGS & ANALYTICS
CAPACITY
SCALED TO MEET
CURRENT & FUTURE DEMAND
TESTING/ANALYTICS
. single gene
. panel
. exome
. genome
. ⊕omics

Genomics **O**pen **C**ore
Enabling **A**rchitecture
for **N**orthern **I**reland **C**are

The dawn of GenOCEANIC

GenOCEANIC

- Platform for PHENOTYPE data linked to GENOMIC data
- Open standards platform - *#openEHR* by design
- FHIR, HL7 from multiple existing sources
- Clinical data available for re-use
- Vendor-neutral, technology-agnostic
- Supporting Agile, DevOps, wide scope
- Synergistic with #encompassNI (Epic)

CAMBIO HEALTHCARE SYSTEMS

FUTURE PERFECT HEALTHCARE

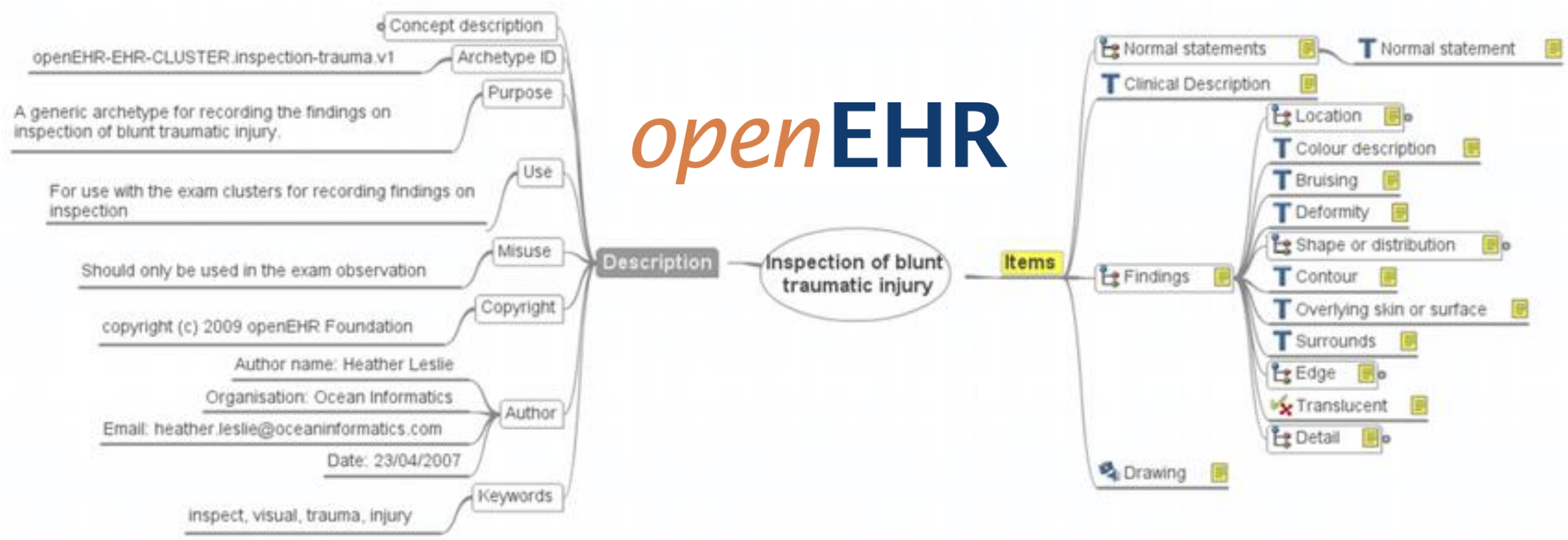
better

ZettaGenomics

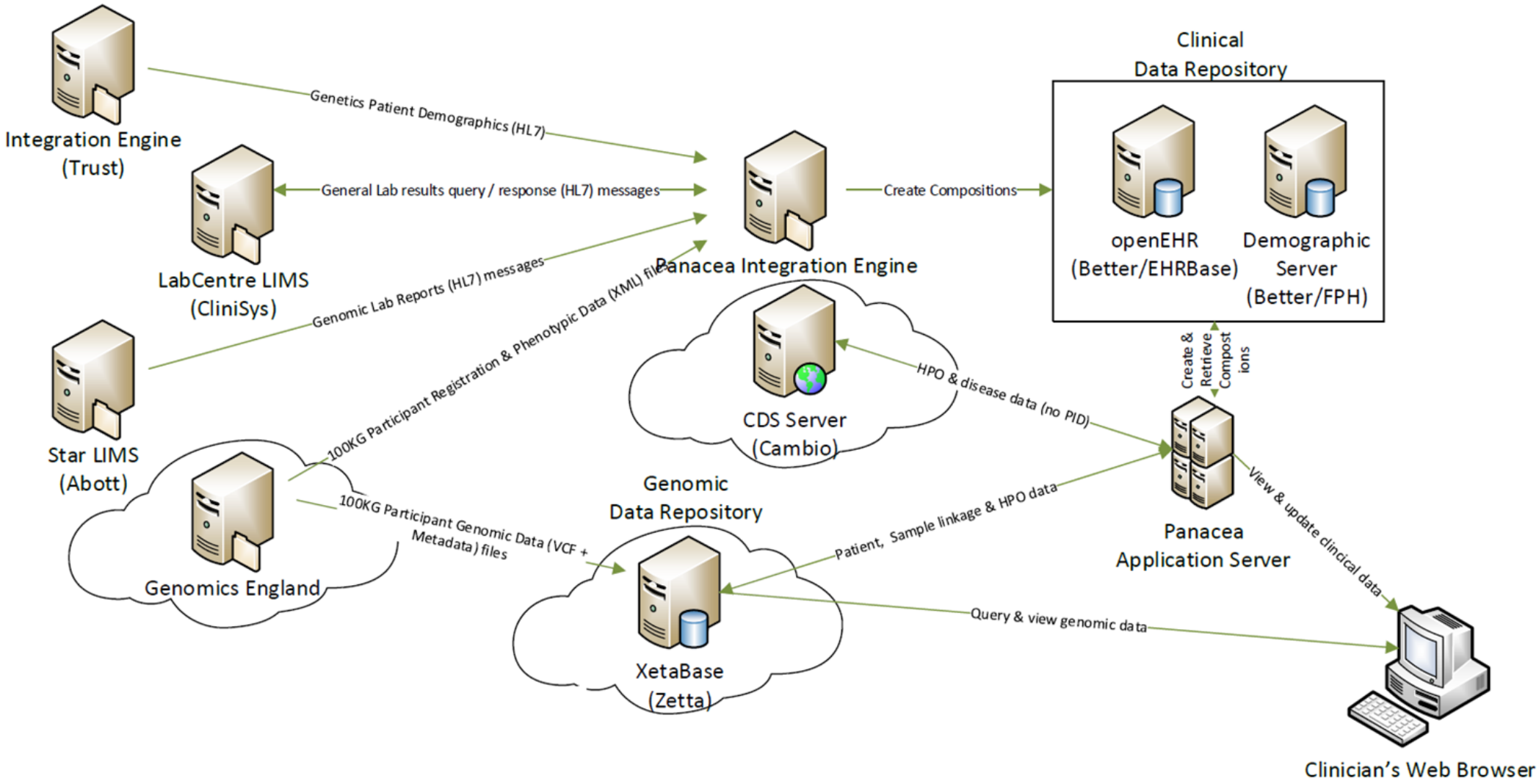
openEHR

www.openehr.org / CAMBIO UK / FuturePerfect / Better Healthcare / Zetta Genomics

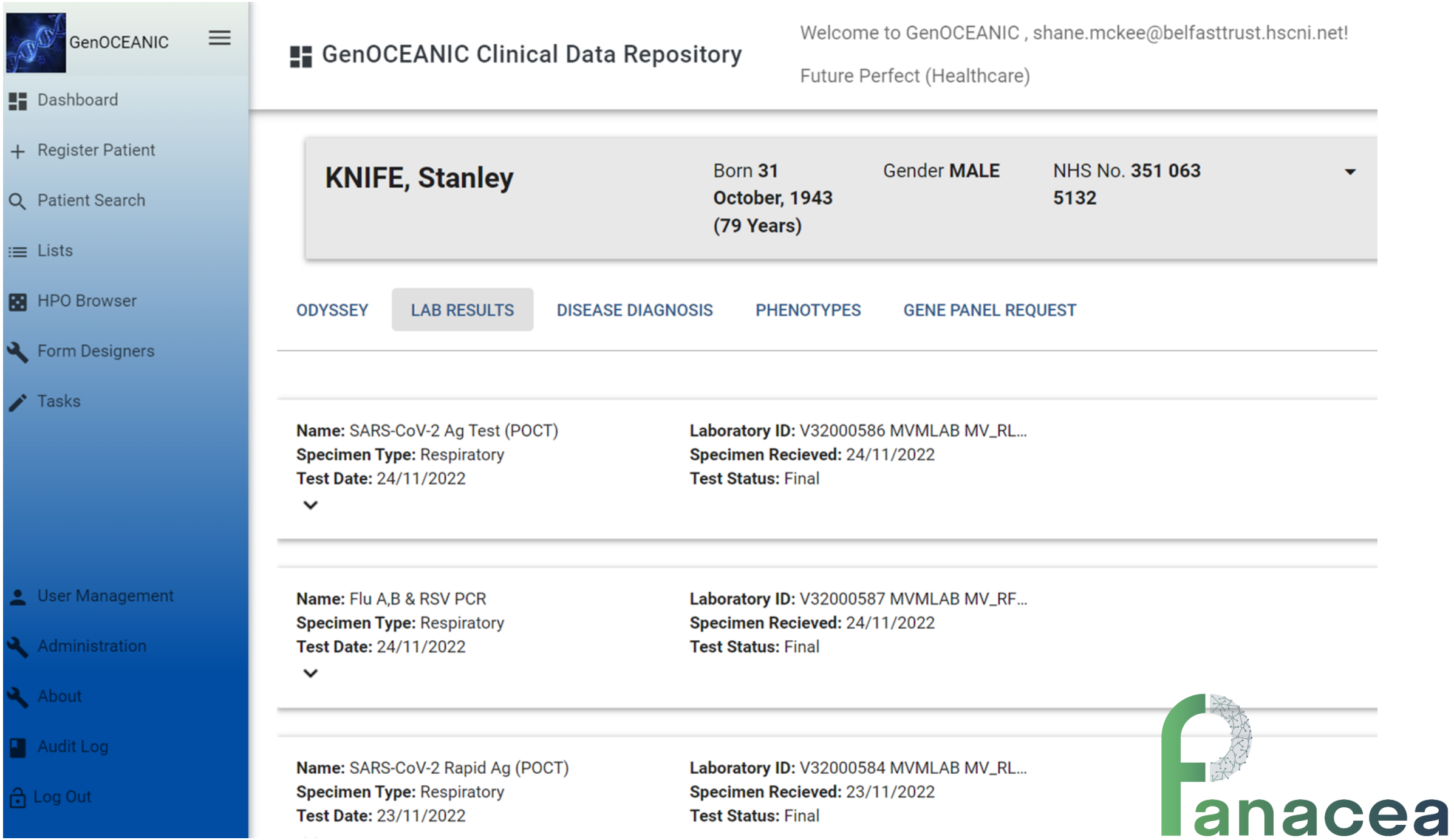
#openEHR – open standards, clinically reviewed archetypes & templates – vendor-neutral clinical data repository



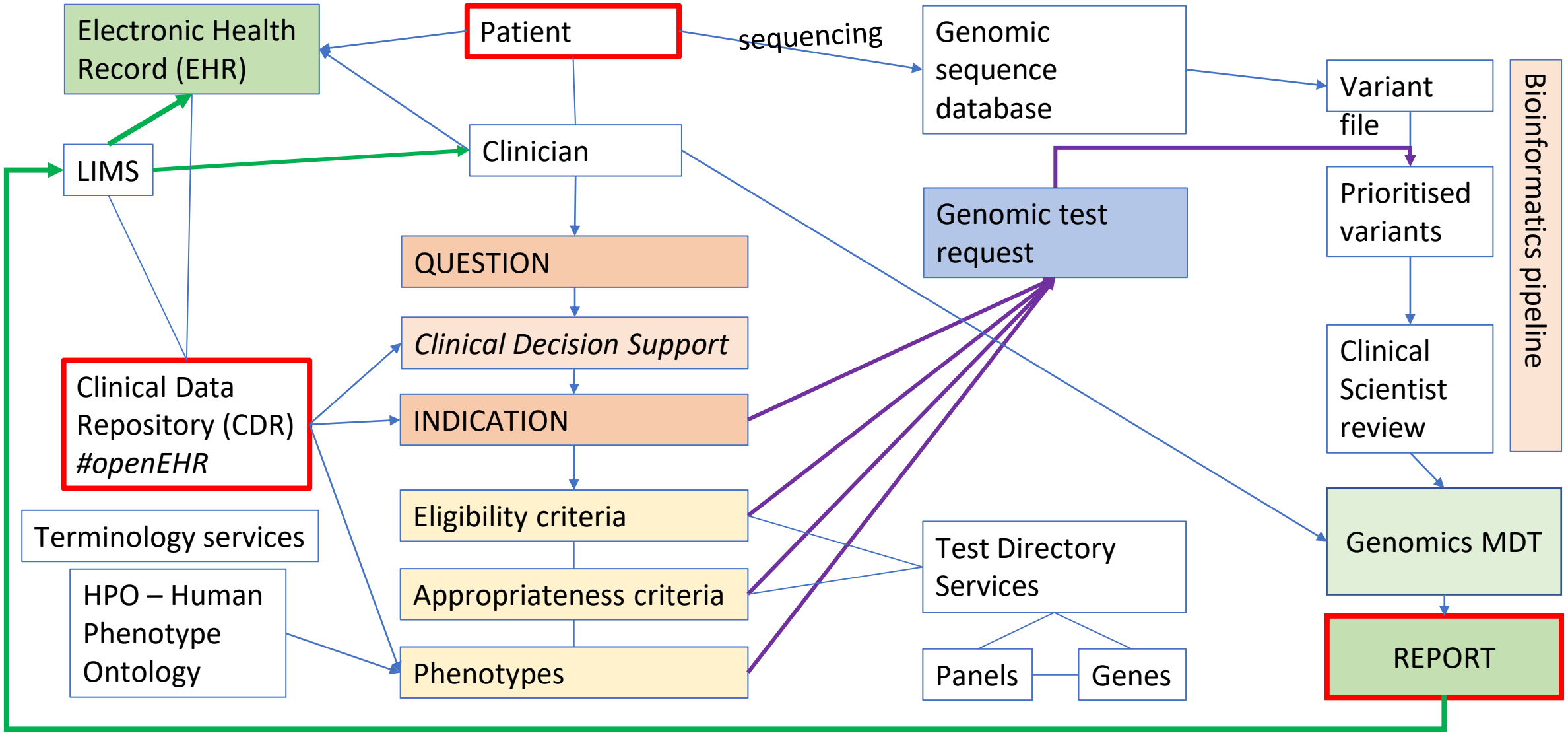
GenOCEANIC Data Flow Diagram – Showing Data Flows into openEHR CDR and XetaBase surfaced by the Panacea Platform Stage 2



* All I.T. components are on site at BHCT apart from where show in cloud


GenOCEANIC
Dashboard
Register Patient
Patient Search
Lists
HPO Browser
Form Designers
Tasks
User Management
Administration
About
Audit Log
Log Out
GenOCEANIC Clinical Data Repository
Welcome to GenOCEANIC , shane.mckee@belfasttrust.hscni.net!
Future Perfect (Healthcare)
KNIFE, Stanley
Born 31 October, 1943 (79 Years)
Gender MALE
NHS No. 351 063 5132
ODYSSEY
LAB RESULTS
DISEASE DIAGNOSIS
PHENOTYPES
GENE PANEL REQUEST
Name: SARS-CoV-2 Ag Test (POCT)
Specimen Type: Respiratory
Test Date: 24/11/2022
Laboratory ID: V32000586 MVMLAB MV_RL...
Specimen Recieved: 24/11/2022
Test Status: Final
Name: Flu A,B & RSV PCR
Specimen Type: Respiratory
Test Date: 24/11/2022
Laboratory ID: V32000587 MVMLAB MV_RF...
Specimen Recieved: 24/11/2022
Test Status: Final
Name: SARS-CoV-2 Rapid Ag (POCT)
Specimen Type: Respiratory
Test Date: 23/11/2022
Laboratory ID: V32000584 MVMLAB MV_RL...
Specimen Recieved: 23/11/2022
Test Status: Final
Fanacea

Building a diagnostic genomics architecture



encompass

DELIVERING CARE TOGETHER

Primary care

Private sector

Out-of-Area

PanOCEANIC

- GenOCEANIC
- PathOCEANIC
- OncOCEANIC
- EtcOCEANIC...

- Apps & innovation
- Out-of-scope services
- Registries, Reporting
- PROMS, PREMS
- Upstreaming / civics
- Research

The odyssey continues...

- NI Regional Genetics team
- Cheryl Flanagan – Project Manager
- Shirley Heggarty - NI Regional Genetics Laboratories
- AJ McKnight – Queen's University Belfast & NI Rare Disease Partnership
- Ryan Wilson & Finola McGrady – NI Dept of Health
- Mark Thornton – Cambio Healthcare & partners
- Regional clinicians
- Patients & families

CAMBIO HEALTHCARE SYSTEMS openEHR ZettaGenomics better FUTURE PERFECT HEALTHCARE

HSC Belfast Health and Social Care Trust
caring supporting improving together

GenOCEANIC – the voyage towards an open standards based platform for clinical genomic analysis

- Part of the challenge of integrating genomics into routine clinical care is to pull together the rich clinical data required to ask the right questions of the genomic data. Arising from the UK 100,000 Genomes Initiative, the GenOCEANIC Project seeks to use the power of electronic health records, artificial intelligence and clinical decision support to make it easier for clinicians to find and order the right genomic tests for their patients, and to integrate the findings back into the patient's record where it's available for care.

- GenOCEANIC uses the openEHR open data standard to ensure interoperability with a wide variety of electronic health systems, and the vision is to create a platform for innovation in the NHS that allows us to get clinically actionable findings back to patients in a way that makes a real difference to their care.

Electronic health records EHRs

- Lots of clinical information
- Ordercomms
- Workflow
- Communication with the laboratory
- When a lab test is ordered, the information supplied needs to be standardised
- Standardised information needs to feed back into the HER
- Eg if "microcephaly" is asserted in a test request, that is a relevant phenotypic feature that needs to be recorded

Challenge for precision medicine

- Getting the genomic data isn't the bottleneck
- Key to precision medicine is asking the right question
- It really is personalising the analysis to the patient, AND their immediate clinical context
- Variant interpretation is hard
- Lots of VUSs. How do we handle this

What are we trying to achieve?

- Trying to get the diagnosis in order to
  - Inform management decisions
  - Clarify expectations
  - Research
  - How can we use this data for research?
  - Registries
  - Provide better follow-up for patients
  - Provide better case ascertainment in populations
  - Make Ireland a place where better research can be done

NHS England plan

- Gather lots of genomic and phenotypic information
- How do we ensure that is relevant?
- How do we link it up to actual clinical questions
- People are still a crucial part of this process;
- Challenge is to get the right data in front of the right person who can make the right decision

Why openEHR?

- Provides a platform
- Open standards

Prospects for Ireland

- OpenEHR infrastructure portable
- Same Epic EHR in NI as planned for CHI
- Federated querying – resolves a lot of data governance issues
- A federated data structure provides opportunities
- Registries

HRB conference, Dublin; 11:30; 15min

- Dr Shane McKee, Department of Medical Genetics, Belfast Health and Social Care Trust: *Creating a data infrastructure for precision clinical genomics*
-

Challenges for the future

- Cross border data linkage
- Connect to registries
- Expansion into cancer
- Integration of AI
- Why are we doing this? Needs to be able to inform decisions & research
- Ultimately not interested in statistics – we need mechanisms & how to improve outcomes

Proposals for Ireland

- CHI Epic & NI encompass should share data via Epicare Link
- Build services on a common shared infrastructure
- Paed Cardiology & NW Radiotherapy on a shared basis – can this be expanded? 1.9M people in NI, 5M ppl in RoI

Genomics hitting the mainstream

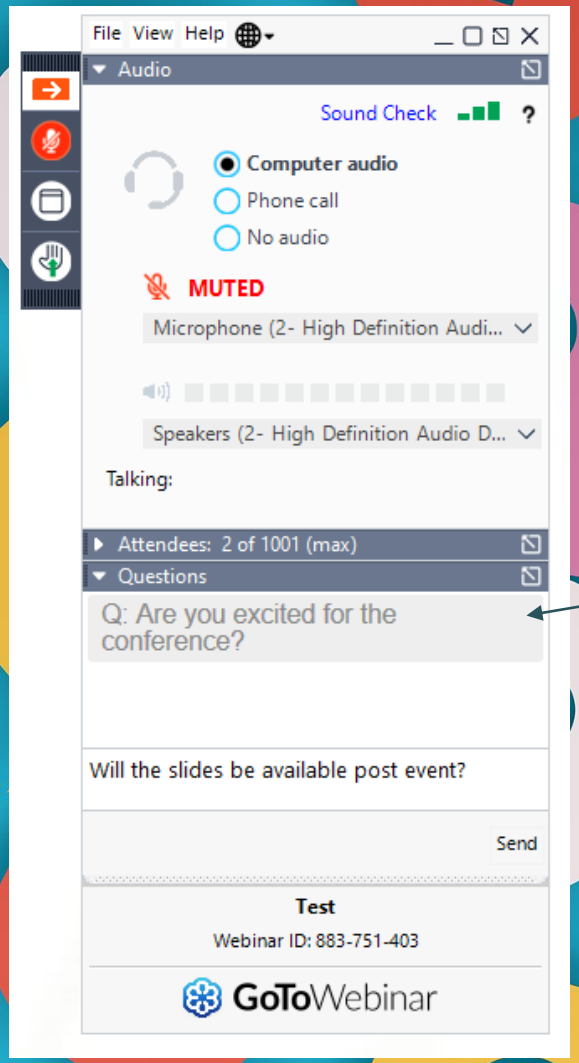
- Clinicians can't be expected to know everything
- Phenotypes relevant to "other specialties" may be missed, eg microcephaly & developmental delay missed by Ophthalmology
- Often difficult to frame the question being asked, particularly if disorder is especially rare.
- BUT we want the *question* itself to enter the patient record
- WHY? It indicates an interaction with a clinician with an objective to finding out something clinically relevant

Eligibility criteria

- Sometimes these are ridiculously vague, eg "disorder with a suspected monogenic cause"
- WHat is the point of that?
- The assertion that a patient fulfils a criterion needs to find a way of being represented in the EHR and available in other settings
- BUT this is not the same as an assertion that this is the best test for this patient!
- Hence the need to supply the lab with full info in case another panel/test may be more appropriate

the data to support genomics

shane mckee



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Understanding Genomics in the NHS Conference 2022

UP NEXT...

