



From Diagnostic Odyssey to Equitable Answers:

Building Aotearoa's Rare Disorder Genomics Future

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Rare Disorders Research Forum
6 Aug 2026





Rare Diseases are not rare

Rare diseases affect more than 300–400 million worldwide, 5% of the global population

At the level of the individual disease affect fewer than
1 in 2,000
individuals¹

There are over
8,000
rare diseases identified^{2,3}

Severe
multisystem disorders
with
a range of phenotypes

80%
of rare diseases have
a genetic origin²

70%
of rare disease start in
childhood⁴

Rare epigenetic
changes in
23%
of patients with
developmental
delays

¹EURORDIS, depends on population

²Haendel et al. Nat Rev Drug Discov <https://doi.org/10.1038/d41573-019-00180-y> (2020)

³Schuy et al. Trends in Genetics <https://doi.org/10.1016/j.tig.2022.06.003> (2022)

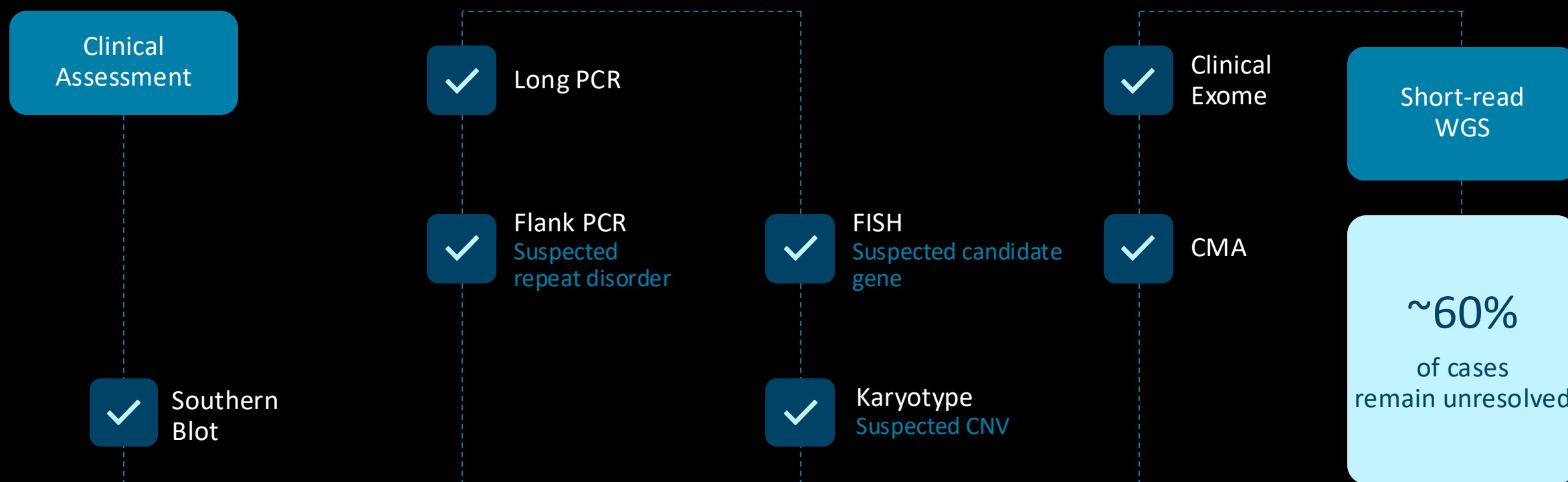
⁴Nguengang Wakap et al. Eur J Hum Genet <https://doi.org/10.1038/s41431-019-050870> (2020)

⁵Editorial Lancet Neurol. 21, 203 (2022)



Clinical pathways are still long and cumbersome

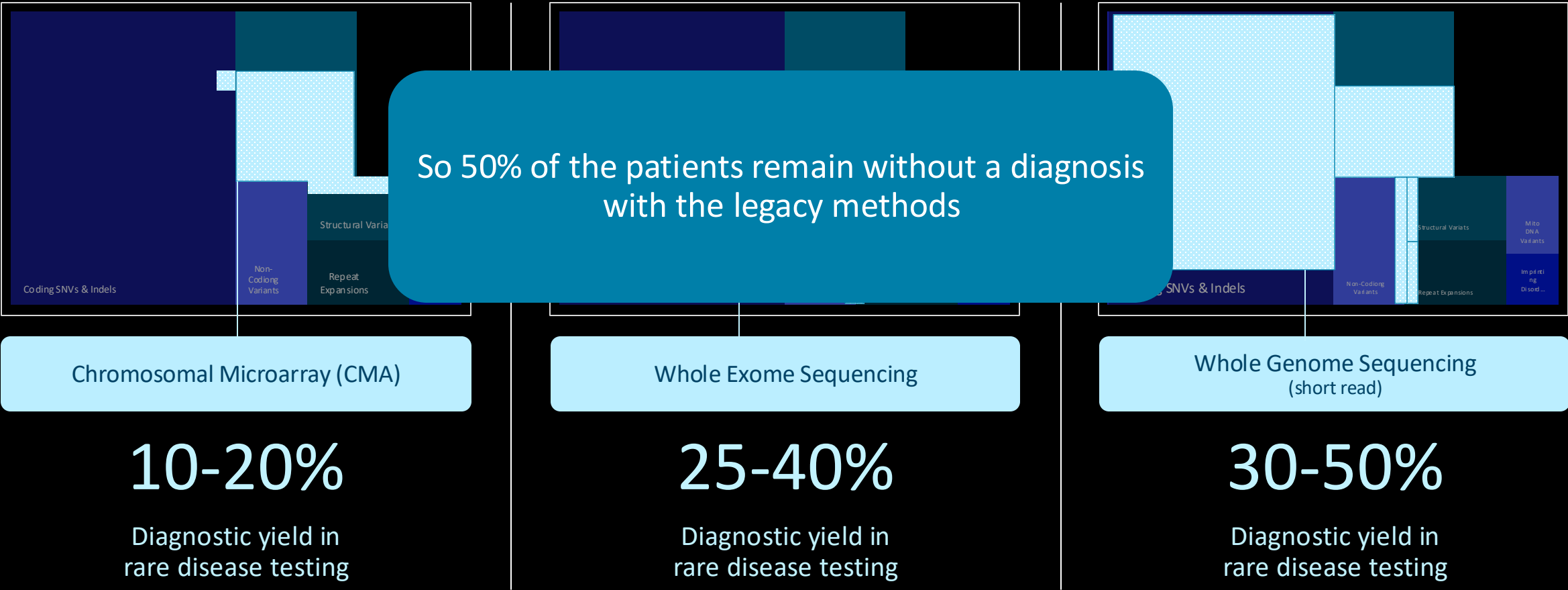
With too many families going through time-consuming, complex diagnostic journeys