Yourgene Health

Understanding Genomics in the NHS Conference 2022

SPEAKING NOW

Dr Andrew Wallace

Laboratory Director
Yourgene Health

I will be discussing…

"The Use of Ranger Technology in Genomic Services"

Yourgene Health

A leading *integrated technologies and services* business, enabling the delivery of genomic medicine

The use of Ranger® Technology in Genomic Services

Dr Andrew Wallace

29 November 2022

Yourgene Health: *experts in cell-free DNA*

100+ products & services

200 employees

Customers in over 65 countries

Operating sites: Manchester - Taipei - Vancouver

Direct commercial presence:

US – Canada - Colombia

Taiwan - Singapore – Thailand – India – Australia

UK - France - Germany

>800,000 patient samples tested in our labs

>2,250,000 pregnancies tested

> 4,250,000 tests overall

Yourgene Health

Experts in cell-free DNA

Genomic Technologies

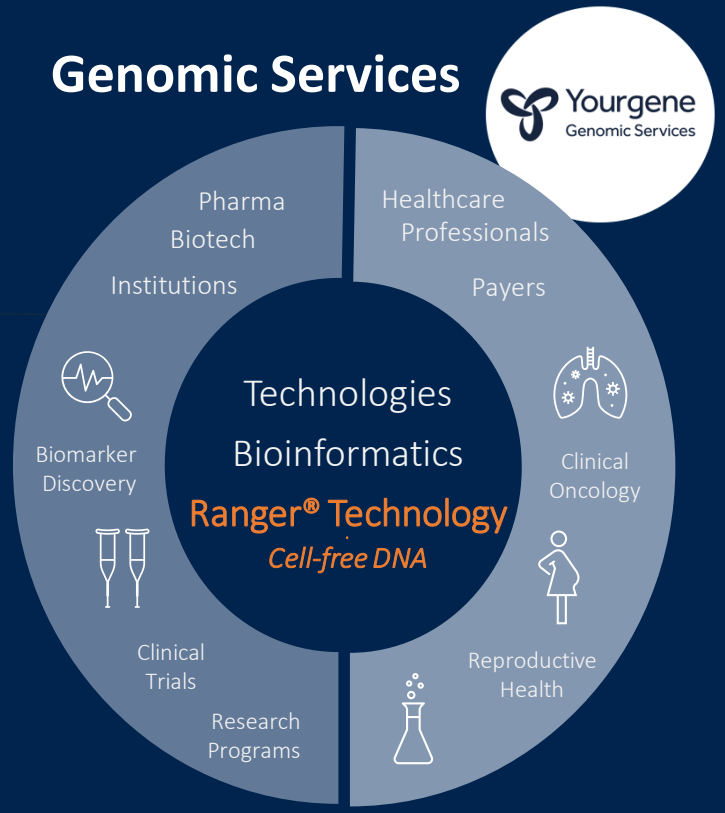
- Precision medicine: Oncology & Pharmacogenomics
- Non-invasive Prenatal Testing
- Reproductive Health

Ranger® Technology:
Next generation size selection for cell free DNA using machine vision for superior precision

cffDNA: Fetal Fraction target enrichment

ctDNA: Liquid biopsies for cancer detection

Genomic Services



10's of institutional studies ongoing globally

supported **>800** clinical trials for pharma and biotech

NEXT GENERATION SEQUENCING · PCR · MICROARRAY

Ranger® Technology

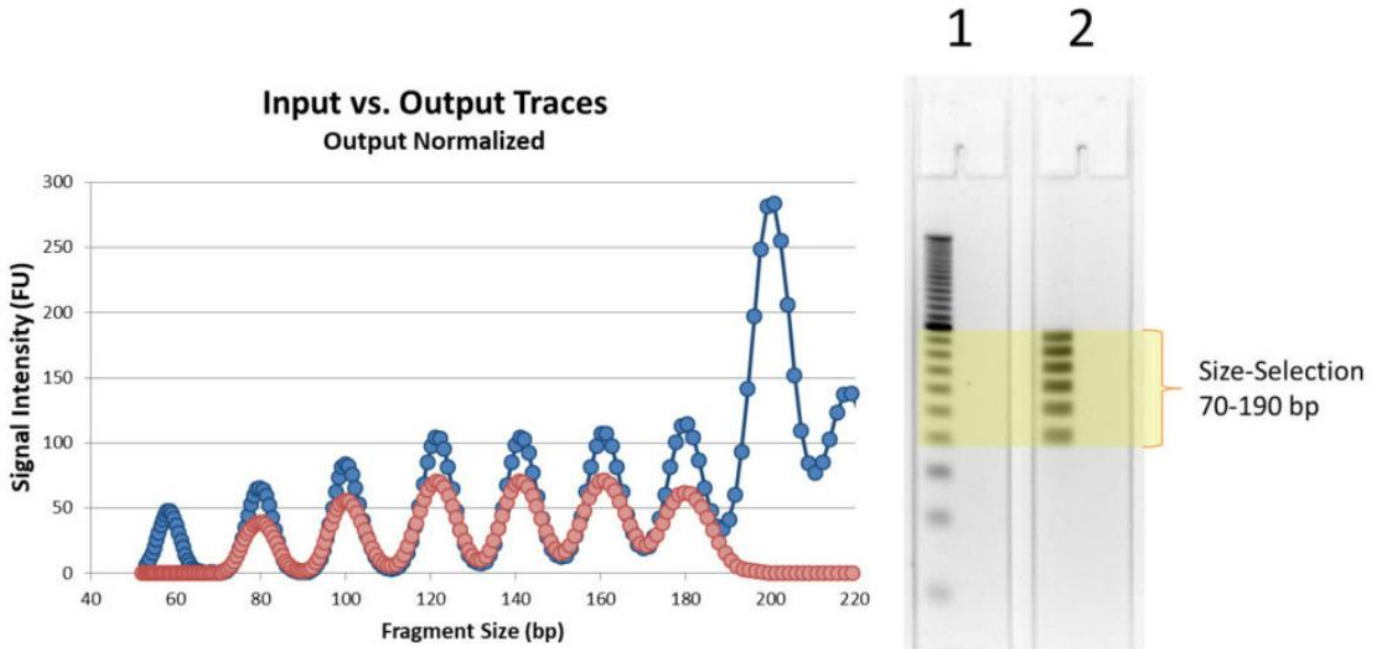
Next generation size selection

Powered by Ranger® Technology

- Ranger® Technology for dynamic target enrichment using machine vision – resulting in superior precision
- IP protected, machine vision algorithms for enhanced target enrichment
- LightBench® Detect – bench sized platform with true walkaway automation to simplify purification at scale
- Benefits:
  - fetal fraction enrichment in NIPT
  - enables labs to enrich target DNA giving superior yield and precision
  - reduce overall workflow costs and improve patient outcomes

Ranger Technology

Controllable size selection & high recovery



1. Lonza 20 bp DNA Ladder (Input)
2. Size-Selection Output (70-190 bp target range)

Ranger® Technology recovered all fragments between 70bp and 190 bp from a 20 bp dsDNA ladder (Lonza). Comparison of the electrophoretic traces of the input and size selected fraction indicate an average recovery yield of 73% across all targeted fragment sizes. Further tests involving solution-based fluorometric assays confirm recovery yields to be in excess of 70% (data not shown).

Case Studies:
NIPT, Oncology & Infectious Disease

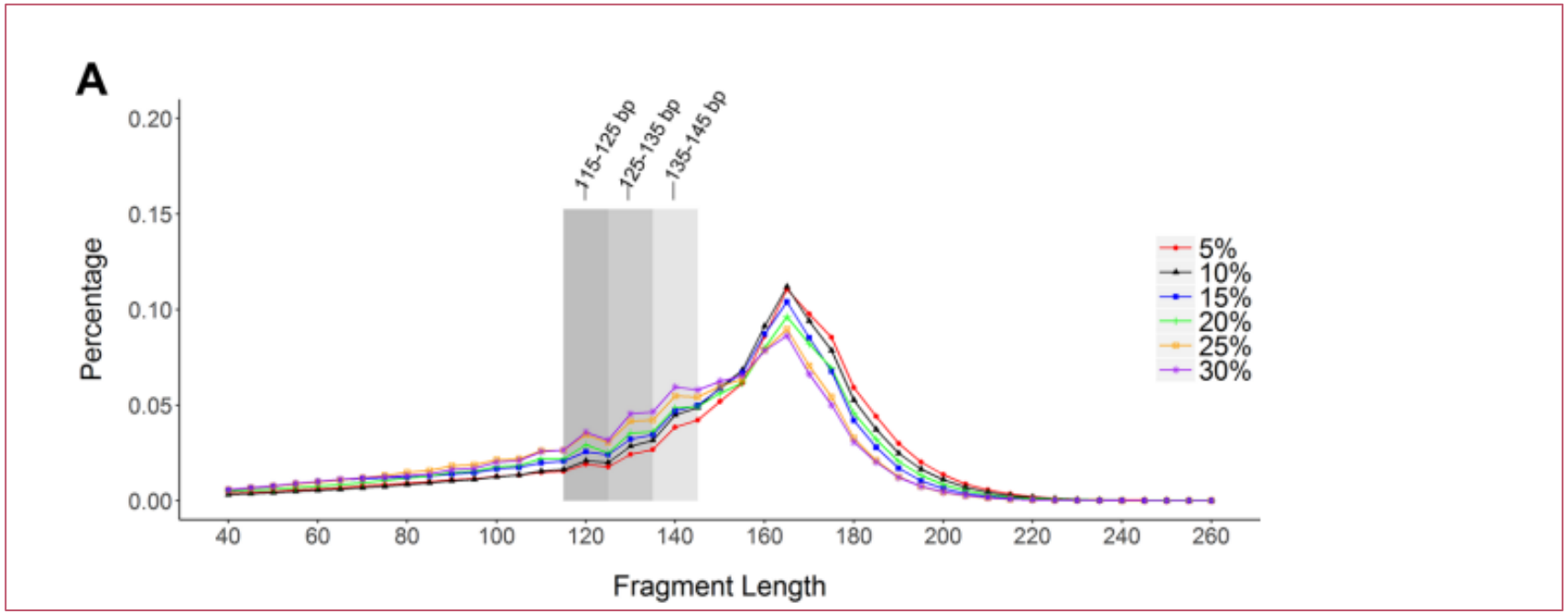
Liquid Biopsy Case Studies

Size Selection in Liquid Biopsy

- Liquid Biopsy (LB) using cell free DNA is in routine use in prenatal screening (NIPT) and under clinical evaluation for cancer screening
- Significant limitation of LBs is that the DNA molecules of interest comprise only a small fraction of the total cell free DNA
- Size selection using Ranger® Technology gives a significant enrichment of the relevant size fraction, (fetal or cancer) or DNA/RNA sequence, (viral or other) thereby improving test performance and reducing test costs

NIPT

cfDNA - fetal cfDNA has a smaller size distribution than maternal cfDNA



Liang B et al (2018) Scientific Reports 8:17675 | DOI:10.1038/s41598-018-35738-0

NIPT Case Studies

Yourgene NIPT portfolio

IONA® Nx
NIPT Workflow

Sage™ 32
NIPT Workflow

- Ranger® Technology is proven: embedded in our NIPT offering over the last 3 years
- Approx. **235,000 samples** processed to date globally
- Enables:
  - Fetal Fraction enrichment – doubles the cfDNA from the fetus
  - Enables accurate test result on samples with as low as 2% fetal fraction
  - Higher performance – lower failure rates, industry low re-draw rates (0.5%)
  - Ranger® enables more flexibility and choice across blood collection tubes – it has proven EDTA capability – giving greater cost efficiencies to the lab and patient*

NIPT Case Studies

Yourgene NIPT portfolio and Ranger Technology

- Ranger Technology is proven: embedded in our NIPT offering over the last 3 years
- Approx. **235,000 samples** processed to date
- Enables:
  - Fetal Fraction enrichment – doubles the cfDNA from the fetus
  - Higher performance – lower failure rates as more focused analysis possible
  - More competitive – USPs with low fetal fraction detection & increased throughput

UNIVERSITÉ LAVAL

Improving Fetal Fraction of EDTA-Gel NIPS Samples Using Gel Based Size Selection (SS)

Dr Francois Rousseau, MD, MSc, FRCPC, FCAHS
Professor in Dept of Molecular Biology, Medical Biochemistry & Pathology

- SS significantly increases FF using EDTA-gel collection tubes
- Improved clinical performance
- SS eliminated all failures due to low FF; reduced redraws
- SS rescued samples contaminated by maternal genomic DNA

https://www.sciencedirect.com/science/article/pii/S1525157822001696

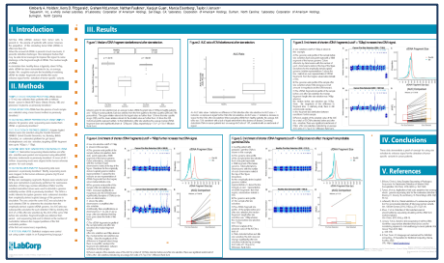
Oncology Case Studies

LabCorp and Ranger® Technology

Kim Holden, PhD
Research Associate III, LabCorp

Size selection of cell-free DNA enhances signal for the detection of tumor-specific variants in cancer patients

LabCorp
Laboratory Corporation of America



Size selection of cell-free DNA enhances signal for the detection of tumor-specific variants in cancer patients

Kim Holden
Research Associate III
Laboratory Corporation of America®, San Diego, California

labcorp Yourgene Health

Connecting to the presentation

Oncology Case Studies

University of Utah & Ranger® Technology

Dr Hunter Underhill, PhD. MD
Assistant Professor of Paediatrics
School of Medicine

THE UNIVERSITY OF UTAH

Detection of primary brain lesions using ctDNA

- Ranger® Technology's automated size selection can reduce sample complexity and improve sensitivity in cancer ctDNA-based applications including detection of very low variant allele frequencies[1]
- Suitable for oncology early detection and disease progression studies

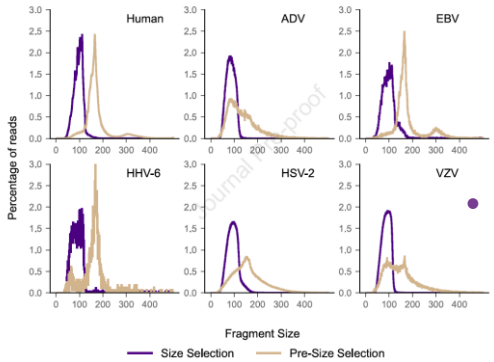
1.Hellwig, S., et al. PLOS ONE, https://doi.org/10.1371/journal.pone.0197333, July 25, 2018
2.https://www.yourgene-health.com/about/the-y-series/your-expert/85-the-y-series/your-expert/1830-yex004-lightbench-enabling-liquid-biopsies-for-cancer-detection

Infectious Disease Case Studies

University of Washington DC & Ranger® Technology

Dr Alexander Greninger MD, PhD, MS, MPhil
Assistant Professor, Dept of Medicine & Pathology

Fragment Size-based Enrichment of Viral Sequences in plasma cell-free DNA



- cfDNA testing for infectious disease diagnostics is limited by inadequate analytical sensitivity
- Selective sequencing of short fragments enriches microbial & CMV-derived cfDNA
  - E.g. Adenovirus, Herpes Simplex 2, Varicella Zoster, Human Herpesvirus
- Ranger ® Technology demonstrated a simple, scalable method for enhanced detection of viral DNA

UNIVERSITY of WASHINGTON

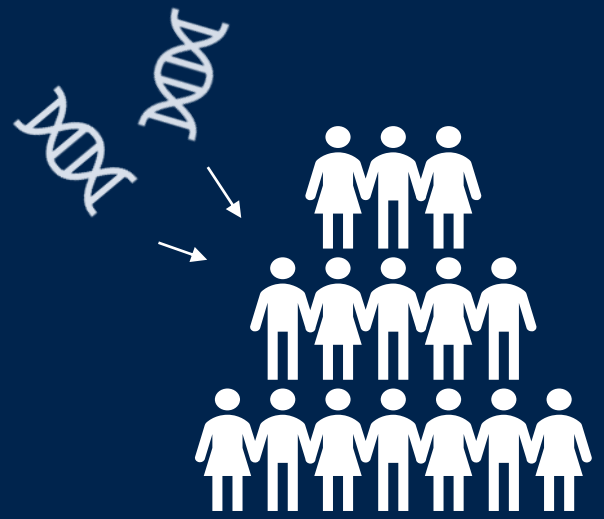
1.Phung, Q., et al. Journal of Molecular Diagnostics, https://doi.org/10.1016/j.jmoldx.2022.01.007, Jan 2022

Seeking Collaborations to explore new applications

- Ranger® Technology has proven capability to improve workflows and test performance in other applications including oncology, infectious disease testing and gene synthesis
- We are always looking for additional collaborators to test our game changing Ranger® Technology in new applications to demonstrate the benefit we know it can bring
- Come and talk to Yourgene about how we can work together

Yourgene Health

Technologies and services to enable the delivery of genomic medicine



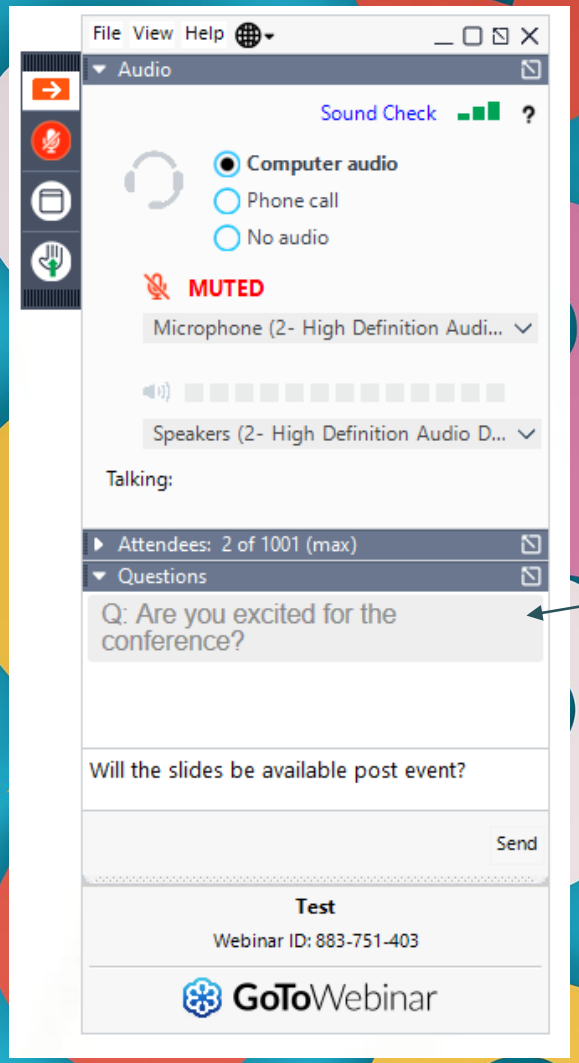
help find the right path to improve patient outcomes

Yourgene Health

Experts in cell-free DNA

Yourgene Health
Skelton House
Lloyd Street North
Manchester
M15 6SH
United Kingdom

www.yourgene-health.com



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Understanding Genomics in the NHS Conference 2022

SPEAKING NOW

Clare Turnbull

Professor of Translational Cancer Genetics
Institute of Cancer Research, London

I will be discussing…

"Cancer Predisposition Genetics for prevention and early detection of Cancer"

Cancer Predisposition Genetics for prevention and early detection of Cancer

ICR The Institute of Cancer Research

The Royal Marsden NHS
NHS Foundation Trust

NHS Digital

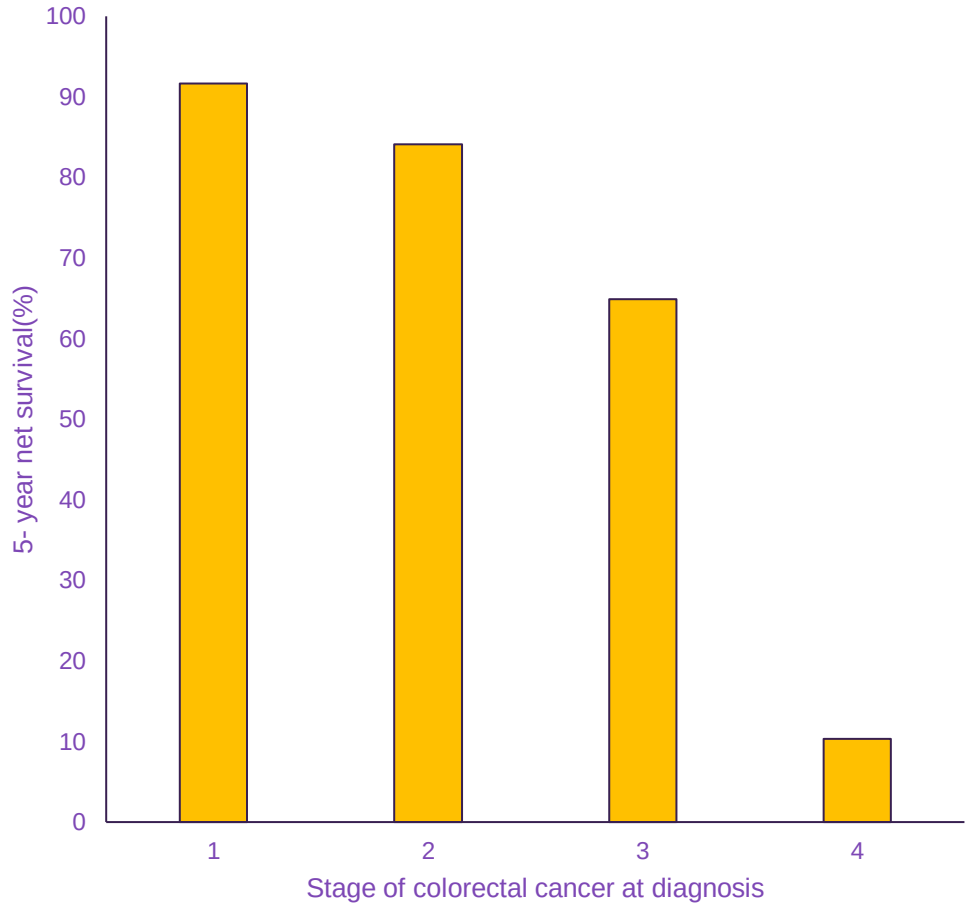
NHS Genomics Conference: 29th November 2022