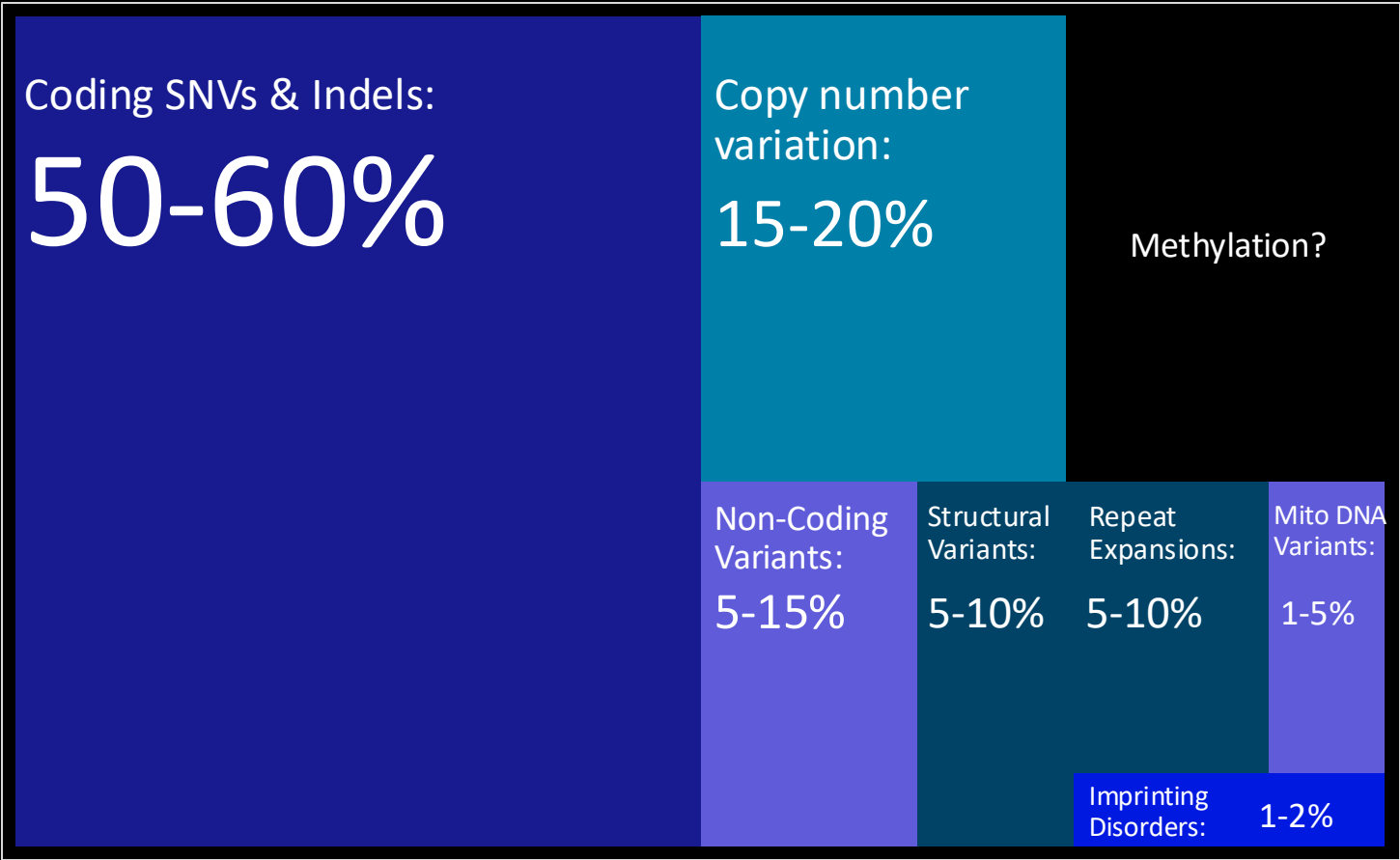
Genetic testing is multi-faceted

Why we use multiple technologies today





Genetic testing is multi-faceted



Contribution of each variant class to diagnostic yield in rare diseases*

* Diagnostic yield is highly dependent on tested population, so this is a generalization



A new generation of single molecule sensing

Features address unmet needs: global reach for substantial global opportunity

Multomics analysis platform:

- Genomics
- Epigenetics
- Transcriptomics,
- Epitranscriptomics

Proteomics in development,
other molecular sensing possible

Validated technology:

>20,000

Customer
Publications

Sustainable growth company:

~28%

5YR revenue CAGR



Established global footprint

>125 countries served

Strong, growing team

>1,300 Employees
(>400 commercial)

Established, scaled manufacturing

ready to meet demand
for next 5 years

All numbers are at 31 December 2025 unless stated otherwise. 2025 numbers are unaudited, preliminary numbers and subject to change.

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Genomics 3.0 — the future is here

Three eras. Two Paradigm shifts. One real-time future

| Genomics 2.0 is the past | Genomics 3.0 is the future | The future is now

Genomics 1.0

Proved sequencing was possible



Sanger sequencing:
Developed in
Cambridge, UK

1977

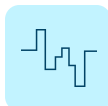
- Proved sequencing was possible
- Low throughput
- Read length ~800-1,000bp
- The foundation of genomics

Paradigm shift 01

From possible to scalable

Genomics 2.0

Scaled sequencing but remained incomplete



Short read sequencing (NGS v1):
Solex technology developed in
Cambridge, UK. Scaled globally following
Illumina acquisition (2007)

2006

★ Enabled large-scale discovery and cost reduction:
Built the data, the tools and the ecosystem

- ⊗ Cuts genome into short pieces
- ⊗ No methylation. No multiomics
- ⊗ Requires batching and wet lab enrichment
- ⊗ Incomplete view of the genome (complex and medically challenging regions missed)
- ⊗ Slower time to answers (weeks)

Paradigm shift 02

From batch to real-time



Oxford Nanopore sequencing:
Developed in Oxford, UK

2026

★ Shifts genomics from batch discovery to real-time clinical decision making :
Enables real-time, data-rich inputs for AI-driven clinical decision making

- ✓ Oxford Nanopore sequencing – any read, any part of the genome
- ✓ Reads entire genome including repetitive and complex and medically challenging regions
- ✓ Native methylation detection (epigenetic signals)
- ✓ True multiomic from the same sample
- ✓ Real-time sequencing and analysis – no batching
- ✓ Adaptive sampling (digital panels) read what matters
- ✓ Eliminates wet lab enrichment – faster, simpler, scalable
- ✓ Higher diagnostic yield and faster time to answer (hours)
- ✓ Lower total cost of ownership

And beyond

All major breakthrough originated in the UK:

Sanger (Cambridge) | Solexa (Cambridge) | Oxford nanopore (Oxford)

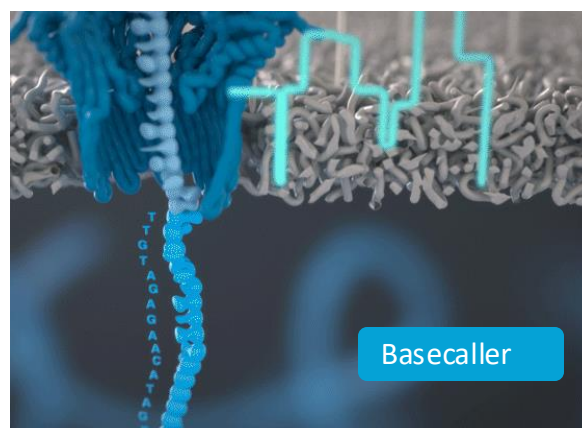
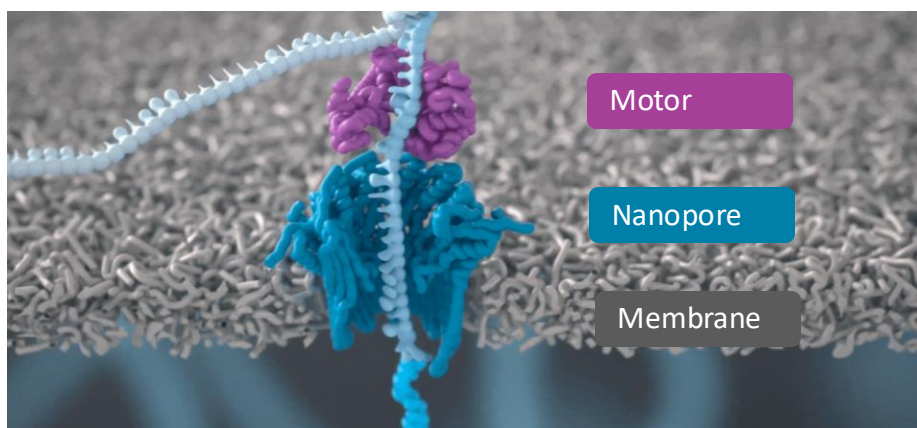


Oxford Nanopore has innovated a sensing platform

From DNA/RNA analysis today, towards proteins in the future

1. Nanopore sensing

Run Conditions (Salt, fuel, software)



2. Flow cells (MinION, PromethION)

Each flow cell contains an array of nanopores



MinION

512 channels



PromethION

2,675 channels

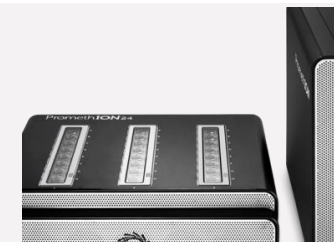
3. Devices



Distributed
sequencers



Benchtop
sequencers



High throughput
sequencers



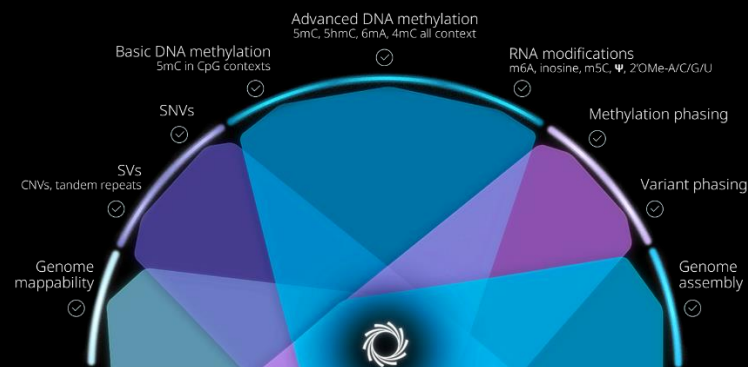
Unlocking unique value through Oxford Nanopore sequencing