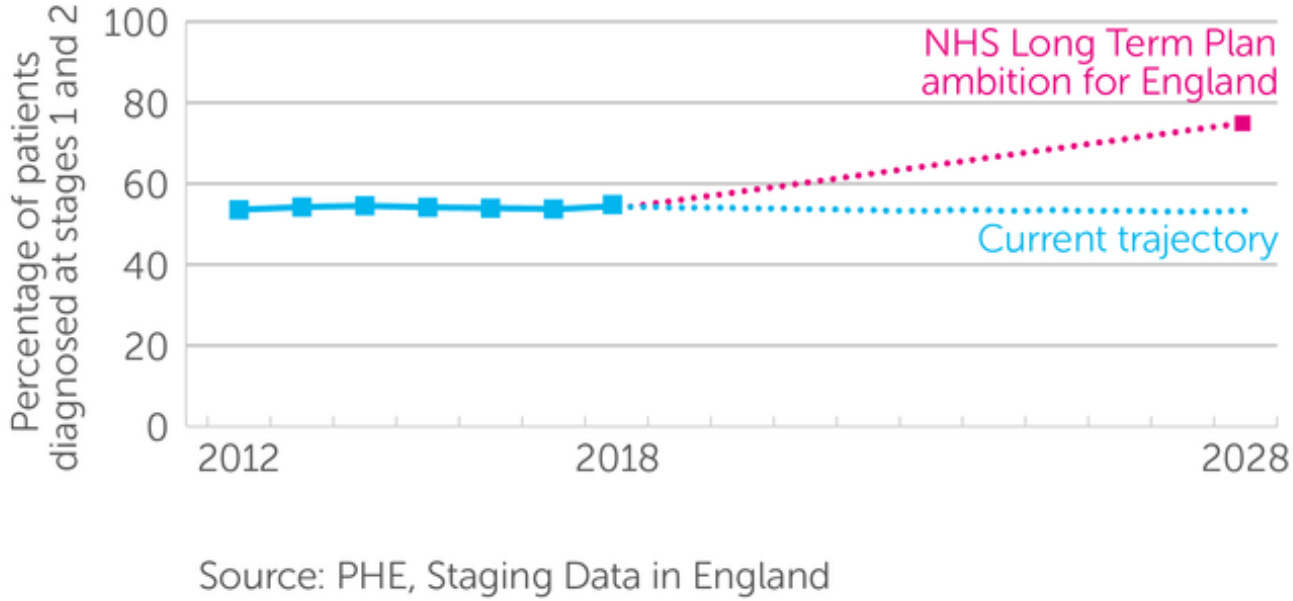
Dr Clare Turnbull

- Professor in Translational Cancer Genetics, Institute of Cancer Research
- NHS consultant in Cancer Genetics (Honorary), Royal Marsden NHS Foundation Trust
- Consultant in Public Health Medicine (Honorary), PHE/NHSD

Funded by CANCER RESEARCH UK

Improving cancer survival
Early detection





Source: PHE, Staging Data in England

Cancer Research UK 2022

Overview

1) Interventions for elevated risk of cancer
2) Architecture of genomic risk of cancer
3) High penetrance alleles (Cancer Susceptibility Genes)
4) Polygenic Risk Score

Genomics for early detection and prevention of cancer

Screening

National screening programmes:
Breast, Colorectal, Cervix

Genomics for early detection and prevention of cancer

Screening

National screening programmes:
Breast, Colorectal, Cervix

Enhanced screening programmes:
Modality MRI
Age of starting 30
Frequency annually

Primary surgical prevention

Mastectomy
Oophorectomy
Colectomy
Gastrectomy

Primary chemoprevention

RE-PURPOSED: aspirin, metformin,
RE-POSITIONED: tamoxifen
TARGETED: denosumab, ?? PARPi

Behavioural

Smoking
Sun exposure
Hormonal factors (? BF, age CB)

Overview

1) Interventions for elevated risk of cancer
2) Architecture of genomic risk of cancer
3) High penetrance alleles (Cancer Susceptibility Genes)
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Genomics for early detection and prevention of cancer

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Colectomy
Gastrectomy

Primary chemoprevention

RE-PURPOSED: aspirin, metformin,
RE-POSITIONED: tamoxifen
TARGETED: denosumab, ?? PARPi

Behavioural

Smoking
Sun exposure
Hormonal factors (? BF, age CB)

Genomics for early detection and prevention of cancer

Non-genetic factors

Screening

National screening programmes:
Breast, Colorectal, Cervix

Enhanced screening programmes:
Modality MRI
Age of starting 30
Frequency annually

Primary surgical prevention

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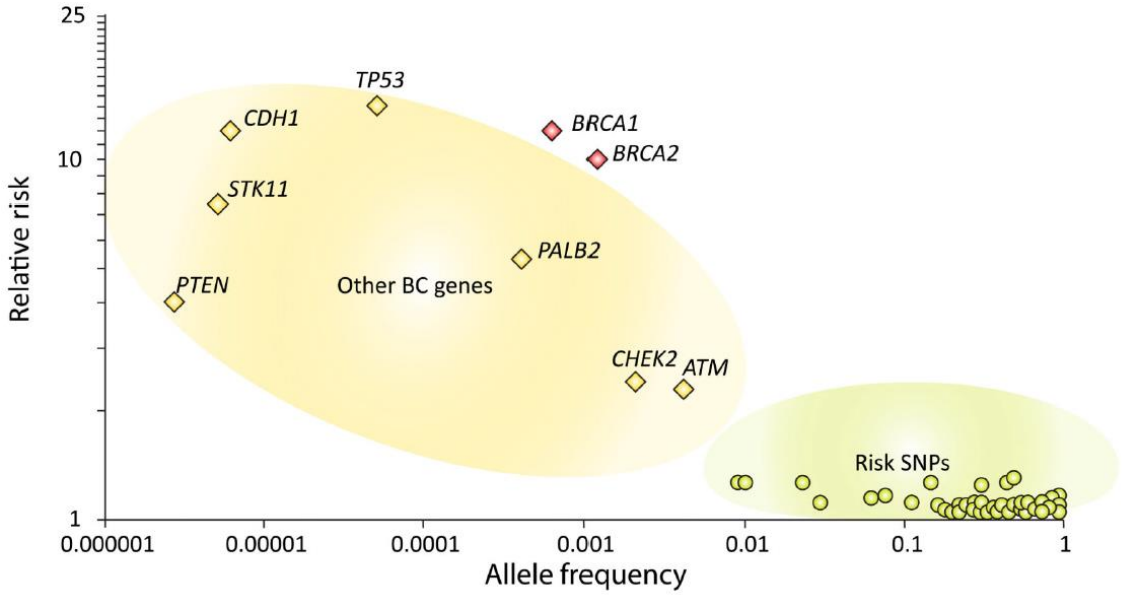

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Overview

1) Interventions for elevated risk of cancer
2) Architecture of genomic risk of cancer
3) High penetrance alleles (Cancer Susceptibility Genes)
4) Polygenic Risk Score

Genomics for early detection and prevention of cancer

Genetic factors

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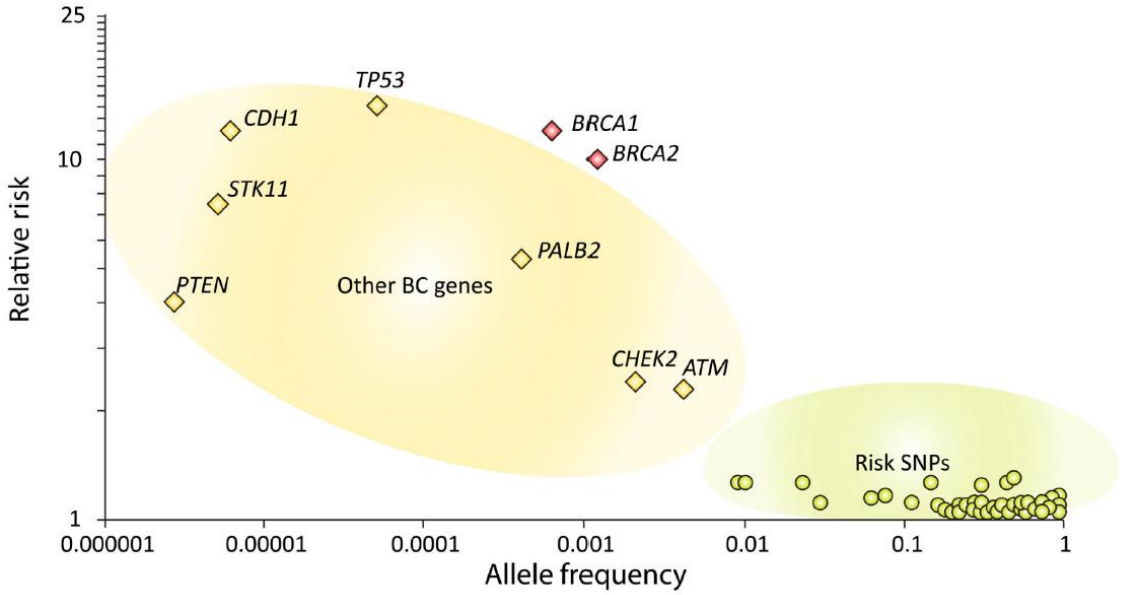

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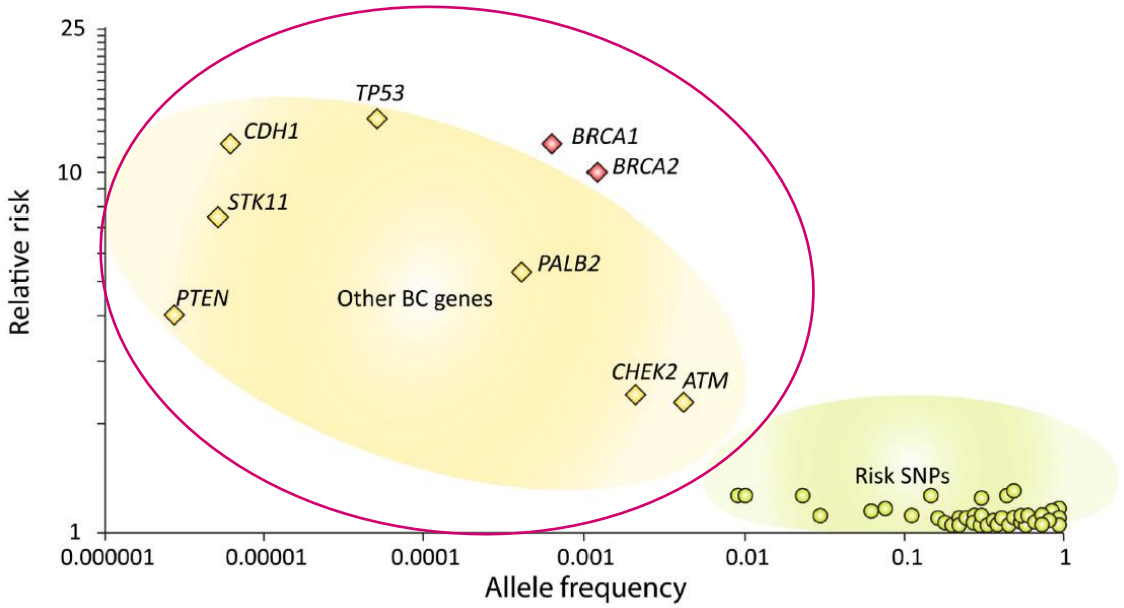

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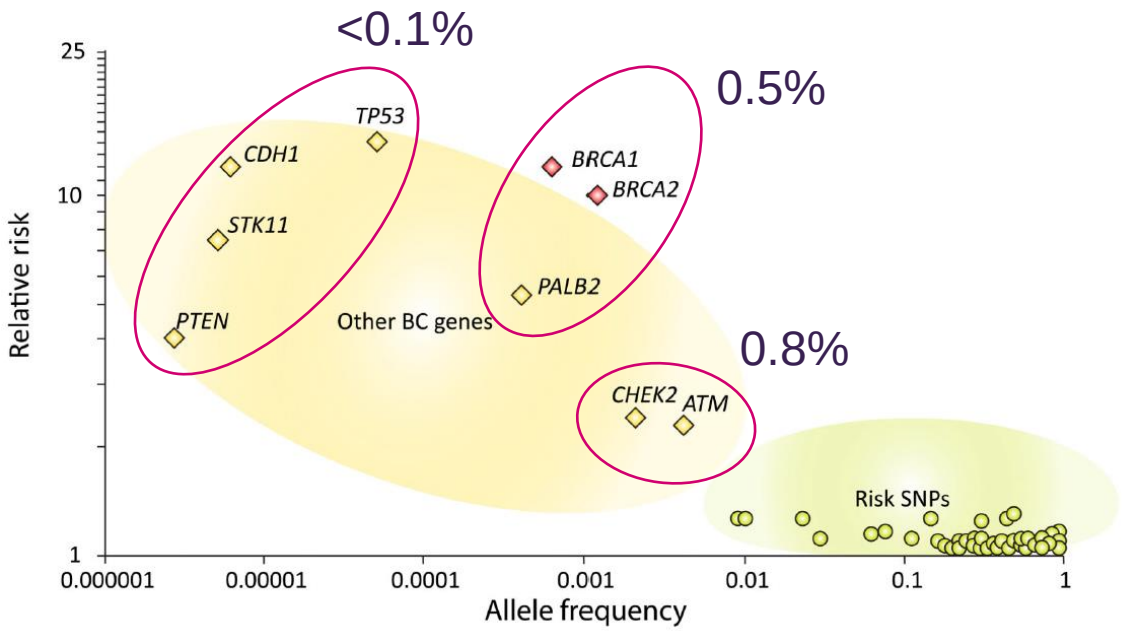

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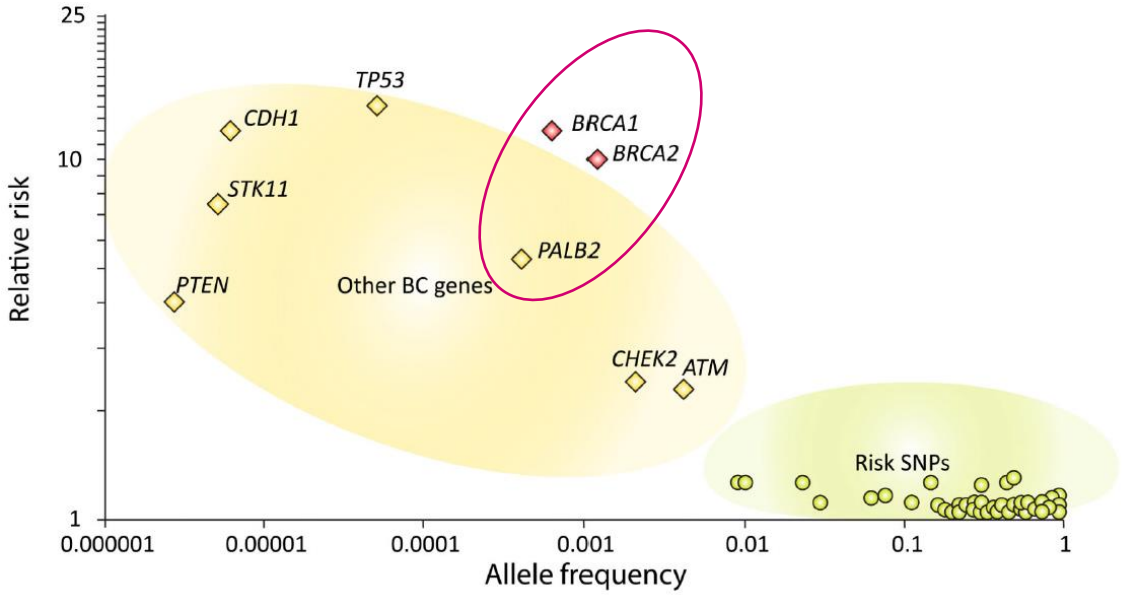

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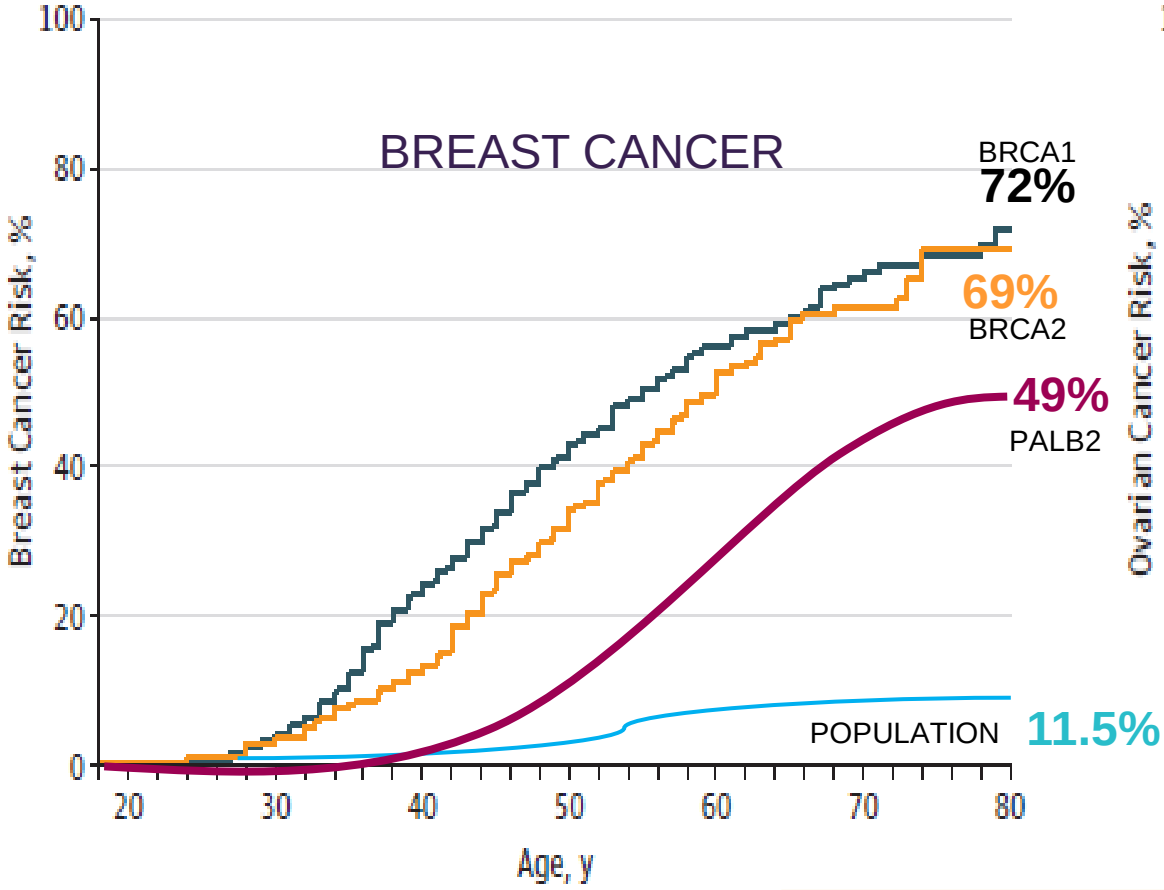
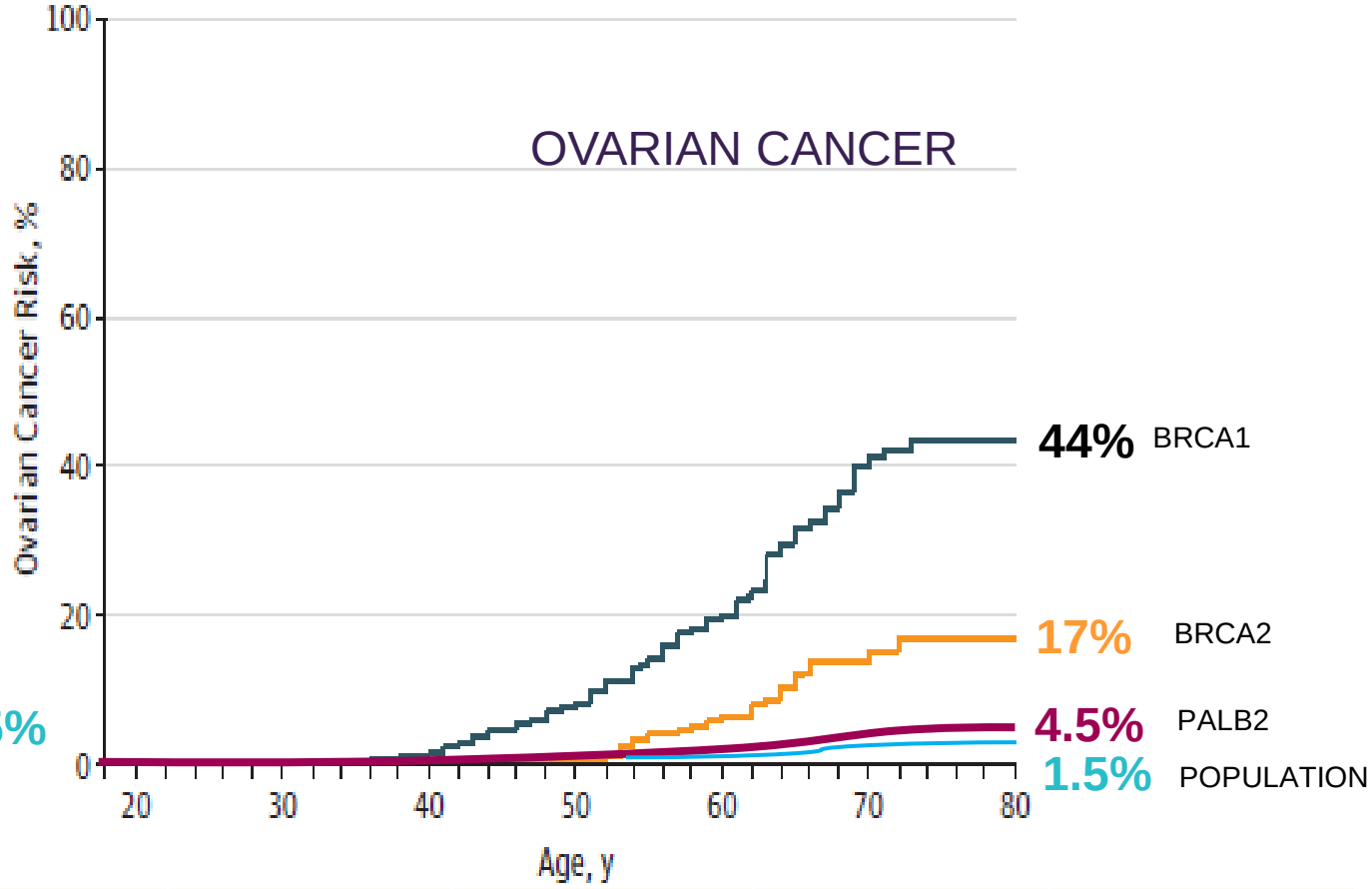
Cancer Risks: BRCA1, BRCA2, PALB2





	population	BRCA1	BRCA2	PALB2
Male Breast Cancer	<0.1%	ns	OR~50	OR~10
Prostate Cancer	18%	ns	OR~2.5	ns
Pancreatic Cancer	2%	ns	OR~3	OR~3

So who is eligible for BRCA-testing?

	BRCA1/ BRCA2/ PALB2 pick-up	Annual cases (UK)	NHSE National Test Directory
Ovarian Cancer	15%	7,500	✓
Male breast Cancer	10%	375	✓
Breast Cancer	3%	56,000	complex criteria ~17%
Prostate Cancer	2%	52,000	complex criteria <10%
Pancreatic Cancer	3%	10,000	complex criteria <10%

.

1. Manchanda R, et al. *J Med Genet.* 2018;55(8):538-545
2. PROCAS data, Evans

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Prostate Cancer	2%	52,000	complex criteria
Pancreatic Cancer	3%	10	

National Test Directory 2022

NHS England

BRCA1/BRCA2/PALB2: full screen including dosage

R208:

- Breast cancer+ family history, pathology adjusted Manchester score ≥15 or CanRisk score ≥10%
- Breast Cancer (age <40 years, excluding Grade 1), OR
- Breast Cancer <45y and one FDR with BC age <45y
- Bilateral breast cancer (age <50 years), OR
- Triple-negative breast cancer (age <60 years), OR
- Breast cancer; Ashkenazi heritage

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1. Manchanda R, et al. *J Med Genet.* 2018;55(8):538-545
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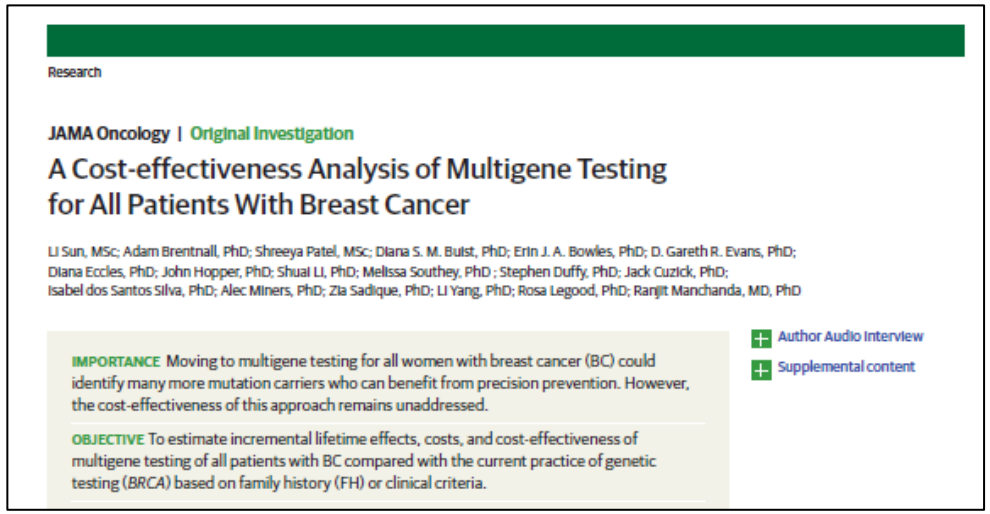
Health Economic Data

- For testing in unselected breast cancer (3% pick-up)



Research

JAMA Oncology | Original Investigation

A Cost-effectiveness Analysis of Multigene Testing for All Patients With Breast Cancer

Li Sun, MSc; Adam Brentnall, PhD; Shreeya Patel, MSc; Diana S. M. Buist, PhD; Erin J. A. Bowles, PhD; D. Gareth R. Evans, PhD; Diana Eccles, PhD; John Hopper, PhD; Shuai Li, PhD; Melissa Southey, PhD ; Stephen Duffy, PhD; Jack Cuzick, PhD; Isabel dos Santos Silva, PhD; Alec Miners, PhD; Zia Sadique, PhD; Li Yang, PhD; Rosa Legood, PhD; Ranjit Manchanda, MD, PhD

Author Audio Interview

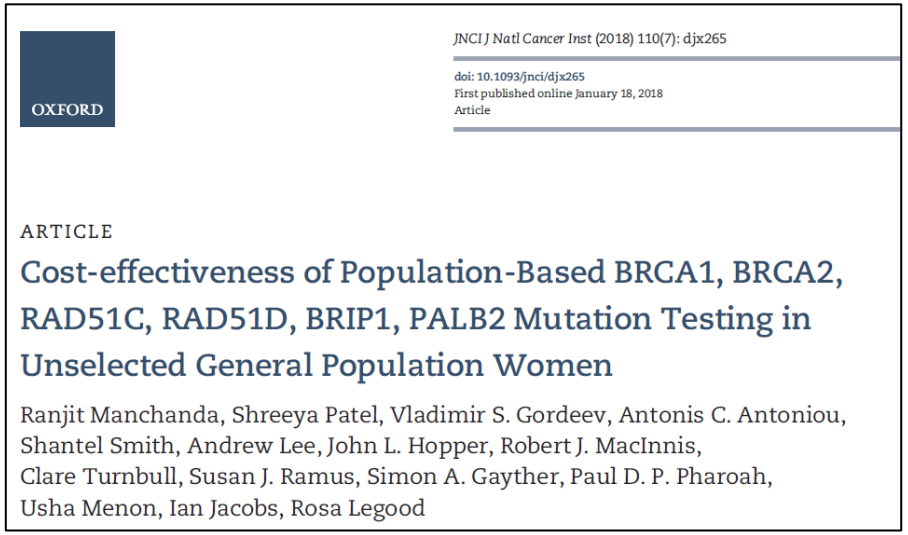
Supplemental content

IMPORTANCE Moving to multigene testing for all women with breast cancer (BC) could identify many more mutation carriers who can benefit from precision prevention. However, the cost-effectiveness of this approach remains unaddressed.

OBJECTIVE To estimate incremental lifetime effects, costs, and cost-effectiveness of multigene testing of all patients with BC compared with the current practice of genetic testing (*BRCA*) based on family history (FH) or clinical criteria.

- UK costing parameters applied; 2018
- Cost effective at NICE WTP threshold* upto per test cost of **£1626** (payer perspective) and £1868 (societal perspective)

- For testing in unselected female population (0.5% pick-up)



OXFORD

JNCI J Natl Cancer Inst (2018) 110(7): djx265

doi: 10.1093/jnci/djx265
First published online January 18, 2018
Article

ARTICLE

Cost-effectiveness of Population-Based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 Mutation Testing in Unselected General Population Women

Ranjit Manchanda, Shreeya Patel, Vladimir S. Gordeev, Antonis C. Antoniou, Shantel Smith, Andrew Lee, John L. Hopper, Robert J. MacInnis, Clare Turnbull, Susan J. Ramus, Simon A. Gayther, Paul D. P. Pharoah, Usha Menon, Ian Jacobs, Rosa Legood

- UK costing parameters applied; 2017
- Cost effective at WTP threshold* upto per test cost of **£250** (payer perspective)
- Funding for trial (Yorkshire Cancer Research) in final approvals

*WTP threshold: NICE £20,000-£30-000/QALY

So who is eligible for BRCA-testing?

	BRCA1/ BRCA2/ PALB2 pick-up	Annual cases (UK)	NHSE National Test Directory	Treatment biomarker
Ovarian Cancer	15%	7,500	✓	✓ adjuvant, maintenance
Male breast Cancer	10%	375	✓	
Breast Cancer	3%	56,000	complex criteria ~17%	✓ Metastatic (TA831) ? early high risk (TA762)
Prostate Cancer	2%	52,000	complex criteria <10%	? metastatic [in trials: PROFOUND]
Pancreatic Cancer	3%	10,000	complex criteria <10%	? advanced [in trials: POLO]

- Ascertainment study for NHS laboratories: **2.6%** of *BRCA1/BRCA2* mutation carriers have been identified of the **~396,000 carriers in UK** (based on data for all NHS testing performed in Greater London, 2018)[1]

1. Manchanda R, et al. *J Med Genet.* 2018;55(8):538-545
2. PROCAS data, Evans

What is limiting delivery of BRCA-testing?

The cost of the lab test?

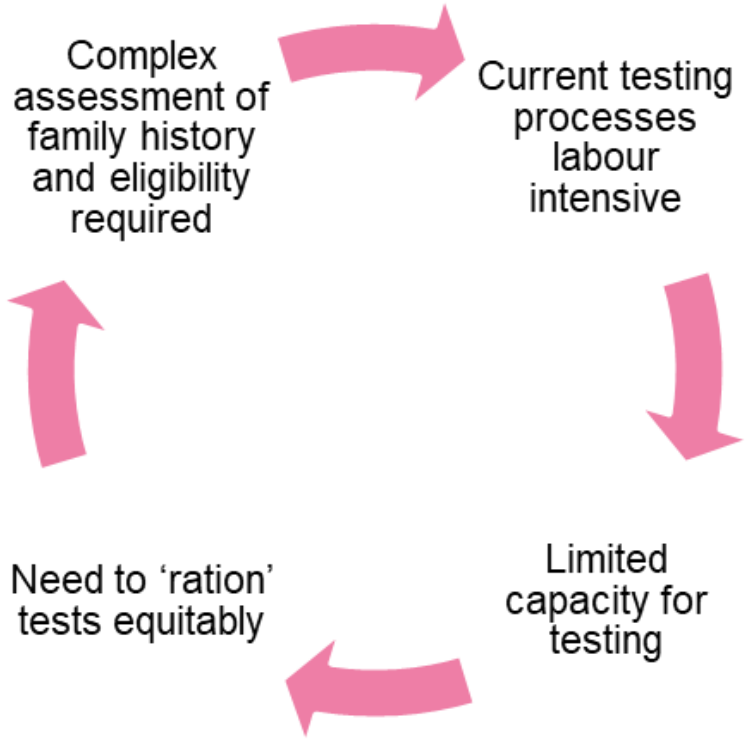
Or the clinical pathway?

Next generation Sequencing Technologies

Direct cost at HT: NovaSeq 18 E/test (reagents, consumables, labcoats)[1]

plus DNA extraction, R&D, capitol investment, indirect costs,

- Historical model of 1:1 genetic consultation/counselling (pre- AND post-test). Based on HD/prenatal scenarios.
- Limited volume of clinical geneticists/genetic counsellors



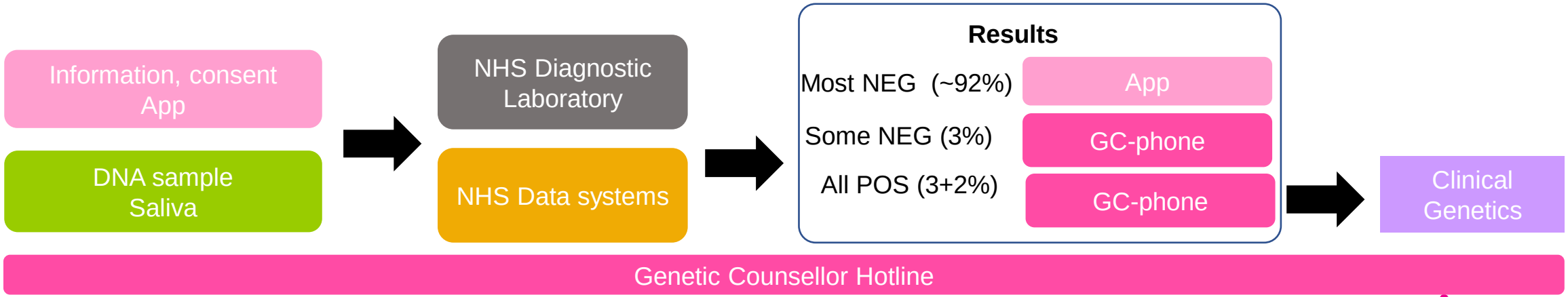
[1] Personal communication, UMC Radbound Nijmegen, (2018)

[2] Hallowell N et al. *Familial cancer* (2019)

[3] Slade I et al. *Genome Med* (2015).

Approaches to mainstreaming BRCA-testing in breast cancer cases

- "Mainstreaming": devolve process from clinical genetics to oncology/primary care
  - face-to-face delivery in oncology clinic (by oncologist or CNS) of laborious work-flow
- BRCA-DIRECT pathway
  - Deliver **generic** elements away from clinic via saliva sampling, bespoke materials, digital-workflow management.
  - Focus clinical resource for **individualised** input (**GC telephone hotline) +** mut positives
  - Maintain **full NHS data integration** with clinical and laboratory data-systems



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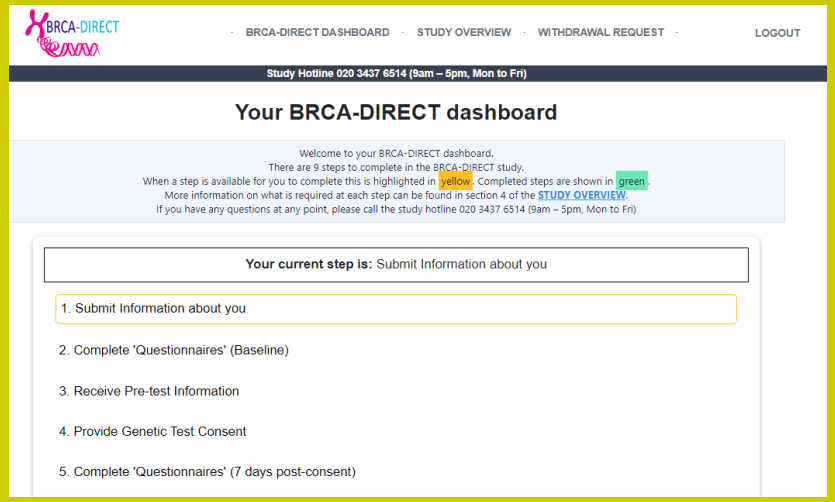
NHS Foundation Trust
BRCA-DIRECT

BRCA-DIRECT: research study 2021-2022

Platform, content, workflows



Lab assay, QC, reporting (ISO 15189)

Feasibility of BRCA-DIRECT Delivery

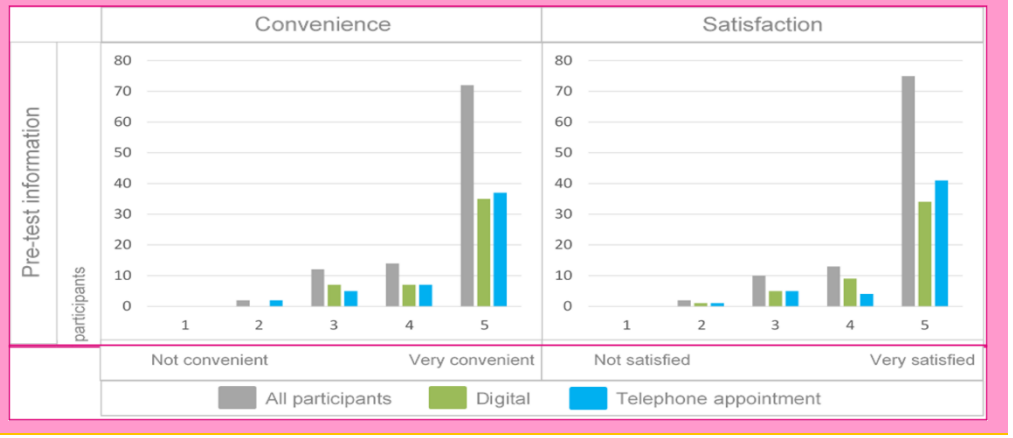
- CRUK-funded REC approved research study
- Delivery of BRCA-DIRECT testing to 1300 patients (July 22)
- 5 hospitals (2 trusts):
  - London (from July 21)
  - Manchester (from Dec 21).

CANCER RESEARCH UK

Outcome Data

Published pilot data of 150 patients[1] demonstrating:

- High rating for **patient satisfaction** and **convenience**
- High rating for **overall clinician satisfaction**
- Non-inferioriority for **patient knowledge** and **anxiety** of digital pre-test information vs 1:1 GC telephone
- <5% use of **GC hotline** (~15% technical calls)



1. Torr et al. JMedGenet *2022*

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The Royal Marsden NHS
NHS Foundation Trust

BRCA-DIRECT

The next step 1: Breast Cancer roll-out (SBRI award 2023)

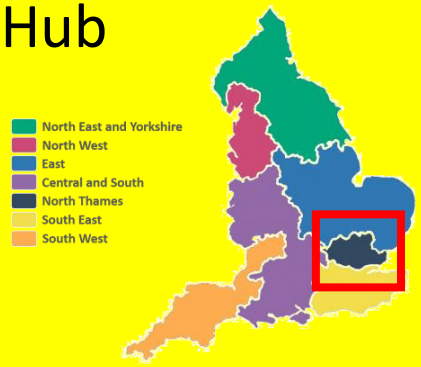
Move into **standard-of-care** (not research)

- **Governance:** relocate IT within NHS firewall
- **Work-flow:** modifications
  - Removal of research consent/pause
  - Removal of research questionnaires
- **Staffing:** previously supported by NIHR/clinical research infra-structure

Delivery via **NHSE genomic infrastructure:**

North Thames Genomic Laboratory Hub

- **GLH Laboratory:** RMH Centre For Molecular Pathology (CMP)
- **GLH Clinical Genetics:** RMH/GOSH
- GLH catchment **NHS breast cancer units**



NHSE 7 Genomic Laboratory Hubs and GMSAs

Scale Delivery

- 6000 tests delivered over 15 months

North Thames GLH Breast Units (NHS Trust delivery partners)

- North Middlesex
- UCLH
- Princess Alexandra
- Royal Free
- Whittington
- Barts (Royal London, Ho
  Newham, Whipps Cross)
- Imperial (Charing Cross)
- Chelsea &Westminster
- Northwick Park
- Royal Marden (Sutton, C
  Kingston)

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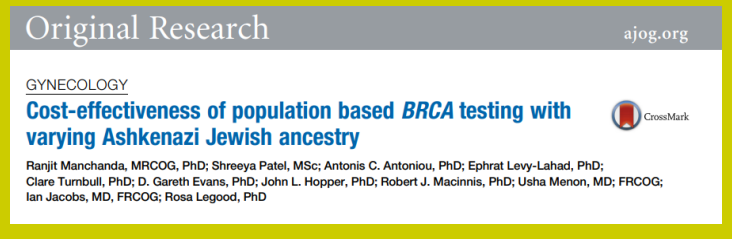
The Royal Marsden NHS
NHS Foundation Trust

The next step 2: Community Testing in Jewish Population (NHSE Cancer Program/NT GMSA)

NHS England

Rationale

- 3 BRCA founder mutations
  - **BRCA1 c. 68_69del** and **c.5266dup**
  - **BRCA2 (c.5946del)**
  - Mutational frequency ~2.5% with four Askenazi grandparents (cf ~0.5%)
- 250,000 Ashkenazi Jews in England (200,000 over 18)
  - **6250 BRCA mutation carriers** (~11% identified)
  - GCaPPs/multiple studies demonstrated
    - acceptability and efficacy
    - cost effectiveness


Original Research ajog.org

GYNECOLOGY

Cost-effectiveness of population based *BRCA* testing with varying Ashkenazi Jewish ancestry

Ranjit Manchanda, MRCOG, PhD; Shreeya Patel, MSc; Antonis C. Antoniou, PhD; Ephrat Levy-Lahad, PhD; Clare Turnbull, PhD; D. Gareth Evans, PhD; John L. Hopper, PhD; Robert J. Macinnis, PhD; Usha Menon, MD; FRCOG; Ian Jacobs, MD, FRCOG; Rosa Legood, PhD

Approach

- **Engagement partner: Jnetics, Chai** (from Jewish Community)
- **Eligible**: any Jewish ancestry
- **Patient registration of interest: v**ia website
- **Pathway:** simplified adaptation of BRCA-DIRECT Paper PIS and consent plus saliva kit sent out
- **Analysis:** full mutational screen of BRCA1/BRCA2
- **Support:** GC hotline 9-5 weekdays
- **Results:** by letter
- **Follow-up:** Mutation positive: GC consult within 5 days by phone, automatic referral to local Clinical Genetics

ICR

The Royal Marsden NHS
NHS Foundation Trust

BRCA-DIRECT

Overview

1) Interventions for elevated risk of cancer
2) Architecture of genomic risk of cancer
3) High penetrance alleles (Cancer Susceptibility Genes)
4) Polygenic Risk Score

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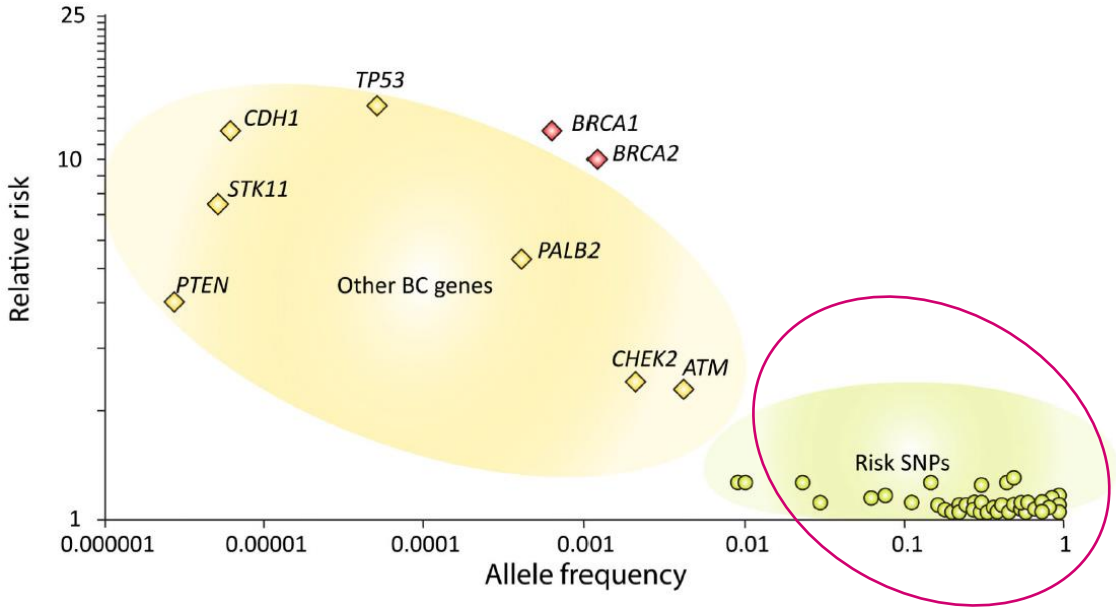