Richer data

Multidimensional insights

Multiomic capability



Flexible & fast

Real-time sequencing

Digital panel capability

No batching requirements



Accessible & affordable

Scalable portfolio

Favourable footprint

Portable



Supporting faster diagnosis and better patient outcomes



Richer insights: from “black and white to colour”

01

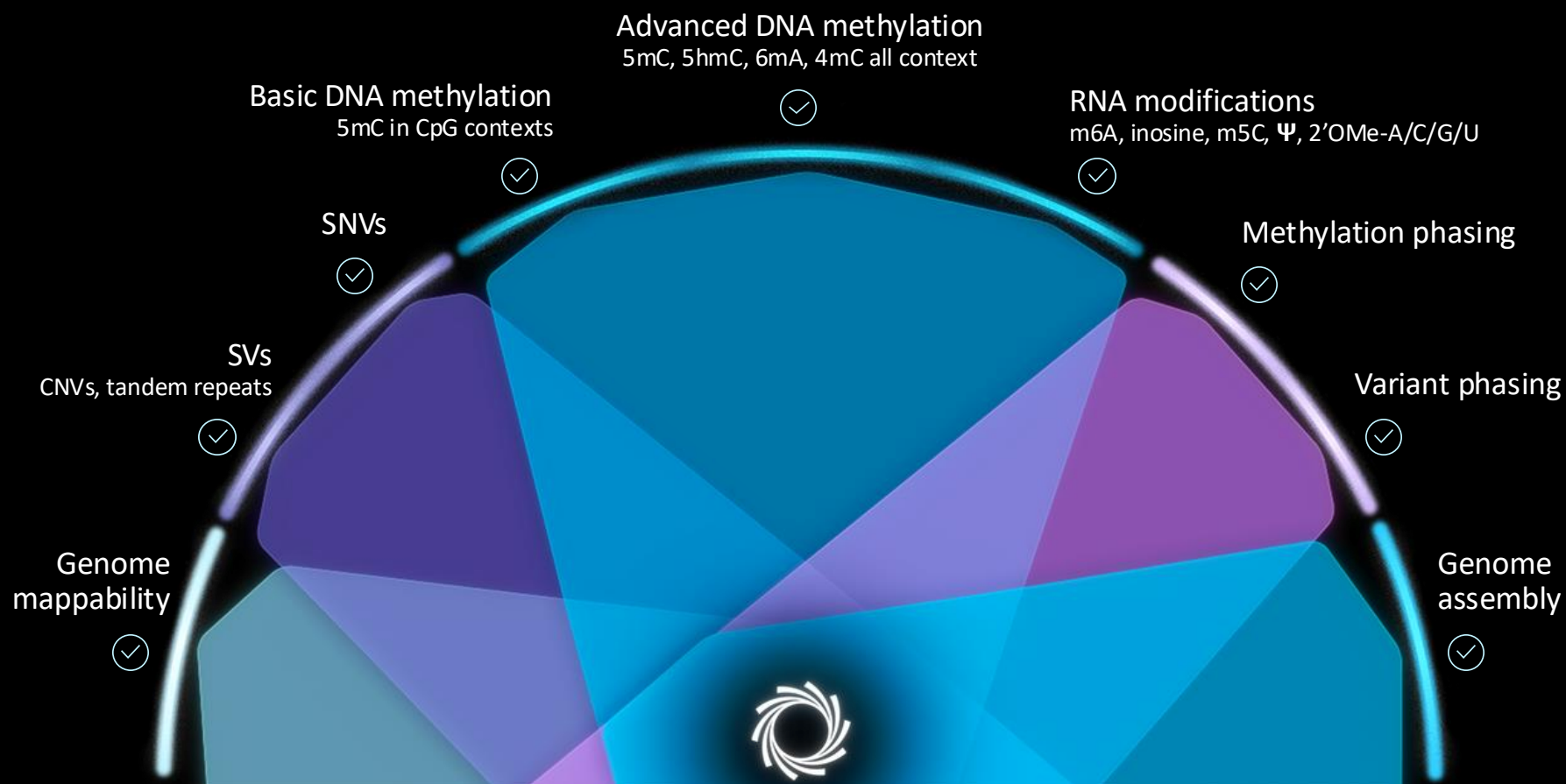
The gold standard
in methylation

02

Short to ultra long
reads

03

Novel direct
RNA capability





Broad range of test application menu

	01 Amplicon: PCR primer- based amplification of targets of interest	02 Hybridization: Probe-based pull-down of targets interest	03 Adaptive sampling: Software based and on-sequence target enrichment	04 Whole genome sequencing
 Number of target genes	<75 genes	<500 genes	Single gene – 10% of genome	Genome wide
 Read lengths	250-3kb	< 8kb	5-20kb	15- 30 Kb
 Sample prep time	2.5-8 hours	2-3 days	<4 hours	1.5 hours
 Variant types	SNVs, SVs	SNVs, SVs	SNVs, SVs, CNY, Methylation	SNVs, SVs CNV, methylation
			Any gene can be targeted 100% flexibility	



Are current assays limiting your ability to provide diagnosis?