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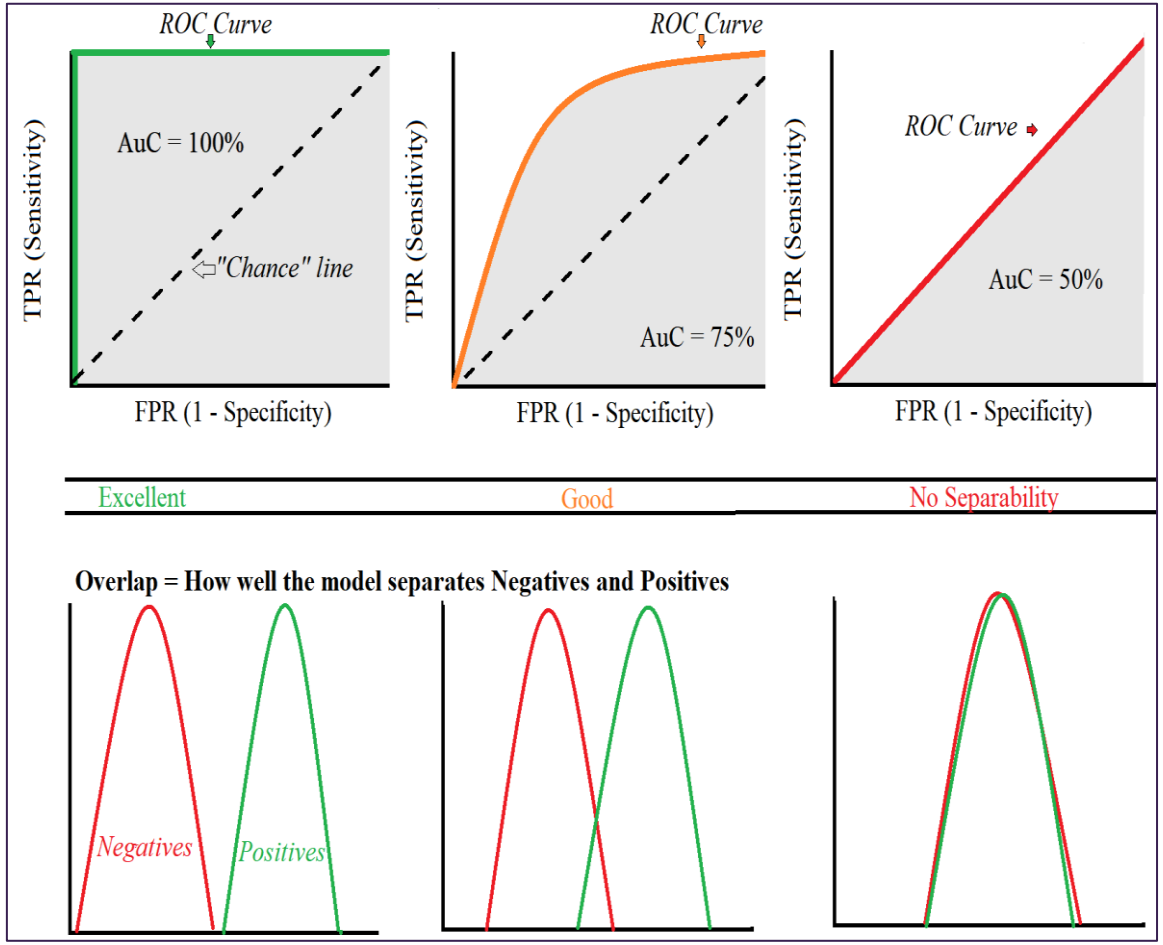
TARGETED: Rank-Ligand inhibition, PARPi

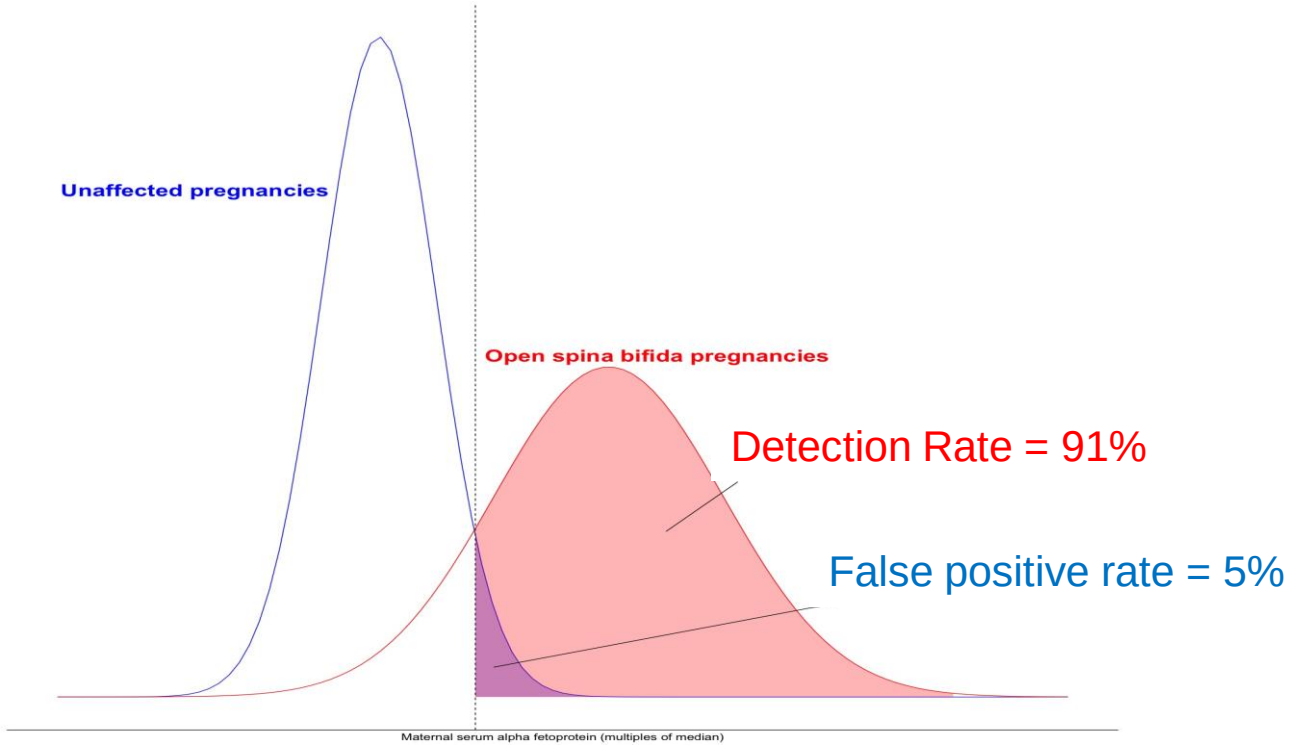
Behavioural

Smoking
Sun exposure
Hormonal factors (? BF, age CB)

Prediction tools: detection rate versus false positive rate

Detection rate = proportion of individuals who develop the disease with a 'positive' PRS
False positive rate = proportion of individuals who do not develop the disease with a 'positive' PRS

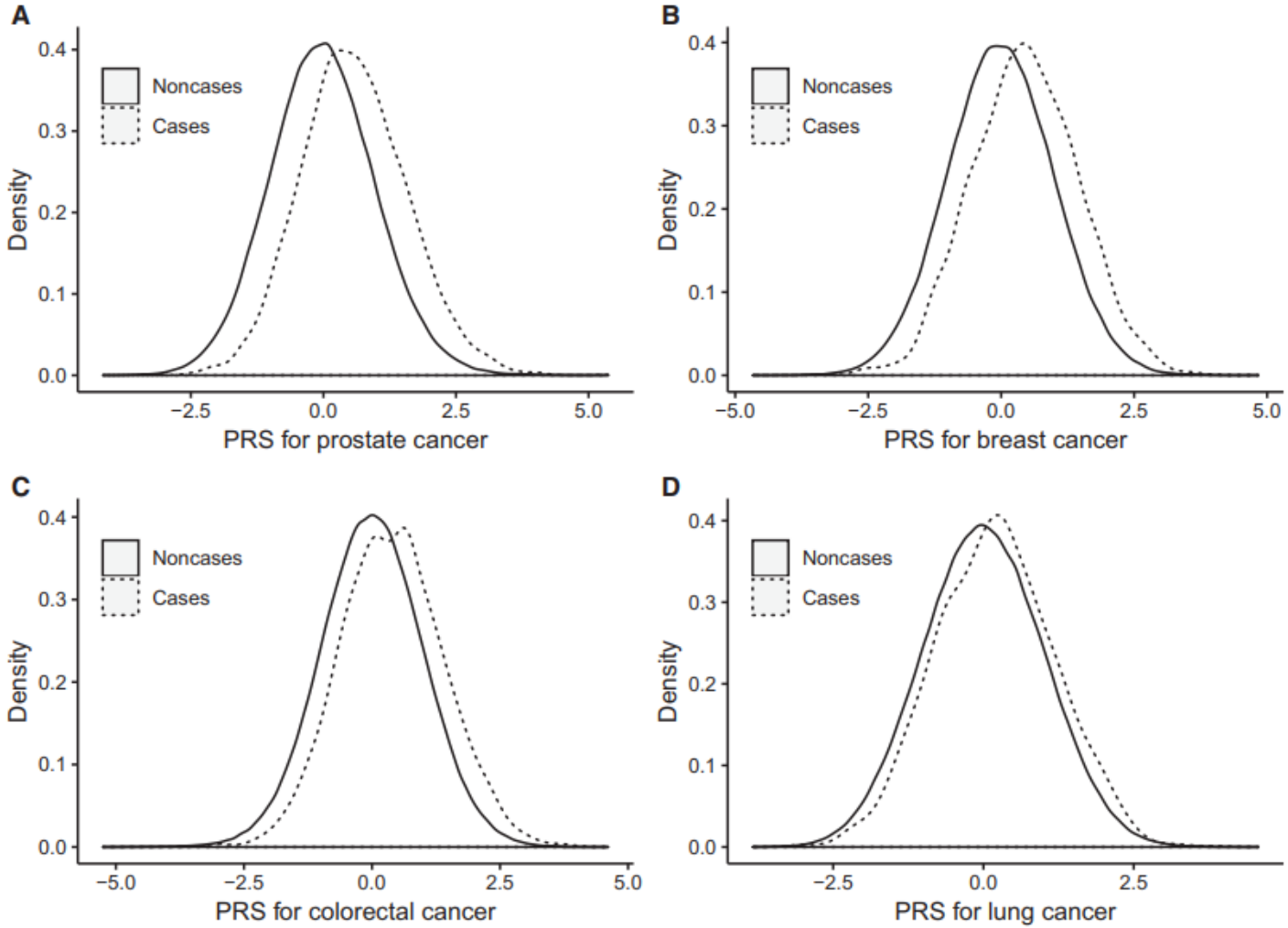




Maternal serum alpha fetoprotein for open spina bifida

Wald N, BMJ 1999
Fritsche, AJHG 2020

Case vs non-case PRS distributions: Prostate, breast, colorectal, lung cancers



Cancers	No. of SNPs	No. of Loci	PRS Cases, mean (SD)	PRS Noncases, mean (SD)	P†	AUC (95% CI)*
Prostate	147	117	12.03 (0.68)	11.63 (0.68)	<.001	0.662 (0.655 to 0.670)
Breast	288	183	16.33 (0.60)	16.05 (0.59)	<.001	0.628 (0.620 to 0.637)
Colorectal	95	74	8.043 (0.47)	7.859 (0.47)	<.001	0.609 (0.598 to 0.620)
Lung	19	14	1.958 (0.37)	1.886 (0.37)	<.001	0.591 (0.576 to 0.606)

Jia et al, JNCI ,2020

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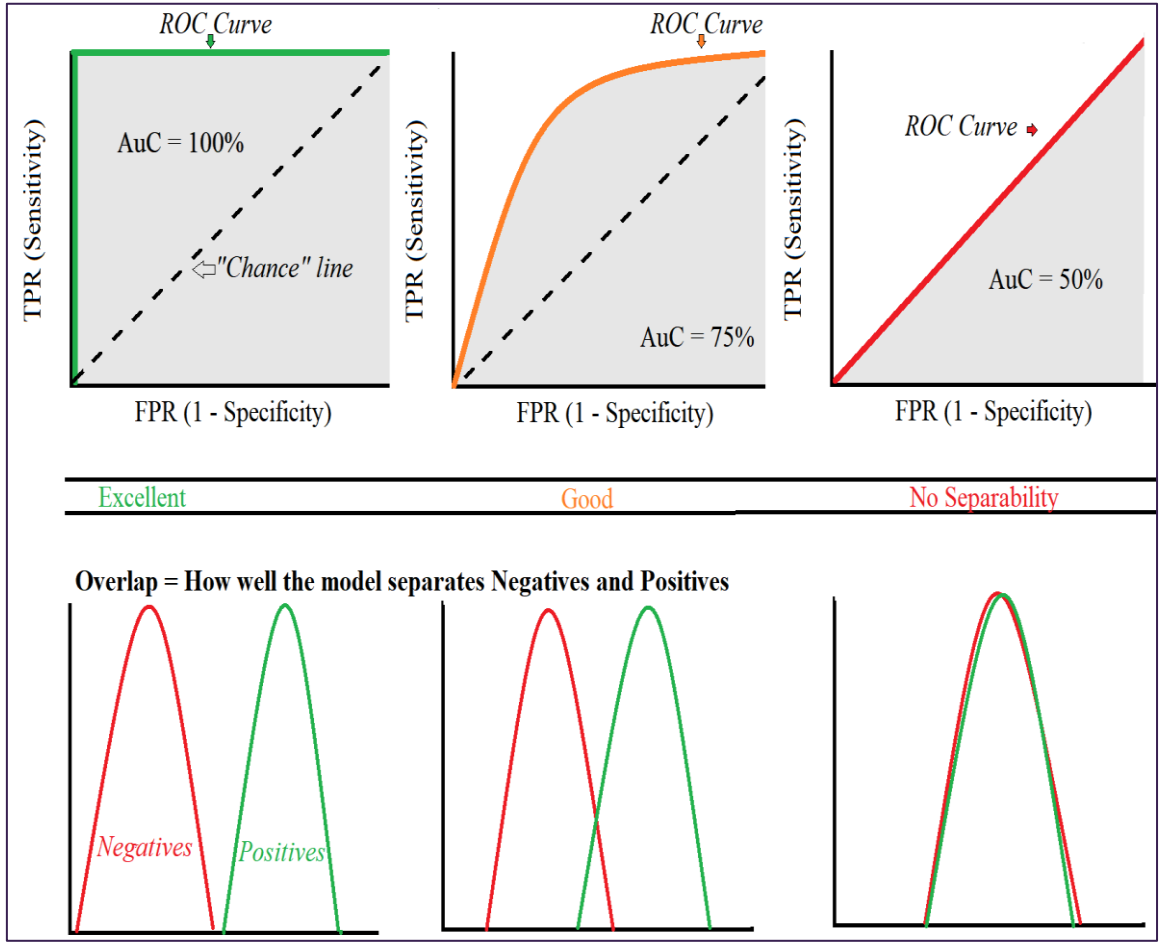

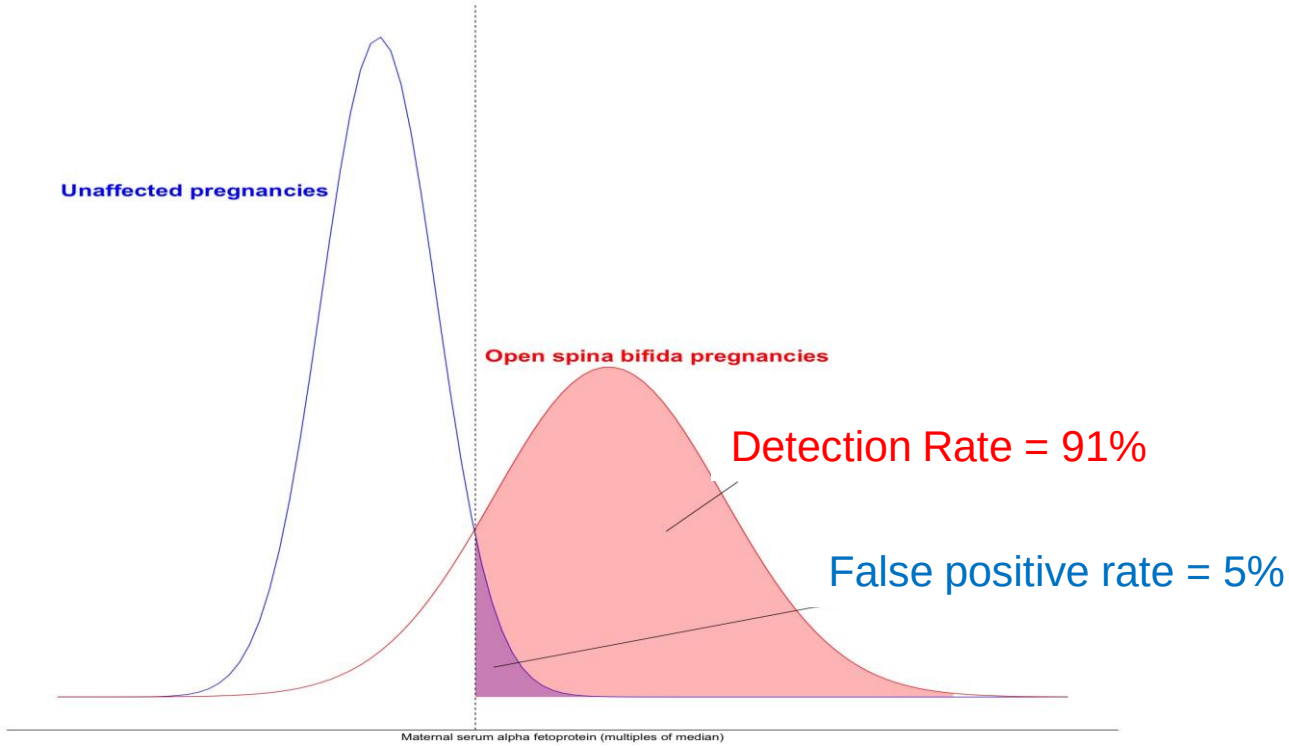

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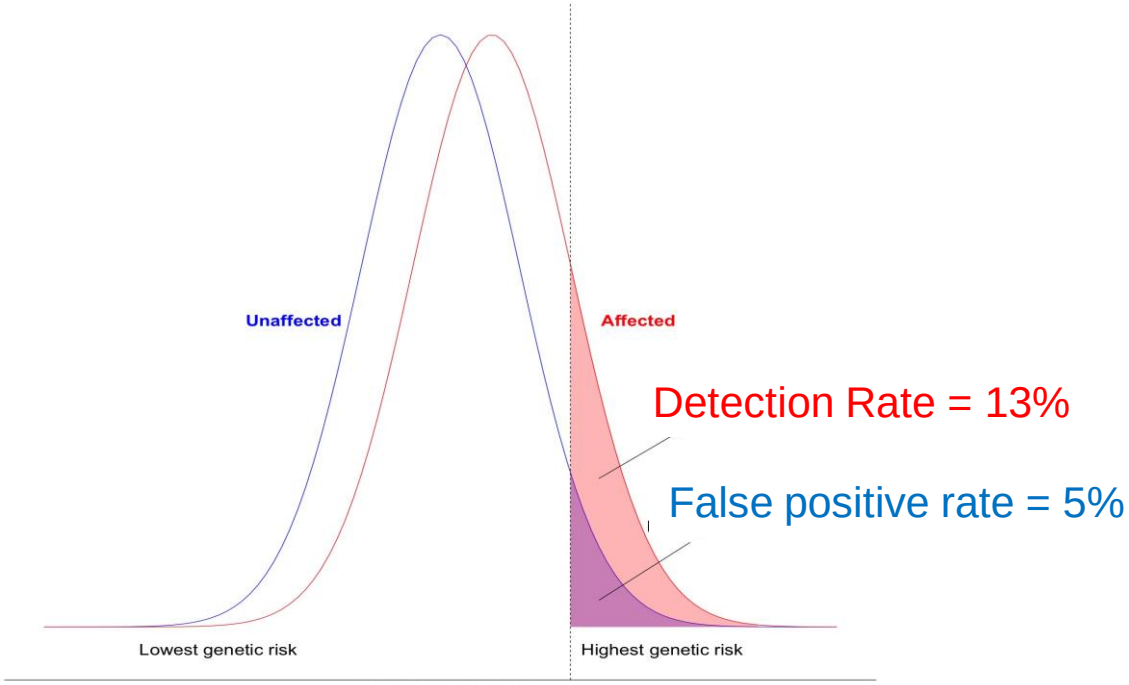
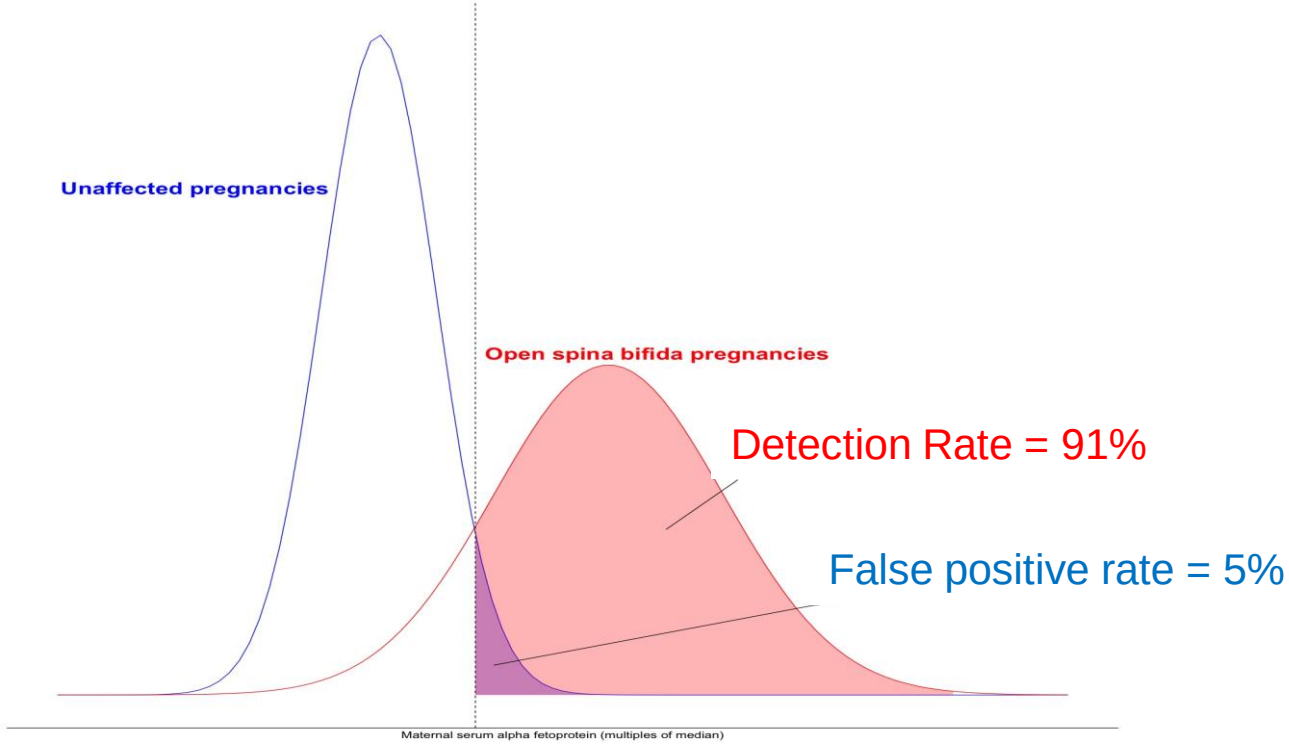


Polygenic risk score for breast cancer (AUC 0.64)



Maternal serum alpha fetoprotein for open spina bifida

1) Remember: unaffected >> cases (esp in younger age cohorts)
2) For PRS+ screening test: combining with imperfect screening test

Wald N, BMJ 1999
Fritsche, AJHG 2020

Applications of PRS to Breast cancer

- **Universal screening** in women aged 50-70 (mammography 3-yearly)
- **Risk-stratified screening** in women aged 40-49
  - PRS (AUC 0.64) to identify those in "high-risk" quintile
  - Annual mammography age 40-59y in this "higher-risk" group.

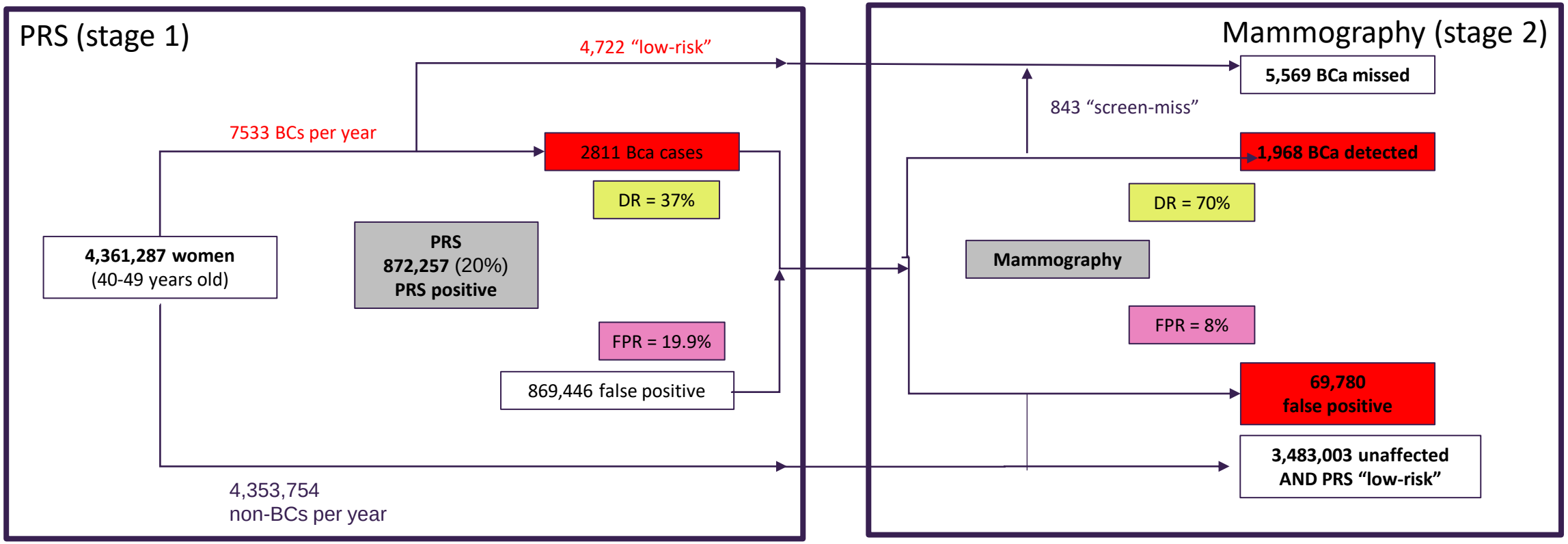


Figure courtesy of Amit Sud, ICR

Sud, Turnbull & Houlston, Nature Precision Oncology 2020

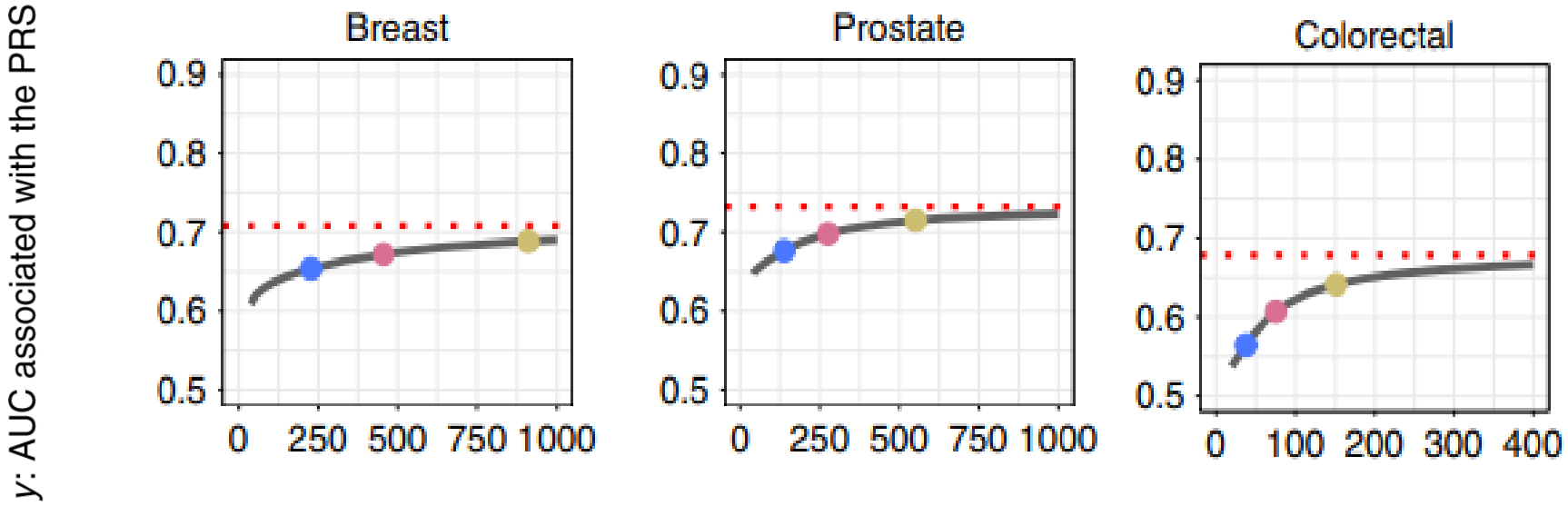
Applications of PRS to Breast cancer

- 4.3 million women aged 40-49 in UK.
- 430,000 turn 40 each year and require PRS per year
- 872,257 additional mammograms per year (top quintile)
- Picks up 1968/7533 (26%) of breast cancers arising in this age group
- 69,780 (8%) false positive mammograms (ie biopsies) per year for 1968 BCs detected (2.8% cancer rate)[1]
- Per year: 102 additional women alive at 10 years post BC diagnosis compared to no screening age 40-49 (1.3% survival improvement in this age group) [2]
- Optimistic scenario
  - Assumes 100% uptake, no PRS test failure, equivalent performance in ethnicity groups
  - Assumes no interval cancers (all cancers arising that year present at annual point of screening)
  - Assumes mammographic performance 40-50y equivalent to 50-70y.
  - Availability of digital mammography (better sensitivity than film mammography)
- Optimised PRS (AUC: 0.69): 122 more women alive at 10 years post BC diagnosis [2,3]

1 Sud, Turnbull & Houlston, Nature Precision Oncology 2020
2 C Huntley et al, manuscript in preparation
3 YD Zhang et al Nature Comms 2020

Additional cautions regarding PRS

1. **Future:** minimal residual boost to PRS attainable (and massive studies required to get minimal improvement)
2. Performance is poorer in **non-white populations** (need for "individualised" PRS based on ethnic admixture)
3. 'Genetic risk profiling' may **reduce uptake** of National Screening Programs
4. Contention of **withdrawing/reducing screening** in "low-risk" population for existing screening programs
5. Complex risk **communication** (patients and health care professionals)



x: sample size (1000s) 1:1 case:control

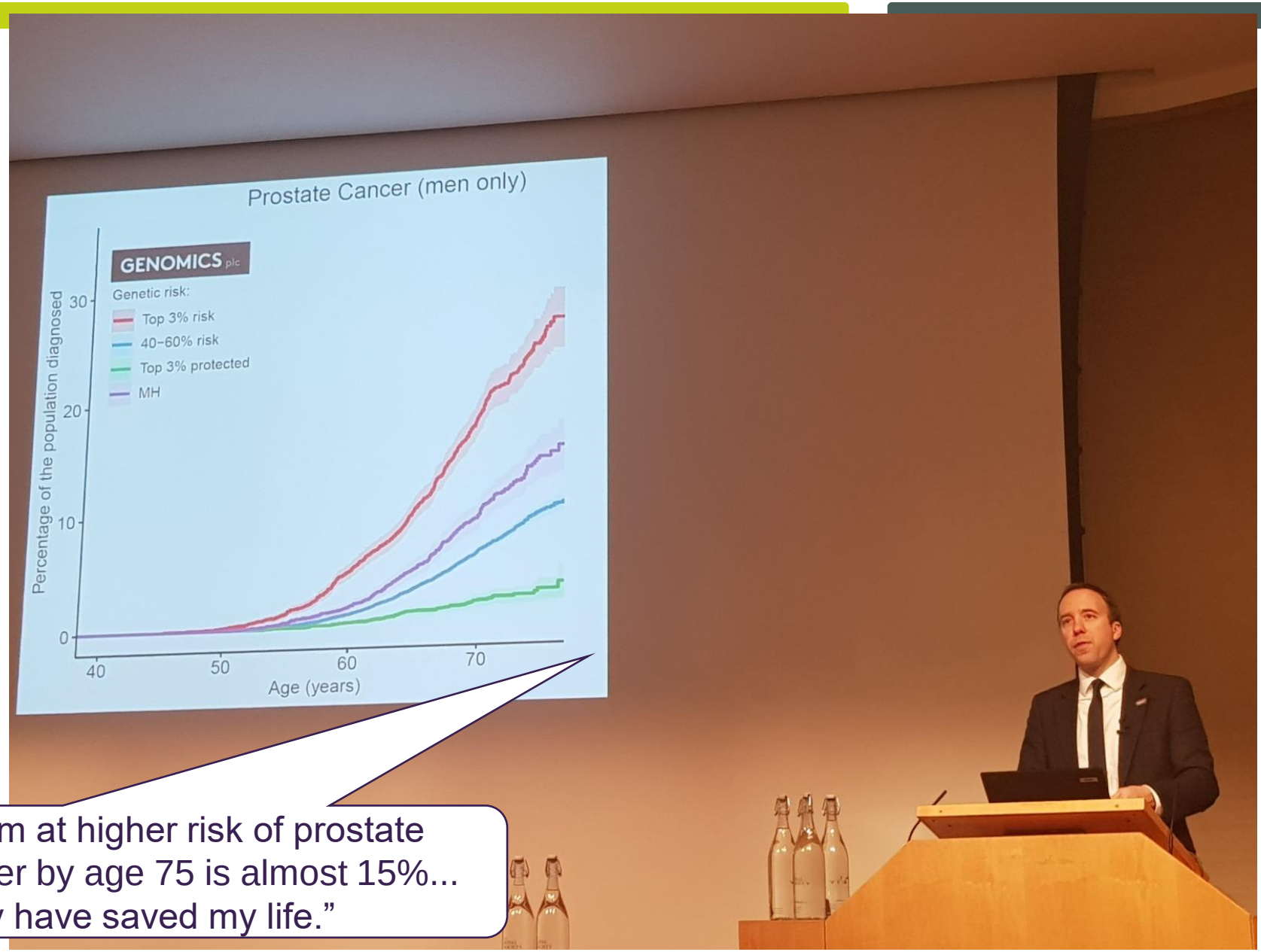
Zhang YD, Nature Comm 2020
Choudhury PP, JNCI 2019

The promise of PRS

Health Secretary Matt Hancock discovers he is at a higher risk of developing prostate cancer after taking DNA test that could revolutionise NHS treatment

- Matt Hancock will reveal results in a speech at the Royal Society on Wednesday
- He is expected to say: 'My risk of prostate cancer by age 75 is almost 15%'
- Mr Hancock will highlight the need for more 'genomic counsellors' on the NHS

By ISABELLA NIKOLIC FOR MAILONLINE
PUBLISHED: 02:01, 20 March 2019 | **UPDATED:** 09:03, 20 March 2019



"But it wasn't all good news. I'm at higher risk of prostate cancer. My risk of prostate cancer by age 75 is almost 15%... The truth is this test may have saved my life."

[The average risk of prostate cancer to age 75 is 13%]

Overview

1) Interventions for elevated risk of cancer
2) Architecture of genomic risk of cancer
3) High penetrance alleles (Cancer Susceptibility Genes)
4) Polygenic Risk Scores

Acknowledgements

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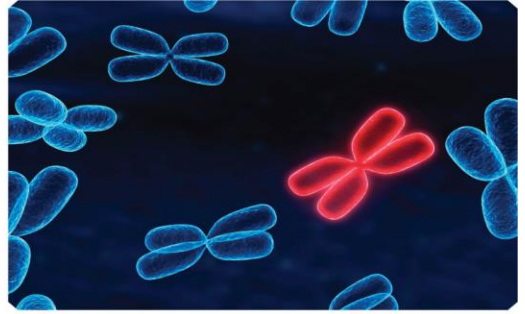
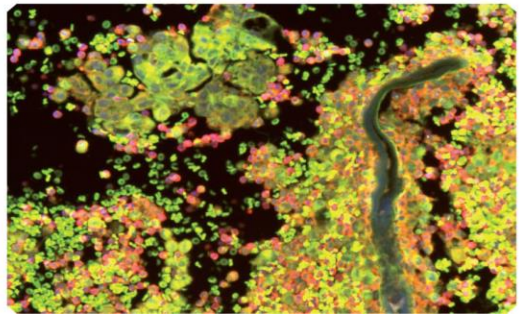
Unrivalled track record

ICR The Institute of Cancer Research

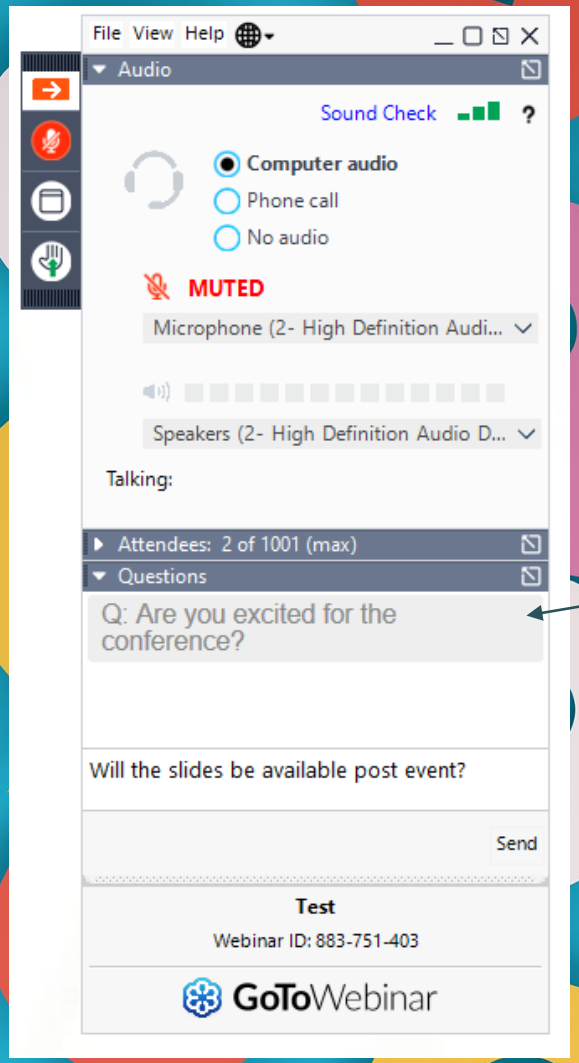


Making the discoveries that defeat cancer

ICR



One of the world's most influential cancer research institutes



If you have any questions or comments for Speakers across the day, please expand the Questions Section on the GoToWebinar panel. You will not be able to see each others questions.

Understanding Genomics in the NHS Conference 2022

SPEAKING NOW

Professor Sandi Deans

Deputy Director for Genomic Science & Laboratory in the Genomics Unit - NHS England

I will be discussing…

"Implementing Genomics in the NHS"

Genomics and Precision Medicine - *driving change in the NHS*

Professor Sandi Deans
Deputy Director – Laboratory & Scientific, Genomics Unit, NHS England

Convenzis, Understanding Genomics in the NHS
29th November 2022

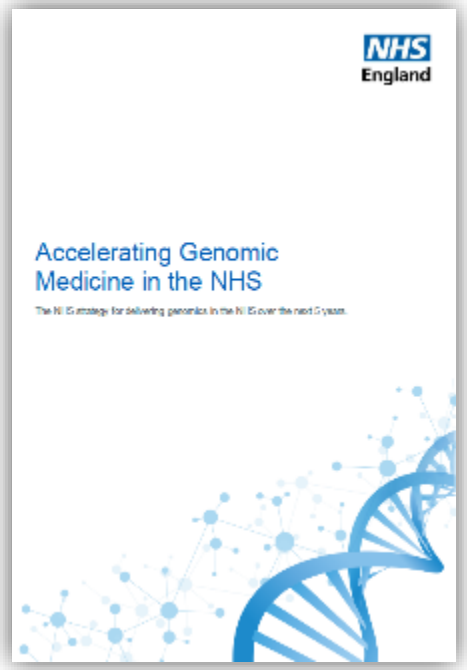
“In many ways this is one of the most exciting bets the NHS is making. So you’ve got an important job to do, and we’re expecting big things. But you’ve also got our backing and you’ve now got a clear strategy to take genomic medicine forward.”

Amanda Pritchard

Chief Executive of NHS England speaking at the launch of the NHS Genomics Strategy at the NHS Genomics Healthcare Summit on 12th October 2022 in London, United Kingdom

Strategic Approach

NHS Genomics Strategy



Key themes include:

1. **Embedding genomics across the NHS**, through a world leading innovative service model from primary and community care through to specialist and tertiary care
2. **Delivering equitable genomic testing for improved outcomes in cancer, rare, inherited and common diseases** and enabling precision medicine and reducing adverse drug reactions
3. **Enabling genomics to be at the forefront of the data and digital revolution**, ensuring genomic data can be interpreted and informed by other diagnostic and clinical data; and
4. **Evolving the service driven by cutting-edge science, research and innovation** to ensure that patients can benefit from rapid implementation of advances

UK Life Sciences Vision sets 10-year strategy for sector to solve some of the biggest healthcare problems of our generation

.