~34%

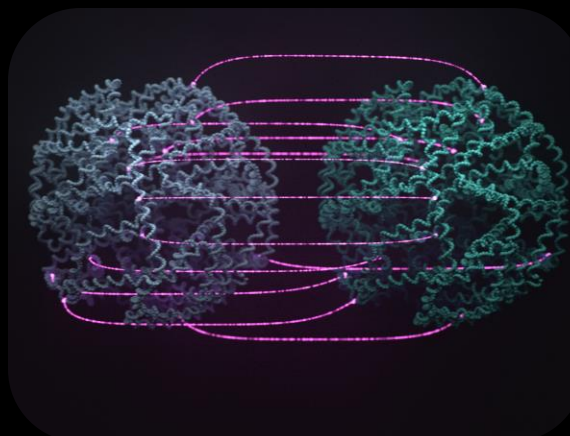
of all disease-causing genetic variants are larger than a single base-pair substitution¹



Can you obtain comprehensive variant detection, including SNVs, SVs, CNVs to uncover novel drug targets?

~15–25%

of hereditary diseases and cancers are linked to alternative splicing²



Can you see full-length isoforms to resolve complete splicing events linked to disease and transcript diversity?

~40%

of gene promoters are linked to CpG islands where methylation regulates expression³



Can you simultaneously capture genomic *and* methylation biomarkers in a single assay?



Richer data – true multiomics

One FC run includes WGS variants, methylation and expression

Announced at LC 2026

>30X

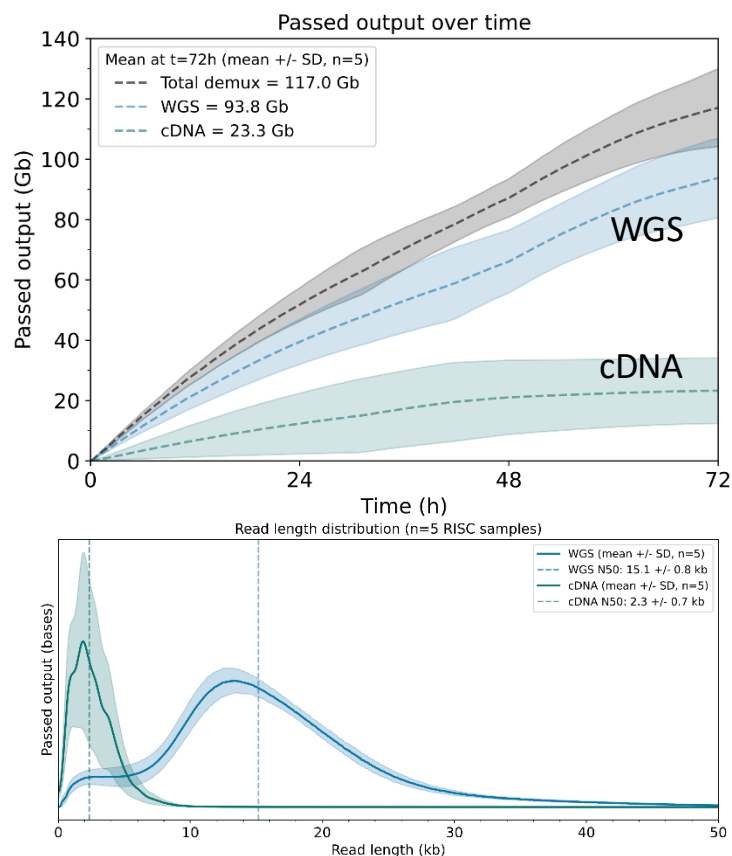
Genome

>28M

CpG sites

>10M

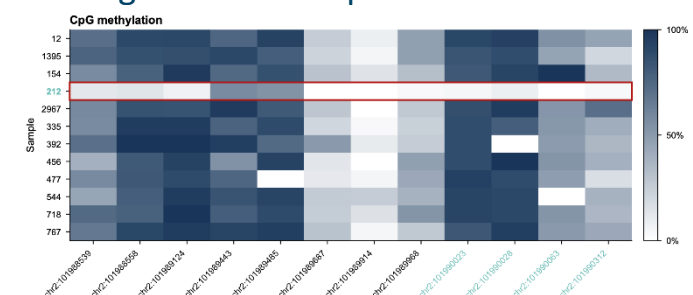
cDNA reads



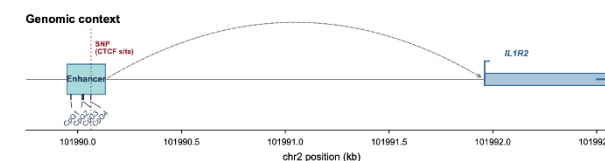
Enabling
true multiomics

Case study: genome/epigenome interaction regulate IL1R2 expression

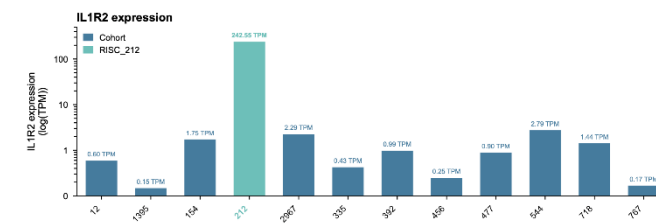
01



02



03





Evidence of additional diagnostic yield with long-read sequencing

Mini-Review

The additional diagnostic yield of long-read sequencing in undiagnosed rare diseases

Giulia F. Del Gobbo¹ and Kym M. Boycott^{1,2}

¹Children's Hospital of Eastern Ontario Research Institute, University of Ottawa, Ottawa, Ontario, Canada K1H 5B2; ²Department of Genetics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada K1H 8L1

Long-read sequencing (LRS) is a promising technology positioned to study the significant proportion of rare diseases (RDs) that remain undiagnosed as it addresses many of the limitations of short-read sequencing, detecting and clarifying additional disease-associated variants that may be missed by the current standard diagnostic workflow for RDs. Some key areas where additional diagnostic yields may be realized include: (1) detection and resolution of structural variants (SVs); (2) detection and characterization of tandem repeat expansions; (3) coverage of regions of high sequence similarity; (4) variant phasing; (5) the use of *de novo* genome assemblies for reference-based or graph genome variant detection; and (6) epigenetic and transcriptomic evaluations. Examples from over 50 studies support that the main areas of added diagnostic yield currently lie in SV detection and characterization, repeat expansion assessment, and phasing (with or without DNA methylation information). Several emerging studies applying LRS in cohorts of undiagnosed RDs also demonstrate that LRS can boost diagnostic yields following negative standard-of-care clinical testing and provide an added yield of 7%–17% following negative short-read genome sequencing. With this evidence of improved diagnostic yield, we discuss the incorporation of LRS into the diagnostic care pathway for undiagnosed RDs, including current challenges and considerations, with the ultimate goal of ending the diagnostic odyssey for countless individuals with RDs.

Rare diseases (RDs) encompass a diverse group of disorders that are individually rare in the population yet represent a significant burden to global health. RDs are conditions that affect fewer than 1 in 2500 individuals (Ferreira 2019), however, with several thousand recognized RDs, they collectively affect up to 1.5%–6.2% of the population globally (Ferreira 2019; Nguengang Wakap et al. 2020). About 70% of RDs are childhood-onset (Nguengang Wakap et al. 2020) and up to 45% are associated with a reduced life span, with about a quarter being potentially life-limiting by 5 years of age (Ferreira 2019). It is estimated that ~70% of RDs have an underlying genetic etiology (Nguengang Wakap et al. 2020). Currently, the Online Mendelian Inheritance in Man database reports over 6400 phenotypes for which a molecular basis is known and over 4500 genes with phenotype-causing variants (<https://www.omim.org/statistics/genemap>), with more disease-gene associations continually discovered. With such large numbers, rarity, and heterogeneity between and within RDs, molecular tools for diagnoses have been of utmost importance. Identifying the molecular cause of RDs provides affected individuals and their families with improved access to support services and potential treatments, information on prognosis and management of the disorder, options for further testing for family planning, and ends often long diagnostic odysseys. Despite the clear importance of reaching a diagnosis, more than half of RDs may remain undiagnosed following standard-of-care clinical genetic testing (Shashi et al. 2014).

Current genetic diagnostic workflows for RDs incorporate the patient's clinical presentation and the suspected mechanism of their rare genetic disease and may use various techniques to achieve a molecular diagnosis (Conlin et al. 2022; Kernohan and

Boycott 2024). Over the last decade, short-read sequencing (SRS) of fragments of DNA 50–300 bp has been increasingly used in clinical settings for RD diagnosis, providing sequencing of targeted regions, the protein-coding exome (SR-ES), or nearly the entire genome (SR-GS). SRS enables a high-throughput method to accurately assess sequence variants (single nucleotide variants [SNVs] or insertions/deletions <50 bp), with the added ability to detect certain copy number variants and some structural variants (SVs), genomic alterations >50 bp in size). Since its more widespread adoption, genome-wide SRS, primarily SR-ES, has emerged as an effective first-tier test for indications such as neurodevelopmental disorders (NDDs) or multiple congenital anomalies (Srivastava et al. 2019; Manickam et al. 2021), with a diagnostic yield of ~30%–35% depending on the indication and previous testing history (Clark et al. 2018; Splinter et al. 2018; Shickh et al. 2021; Chung et al. 2023; Hartley et al. 2024). While this has been a transformative technology, this still leaves nearly two-thirds of patients undiagnosed following SR-ES. Expanding beyond the protein-coding portion of the genome using SR-GS improves the assessment of noncoding sequence variants and detection of copy number variants and SVs; however, to date, the evidence for incremental diagnostic yield over SR-ES has been limited and may only be up to 10% (Evans et al. 2022).

Several factors may contribute to the high rate of undiagnosed RDs following genome-wide SRS, including interpretation challenges for variants of uncertain significance (VUSs), variants residing in novel disease genes, and complex genetic and/or environmental causes of disease. Additionally, inherent limitations to SRS technology may be a significant contributor. Given the nature of the short reads, SRS struggles in alignment of nonunique sequences such as regions of the genome that are highly repetitive

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15:1–13 Published by Cold Spring Harbor Laboratory Press, ISSN 1089-9031/25; www.genome.org

Genome Research 1
www.genome.org

50 studies

Improved ability to detect
SVs compared to SRS

Improved mapping in regions of high
sequence similarity (pseudogene resolution)

De novo assembly
(graph genome)

Accurate detection
of tandem repeat expansions

Long-range
phasing (compound het)

Simultaneous assessment
of methylation profile

“LRS can boost diagnostic yields following negative standard-of-care clinical testing and provide an added yield of 7%–17% following negative short-read genome sequencing.”