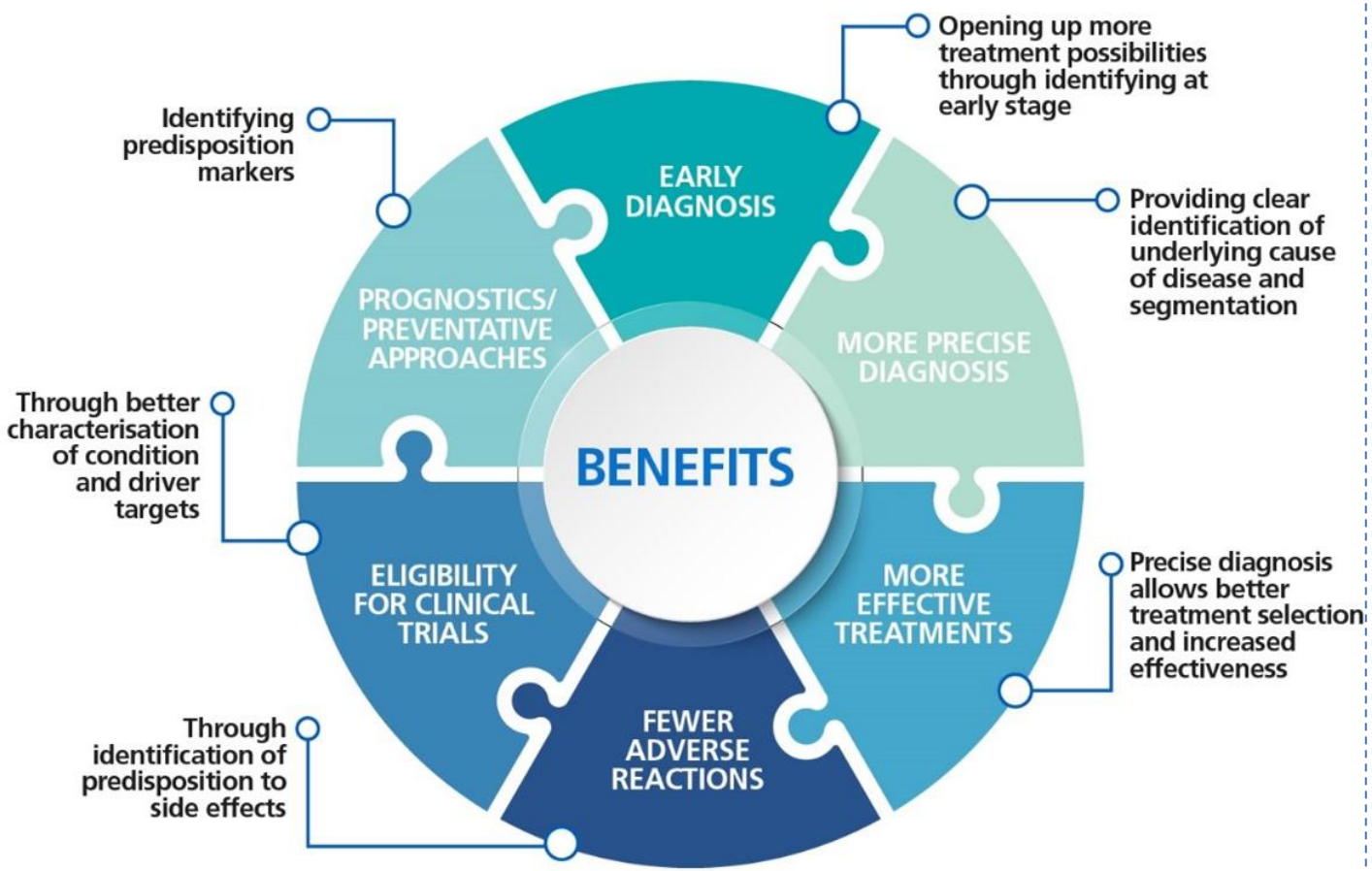
Genome UK; the future of healthcare sets out a 10 year vision how we will achieve progress in genomic medicine across Diagnosis & Personalised medicine, Prevention and Research

NHS Long Term Plan genomics commitments

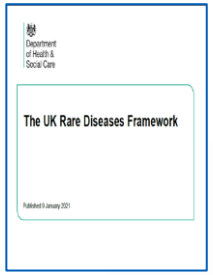
Genomics driving a new paradigm in care

NHS England

Benefits of genomic medicine



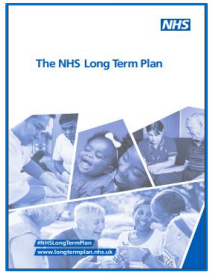
- **Supports delivery of disease specific strategies**:



UK Rare Disease Framework has four key priorities:

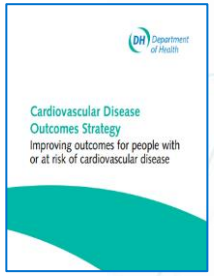
- Helping patients get a **final diagnosis faster**
- **Increasing awareness** among healthcare professionals
- **Better coordination** of care
- Improving access to **specialist care, treatments and drugs**

An action plan will be published to support implementation



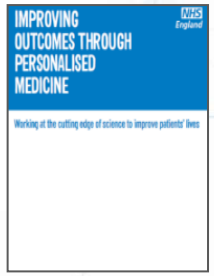
NHS LTP ambitions for cancer:

- by 2028, **55,000 more people each year will survive** their cancer for five years or more; and
- by 2028, **75% of people with cancer will be diagnosed at an early stage** (stage one or two)



DHSC Cardiovascular Outcomes Strategy:

- Focus on **prevention** through risk minimisation and genomics
- Support **early detection**
- **Reduce premature deaths** from cardiovascular disease
- Ensure **equity of access** to services

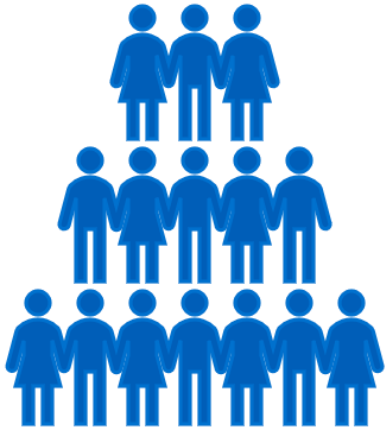


Improving Outcomes through Personalised Medicine

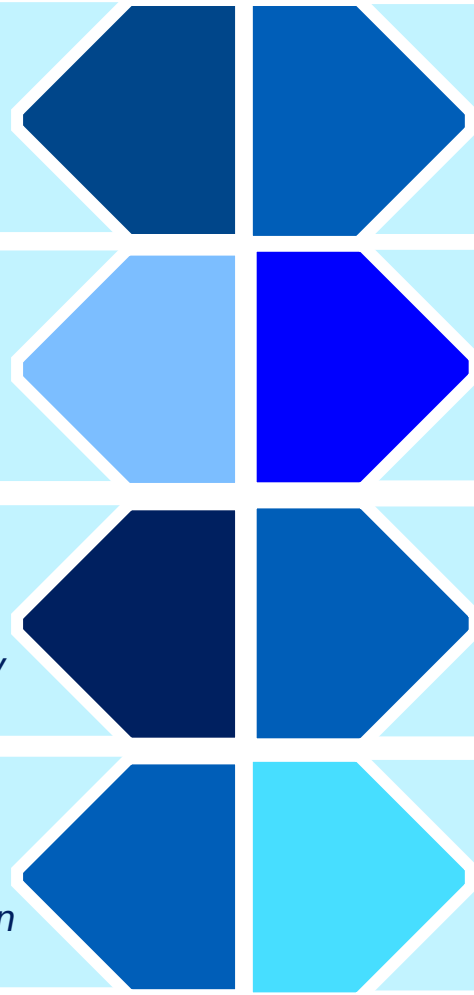
10-year framework for delivery of personalised medicine across the NHS, including:

- improved p**rediction and prevention** based on predisposition
- more **precise (and prompt) diagnosis** based on cause
- **targeted interventions** through the use of companion diagnostics to personalise effective treatments

NHS Genomic Medicine Service - implementation at scale



NHS Genomic Medicine Service key principles



Be clinically and scientifically led.
Funded positions within the infrastructure including multi-professional and research and innovation leaders

Standardised model of delivery and commissioning across the country.
Standardised operating protocols, contracting, and financial models and management data

Have patients and the public involved at all levels.
At a regional and national level through the NHS GMS People and Communities Forum

Routine care aligned with research and development for patient benefit.
Patient choice model enabling WGS data to be available for research and development

Ensure equity of access for all patients.
A single mandated testing offer in the NHS outlined in the National Genomic Test Directory

Responsive to innovation and new technologies.
Introduction of innovative genomic sequencing techniques such as ctDNA and RNA sequencing

Enable rapid access to precision and targeted treatments.
Aligned with commercial medicine framework and NICE approvals and Medicines Optimisation programme.

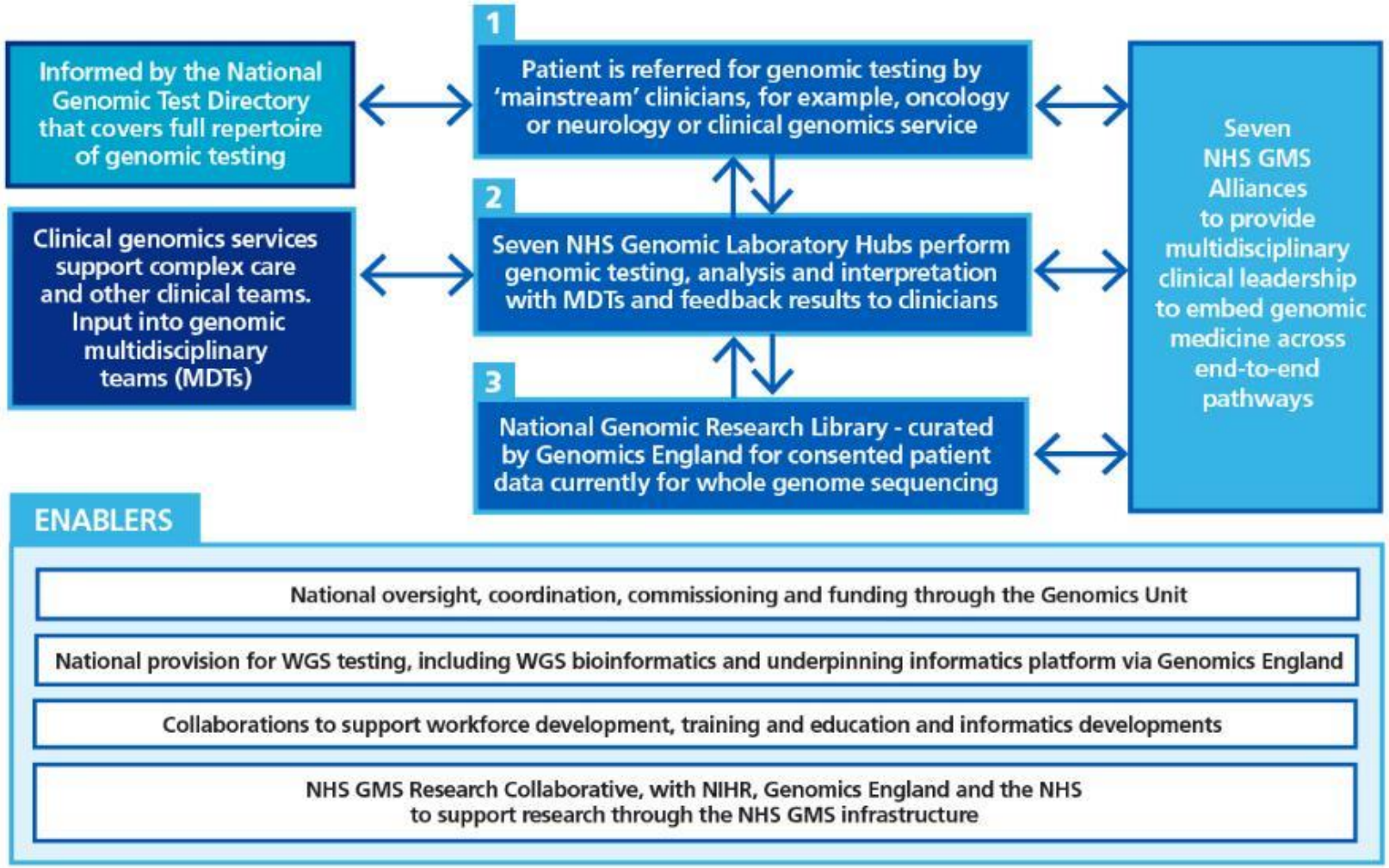
Inform and drive change using data led insights.
Operational data to drive service improvements and data to enable diagnostic discovery

185

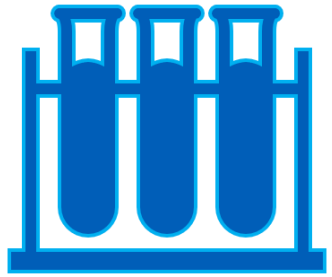
NHS Genomic Medicine Service infrastructure

Informed by previous NHS service and 100,000 Genomes Project

Our vision is that the power of genomics in predicting, preventing and diagnosing disease, and targeting treatment is accessible to all as part of routine care in the NHS.



Genomic Testing and Outcomes



Delivering the full range of genomic testing

National Genomic Test Directory covers full repertoire of testing technologies covering ~3200 rare diseases and all solid cancer and haematological malignancies.
To keep pace with **scientific and technical developments** it is updated annually (including gene targets) through the Test Evaluation Working Groups *(updated Test Directory on 31st October 2022 with over 150 new applications)*

Population based → Predictive → Disease focussed → Informing treatment decisions → Horizon scanning

Multimodal approach

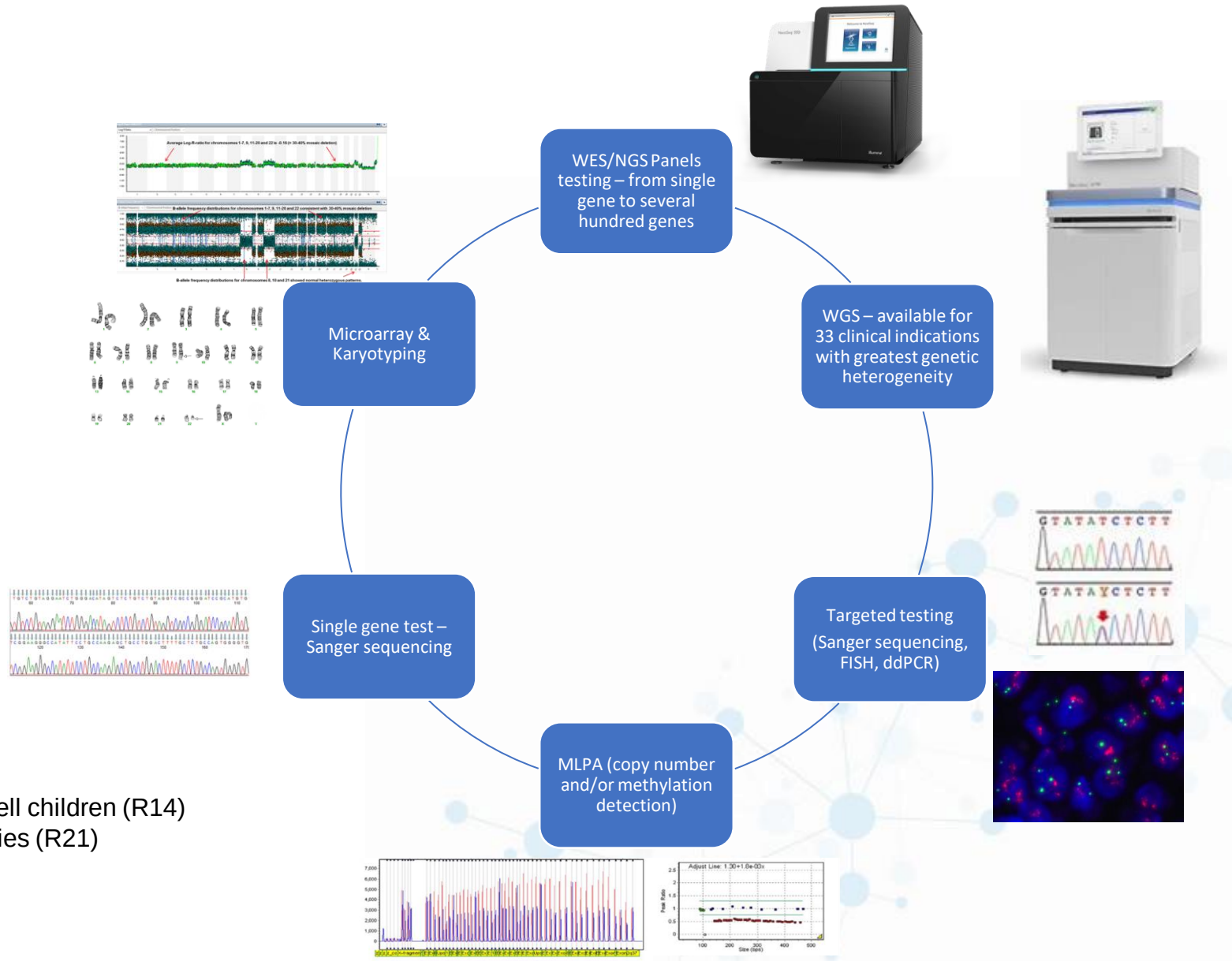
Targeted Testing	Panels (10s-100s of genes)	Exome Sequencing	Whole Genome Sequencing
For known causes of genetic disease eg Huntington's Disease.	Small and extensive next generation sequencing	• Standardising rapid NICU/PICU testing • Fetal Exome testing • Interim testing while WGS established.	Look across the genome for diagnostic, therapeutic and predictive information.
Currently 90% of NHS testing			Currently 10% of NHS testing

For example :
- Building the evidence for functional genomics
- Clinical trial targets

Rare and inherited disease testing

Specialist areas

Audiology
Cardiology
Dermatology
Endocrinology
Gastrohepatology
Haematology
Immunology
Inherited cancer
Metabolic
Mitochondrial
Musculoskeletal
Neurology
NIPD
Ophthalmology
Renal
Respiratory



Types of Tests

Diagnostic
Pre-symptomatic
Predictive
Prenatal
Carrier
NIPD

Rapid Services

Rapid WGS for acutely unwell children (R14)
Rapid WES for fetal anomalies (R21)

Pharmacogenomics

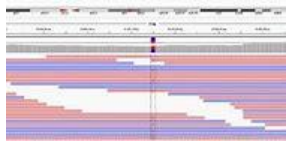
Pharmacogenomic tests, such as laboratory test for *MT-RNR1* variant m.1555A>G, for individuals with long-term conditions where they are likely to receive aminoglycoside antibiotics (such as in cystic fibrosis) so decisions can be made about future treatment based on likelihood of developing ototoxicity)

Providing more extensive cancer genomics testing - a multimodal approach

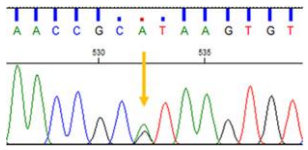
NHS England

Germline testing

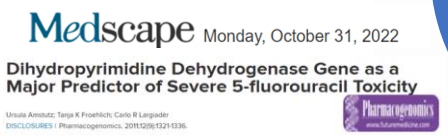
Germline testing for BRCA & Lynch syndrome



Cascade testing enabling early cancer detection/ monitoring



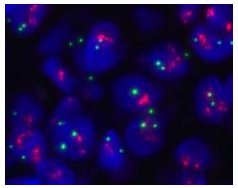
Pharmacogenomics germline testing e.g. *DYPD*



Focussed rapid testing

Rapid genomic diagnostic testing

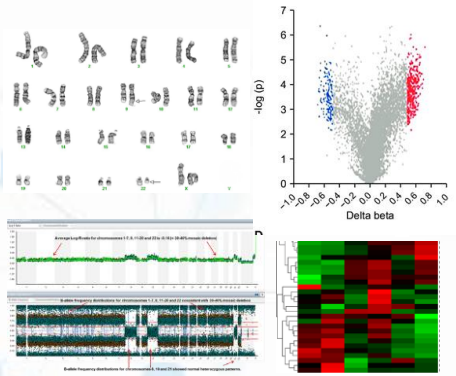
FISH/single gene tests



Treatment determining – Large NGS panels

*Karyotyping *NGS
*SNP array *RNA seq
*MRD *Methylation
*Long read sequencing

Multimodal – cytogenomics, molecular, expression assays



Whole Genome Sequencing

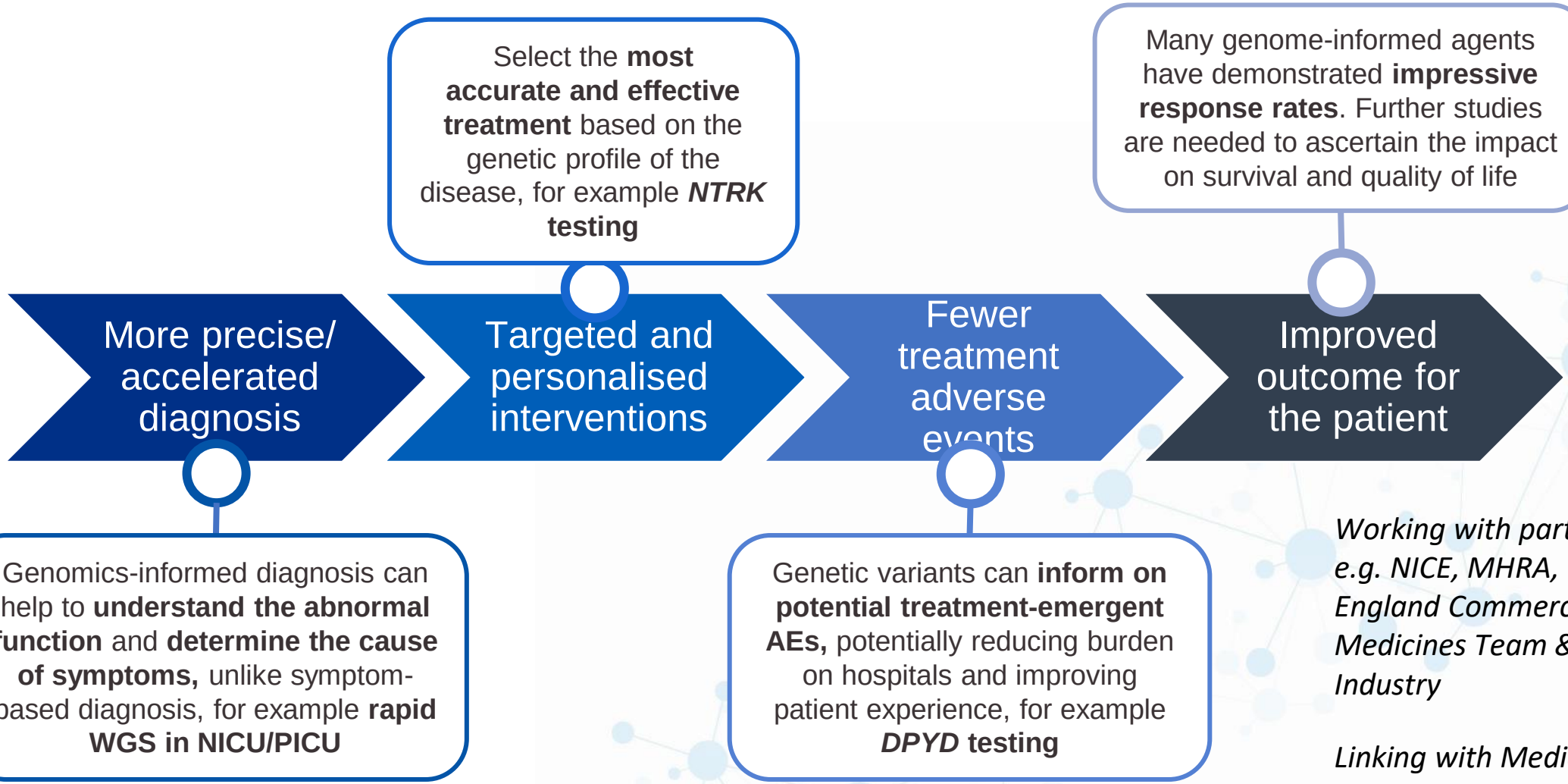
157 clinical indications

46 paediatric cancers,
31 neurological cancers

49 sarcomas, 48 haemonc malignancies, 3 solid tumours

Precision Medicine Pathways

NHS England



Working with partners e.g. NICE, MHRA, NHS England Commercial Medicines Team & Industry

Linking with Medicines governance and optimisation programme

WGS transforming patient care

Baby Oliver
(here with Professor Dame Sue Hill)

Oliver was born with a 6cm lump on his leg and initial investigations suggested infantile fibrosarcoma. He was referred for WGS and it was found that the mass was in fact a myofibroma, a benign tumour so no treatment was needed.