Redefining rare disease outcomes in the time required

Changing critical care setting



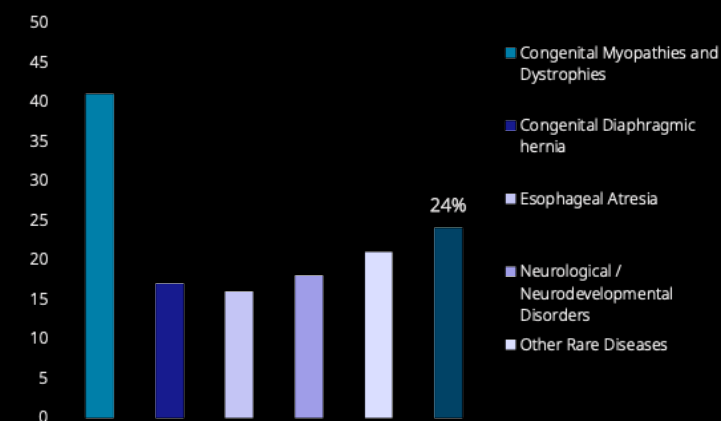
- Sample to answer in <8 hours¹
- With nanopore data they achieve 12% higher causative variant detection with Nanopore than with conventional methods

1st line test for standard care



- European Long-Read Innovation Network, 3-year EU initiative²
- >25 countries committed to implementing ONT for standard care for rare disease & germline cancer

Improved diagnostic outcomes



- Dr. Wendy Chung – Beacon Project, delivering +24% in diagnostic yield for unsolved rare disease cases³
- Cases previously unsolved by short-read sequencing

1. <https://www.nejm.org/doi/full/10.1056/NEJMc2112090>

2. <https://nanoporetech.com/news/pioneering-european-collaboration-to-advance-genetic-diagnostics-introducing-the-european-long-read-innovation-network-elrin->

3. Dr. Wendy Chung, ACMG 2025



Clinical-grade sequencing at scale across the Australasia

Clinical WGS & adaptive sampling

NATA Accreditation completed
Clinical WGS & Adaptive Sampling
>1,000's of samples per month

Victorian Clinical
Genetics Services



Clinical WGS & adaptive sampling

NATA Accreditation
Clinical WGS/Adaptive Sampling: Imprinting &
Neurological disorders & Hereditary Cancer



Health
Pathology

Low pass clinical WGS

Regular PGT-Aneuploidy screening using Low Pass
Clinical WGS to enhance IVF Success rates in
Middle-east region
~2000 samples sequenced thus far, total 50K
samples/yr



Clinical WGS & adaptive sampling

Rapid HLA Typing for Transplants with results in 4 to
4.5 hrs improving transplant outcomes
Sample volume: ~40% of the HLA Typing seq in
Australia
Infectious disease surveillance



Rapid tumor profiling

Can detect profile tumors within 24 hours
In brain cancer, fast diagnosis is critical for
treatment decisions
Standard approaches currently take up to six weeks
for some patient



LRS WGS for inherited cardiac disease

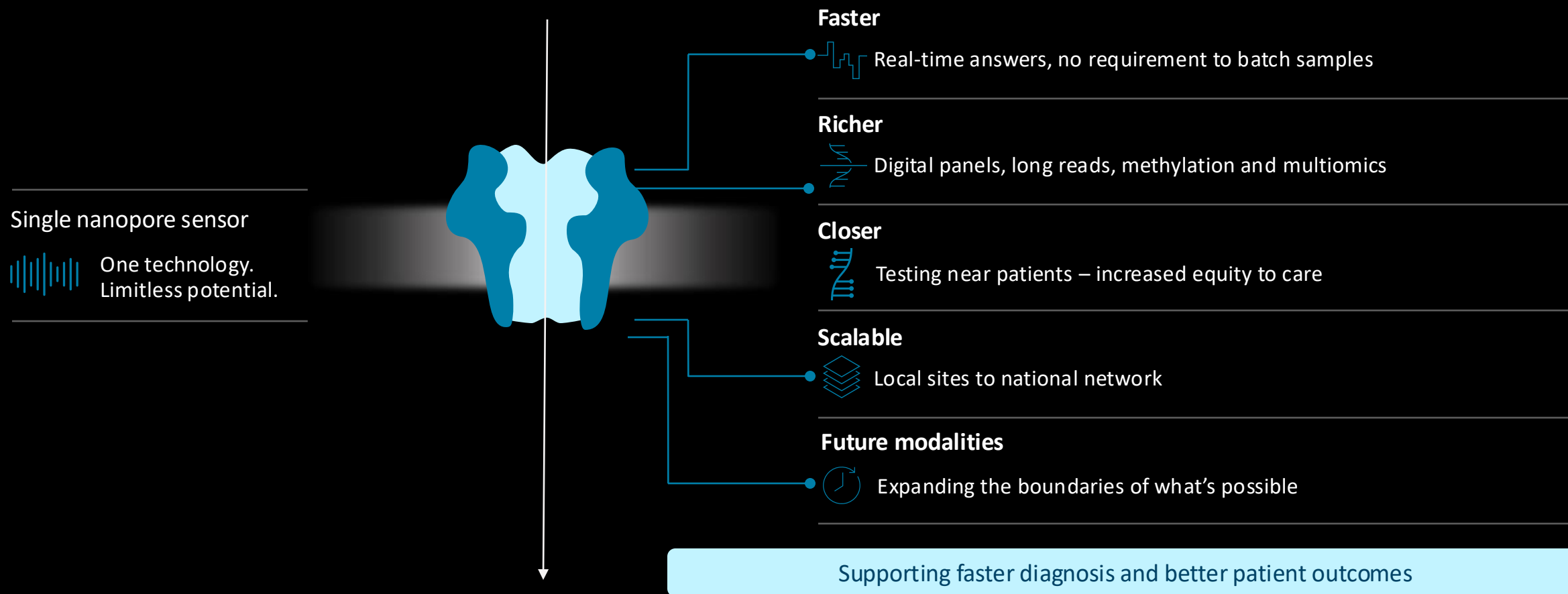
Long-read sequencing identified a DMPK repeat
expansion missed by standard testing
Helped explain sudden cardiac deaths in 1 NZ family
and 2 Australian families
Supports improved care and prevention for families
at risk





Clinical implementation with Oxford Nanopore Technologies

Choose the right sequencing approach for the clinical question – then scale from targeted answers to comprehensive WGS