"This miracle test was everything, it changed everything for us." Oliver's Dad, Michael

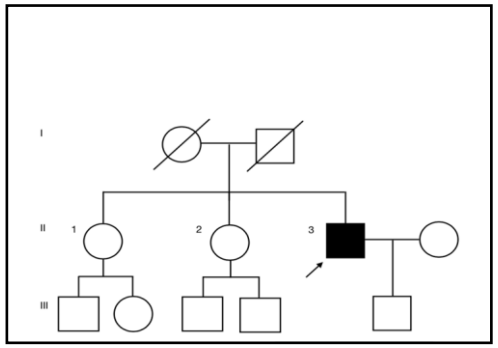
Paediatric cancer patient

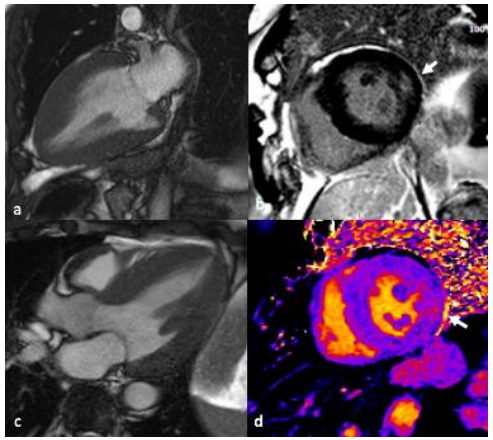
A particularly heartening example was that of my patient X whose mother (a single mother of six children, with very little income) asked about WGS as she had wanted to fundraise to pay for this privately

"It was wonderful to be able to offer X, as one of our first patients of the live programme, WGS "on the NHS"

Patient had a difficult to classify sarcoma. FISH had suggested the presence of a diagnostic fusion, which the RNAseq panel could not confirm. WGS then resolved the case by showing that the fusion was caused by a genomic configuration that is not detectable by RNAseq

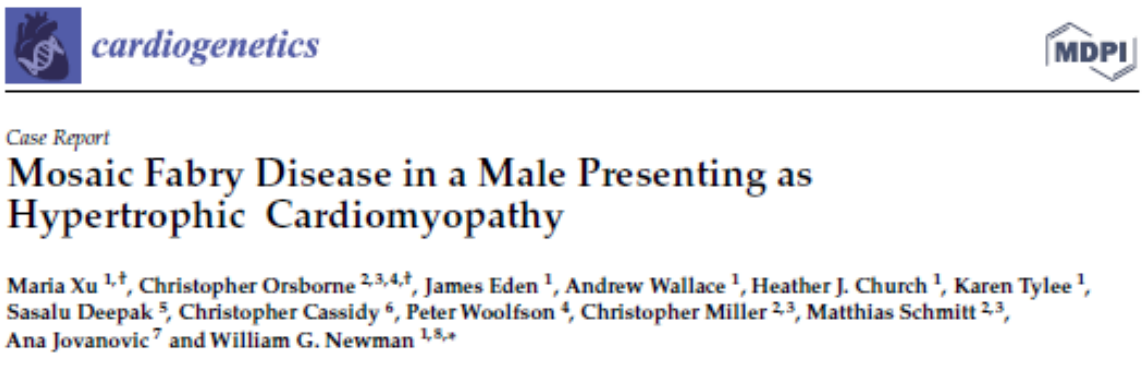
55 year old male with hypertrophic cardiomyopathy





- Patient presented with palpitations and chest pain, mild hypertension. Normal alpha-galactosidase enzyme levels excluded Fabry disease
- Heterozygous variant in *GLA gene c.901C>T p.(Arg301Ter) – known pathogenic variant – consistent with diagnosis of Fabry disease. Male is mosaic for the variant*
- Treatment & Lessons
  - Excellent response to enzyme replacement treatment - heart wall thickness has reduced
  - Patient is now asymptomatic
  - Son and sisters at no risk so no need for cardiac screening
  - Advanced genetic testing can diagnose Fabry disease even if normal alpha galactosidase

Diagnosis only possible through the NGS panel approach which is far more sensitive than traditional sequencing methods



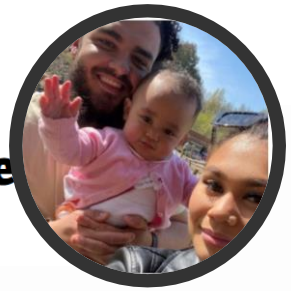
With thanks to North West NHS Genomic Laboratory Hub

Making a difference for patients

NHS England

Thousands of cancer patients are benefitting from the introduction of **DPYD testing** which can prevent adverse drug reactions and **NTRK gene fusion testing** to support new histology independent cancer treatments

The simple genetic test for newborns that can prevent profound deafness and save the NHS millions every year



sky news

'World-first' NHS England rapid genetic tests 'could save thousands of children'

The **GRAIL partnership** is looking at early detection of cancer and is being piloted in 165,000 patients

BBC NEWS

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

NHS to pilot blood test that coul detect over 50 different cancer types

CANCER RESEARCH UK

Rollout of **Non-Invasive Pre-natal Diagnosis** for Retinoblastoma, one of more than 15 new tests and amendments to the National Genomic Test Directory.

BBC NEWS

Gene test spares bay unnecessary chemotherapy

Oliver was born with a 6cm lump on his leg and initial investigations suggested infantile fibrosarcoma. He was referred for WGS and it was found that the mass was in fact a myofibroma, a benign tumour so no treatment was needed.

BBC NEWS

Genetic tests to detect rare cancer in unborn babies rolled out

Mainstreaming and embedding genomics

Education and training: supporting clinicians

NHS England

Pharmacy programme

Creating national networks to support and develop the role of pharmacists in genomics and driving personalised medicine through the sharing of good practice and strategic workforce development.

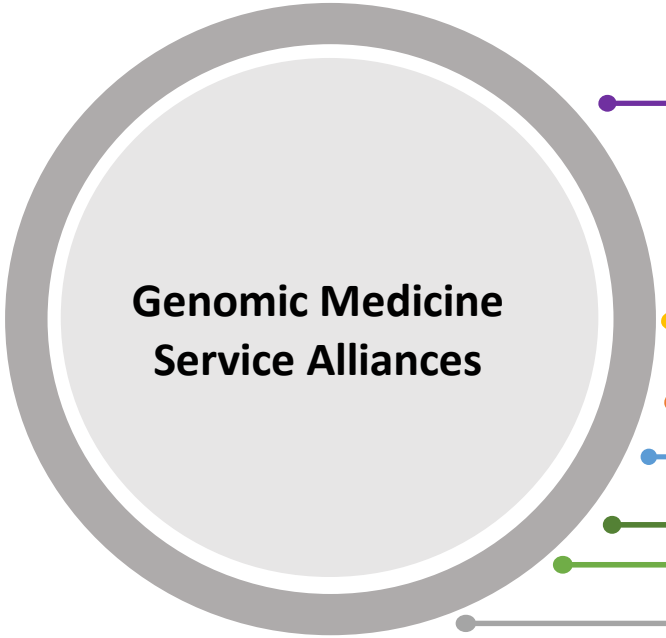
Nurse & Midwifery led Genomics Collaborative

Working with Chief Nurses across England to systematically and sustainably embed genomics into nursing and midwifery roles and responsibilities

Medical Programme

Working with the Academy of Medical Royal Colleges to support the systematic roll out of genomic medicine within clinical pathways and to ensure clinicians have access to the right education and information at the right point

Driving transformation



Understanding and monitoring equity of access

Delivering national and local transformation projects:

- Lynch syndrome
- Monogenic diabetes
- Sudden cardiac death
- DPYD
- Nursing and midwifery
- RNASeq
- Pharmacogenomics
- ctDNA

Supporting defined research projects with Genomics England

Supporting the multi-professional workforce to use genomics safely, effectively and efficiently, including supporting nurse leaders to systematically integrate genomics.

Maximising opportunities to facilitate and participate in research and innovation

Integrating genomic testing in pathways, including creating and improving cancer and pathology pathways

Advancing opportunities to deliver precision medicine and monitoring uptake

Expanding the use of ctDNA in the NHS: NHS GMS Alliances working with industry to provide evidence for the expansion of ctDNA testing to support early diagnosis of cancer and diagnosis of cancer for patients who currently cannot have a tumour biopsy or do not yet have a confirmed diagnosis.

Pharmacogenomics: A regional pilot to explore some of the elements that would need to be consider to introduce pharmacogenomics in the NHS.

RNASeq: Explore implementation of RNA-based and long-read DNA sequencing diagnostic services in the NHS.

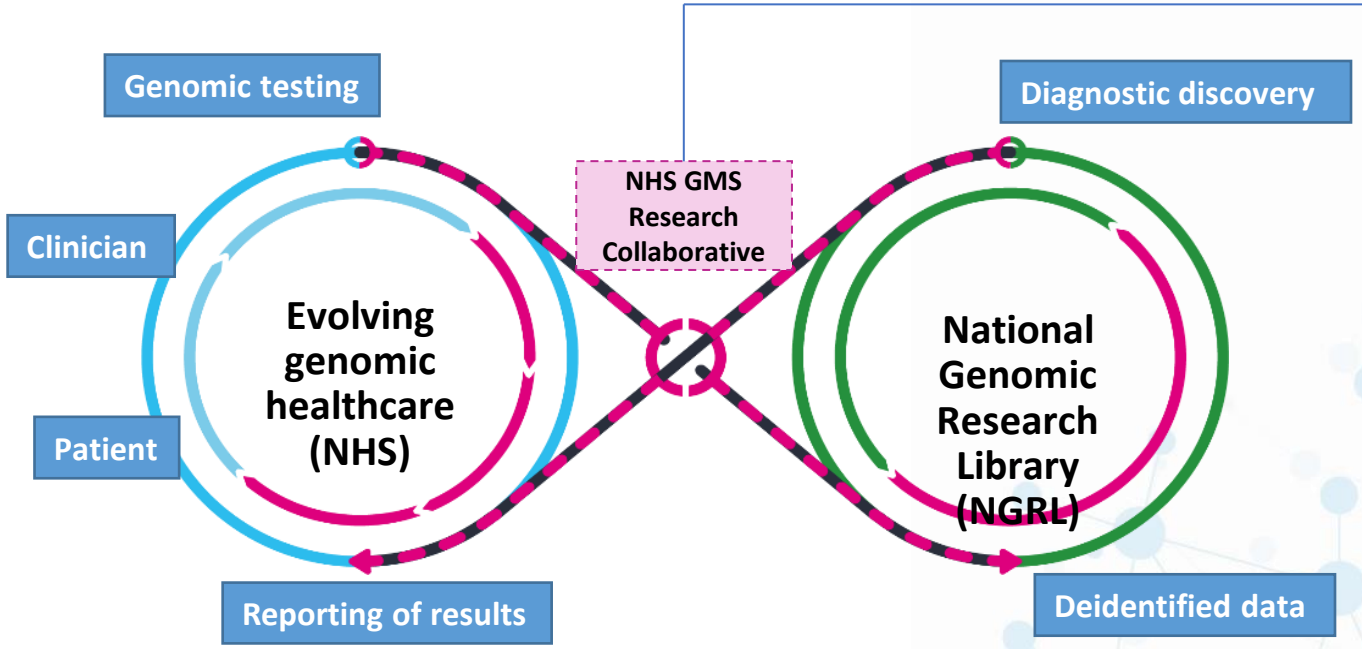
Translation, Research and Development

Aligning NHS GMS with research and innovation

NHS England

The single biggest driver of genomic medicine success is the ability to build and create partnerships – within and across organisations and across the globe

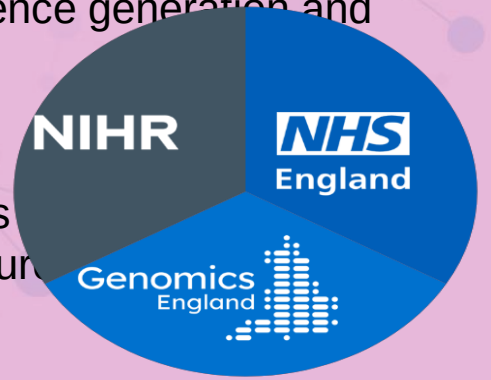
Discovery	Translation	Adoption	Diffusion
• Discovery of new drugs and genomic variants • Exchanging information, sharing resources and best practice	• Establishing evidence synthesis against agreed policy domains • Proof of concept studies • Real world evidence studies • Example liquid biopsy / long read sequencing	• Reviewing the evidence for commissioning and contracting • Trailblazers / early adopters • Agreeing common outcome metrics incorporating the design of policy levers	• Commissioning and finance alignment • Standardisation of services • Equity of access



Systematic approach to evidence generation and adoption.

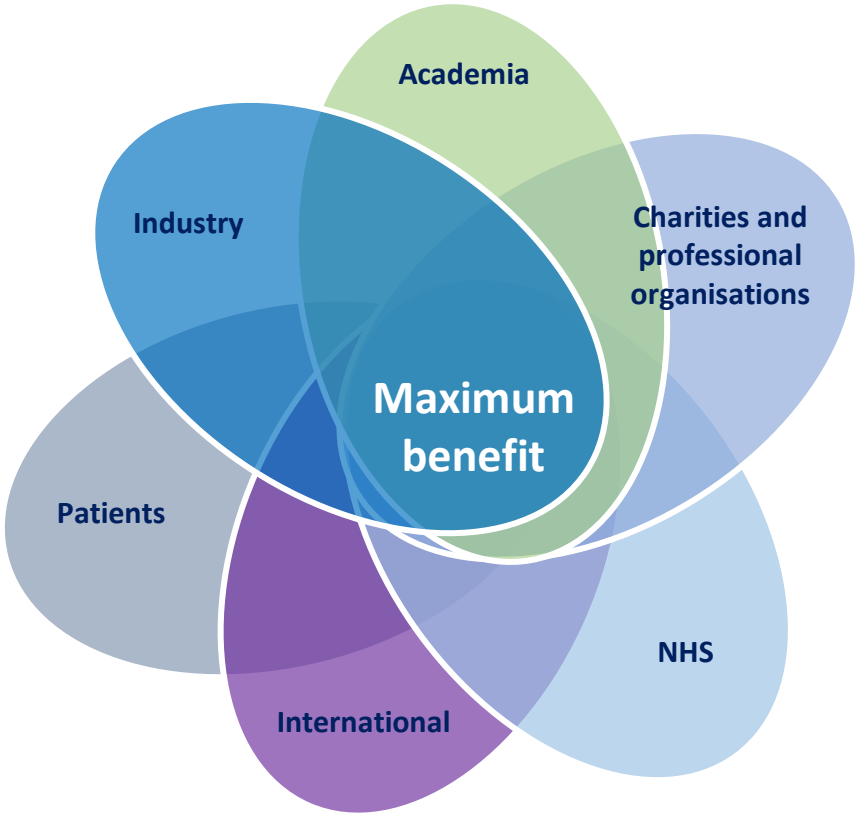
Focus on:

- Academic research projects
- Data and tooling infrastructur
- Exploratory clinical studies
- Clinical trials support
- Industry / biotech research and development
- Review and validation of emerging technology
- Diagnostic discovery



What does the future hold?

Building successful partnerships



The single biggest driver of genomic medicine success has been the ability to build and create partnerships – within & across organisations and across the globe and initiatives such as the Global Alliance for Genomics and Health and the Global Genomic Medicine Collaborative

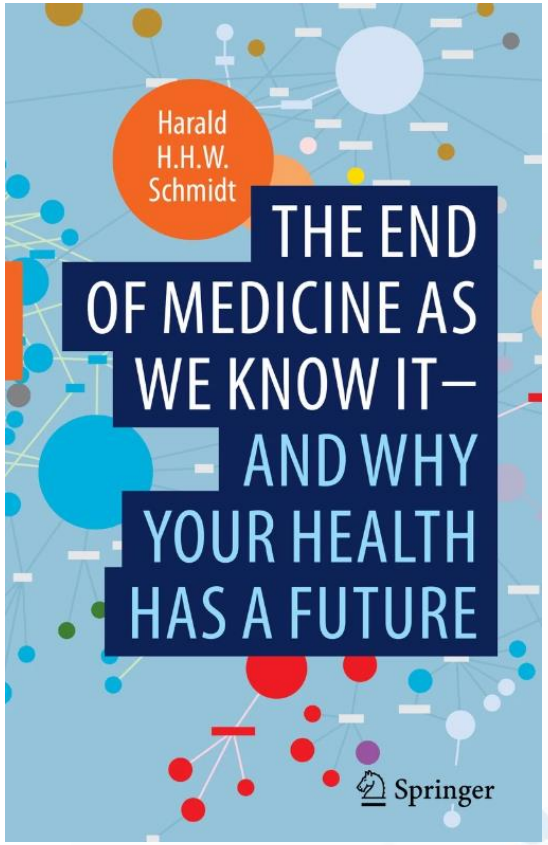
Particular areas for genomic partnerships include:

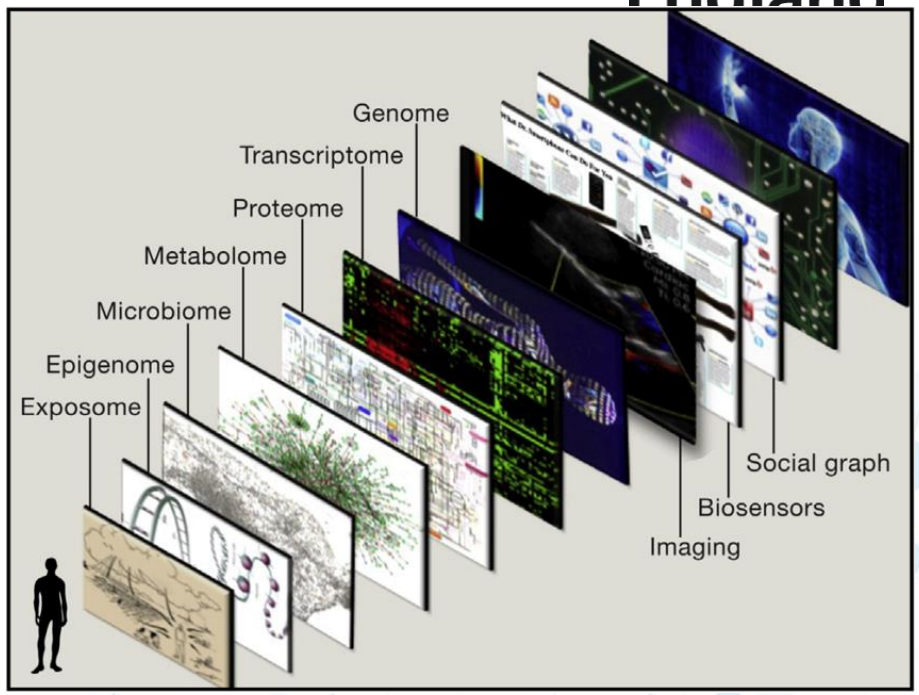
- Exchanging information, sharing data and best practice
- Establishing evidence synthesis against agreed policy domains
- Agreeing common standards and outcome metrics
- Enhancing interpretation of complex information and establishing global resources
- Communication and engagement

We are at a tipping point

- **DNA technologies alone or in combination is not enough** – what matters is how this is translated into practice – mRNA, proteins, metabolites – the **functional genomic pathway**

- Bringing together the multiple maps of the various stages of the functional genomic pathway in an individual, together with related environmental and social information, will provide a panoromic 'Google Earth' type map of an individual – offering an even richer opportunity to shape care





"With personal technology, doctors can see a full, continuously updated picture of each patient and treat each individually" *Topol. 2014. Cell*

"We are in the midst of a reactive sickcare crisis which needs to adopt a predictive, preventative and proactive systems approach. The basic fundamentals of course underpin precision medicine"

Professor Harald Schmidt, Head of the Department of Pharmacology and Personalised Medicine, Faculty for Health, Medicine and Life Sciences at the University of Maastricht

Thank you and keep in touch

Professor Sandi Deans
Deputy Director – Laboratory & Scientific, Genomics Unit, NHS England

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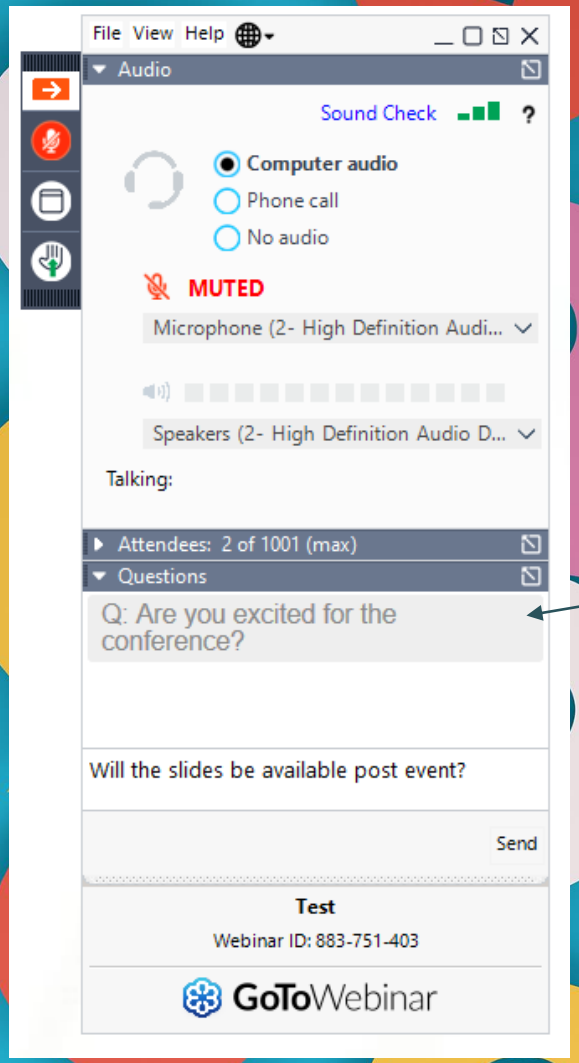

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THANKS FOR ATTENDING

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