Thank you

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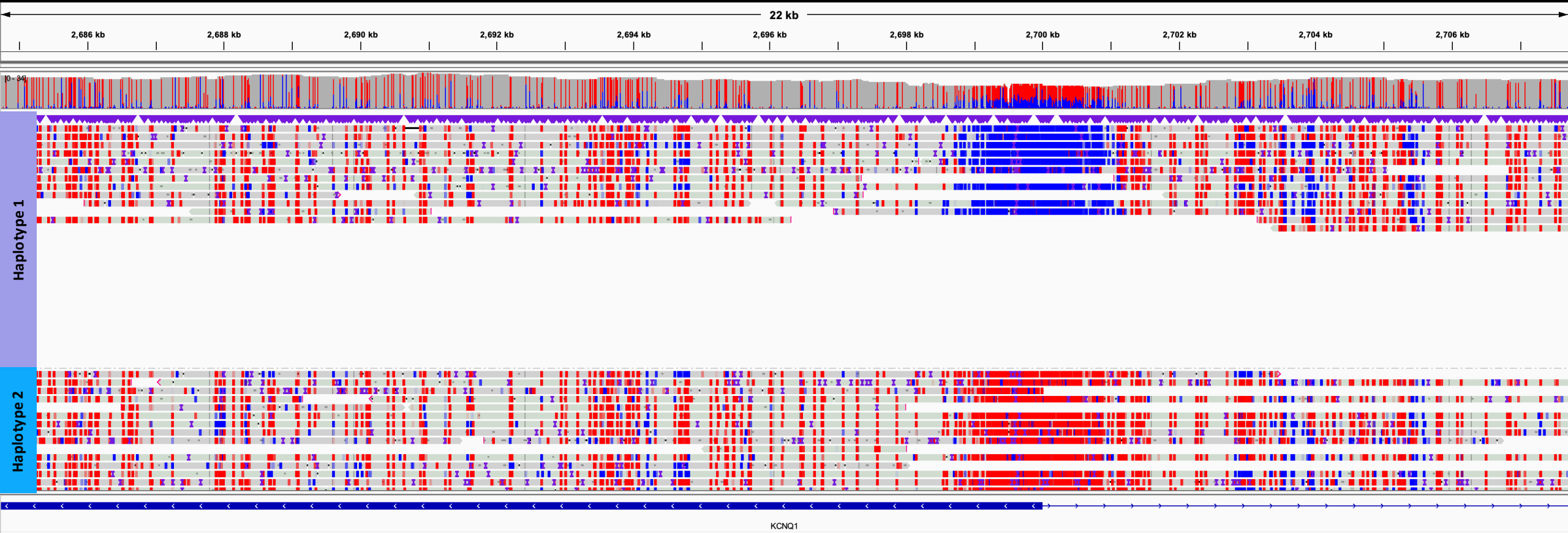
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Methylation and rare diseases



Oxford Nanopore data is information-rich

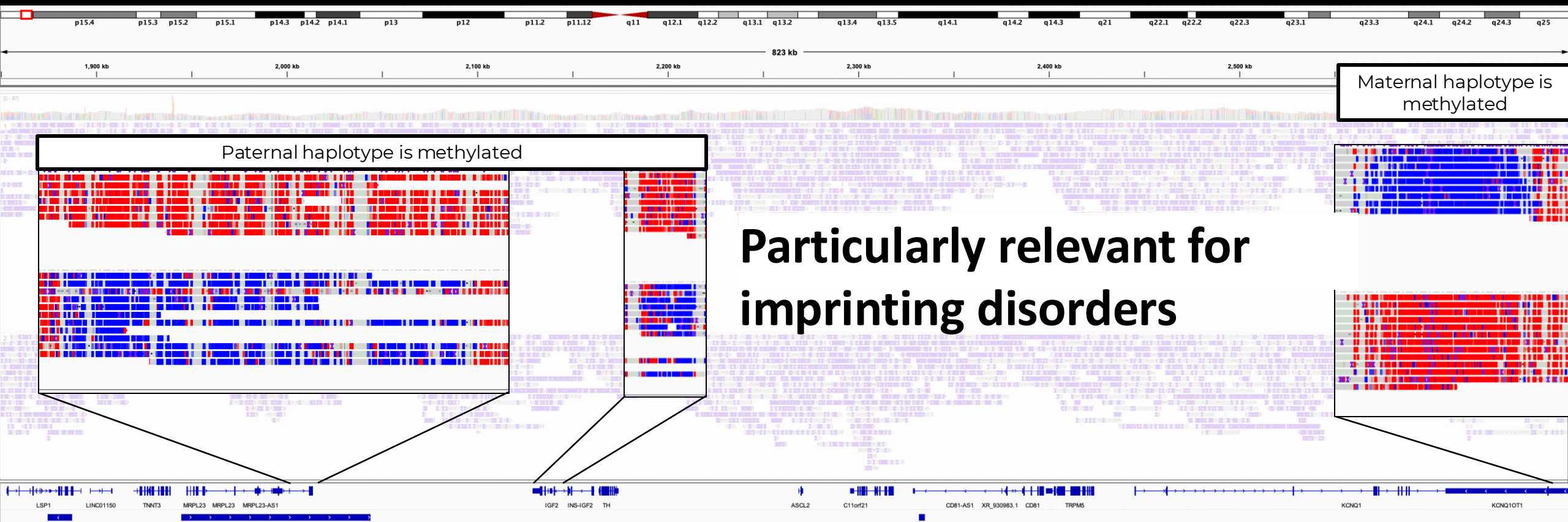
Enabling phasing and haplotype-level methylation





Oxford Nanopore data is information-rich

Phasing over large loci

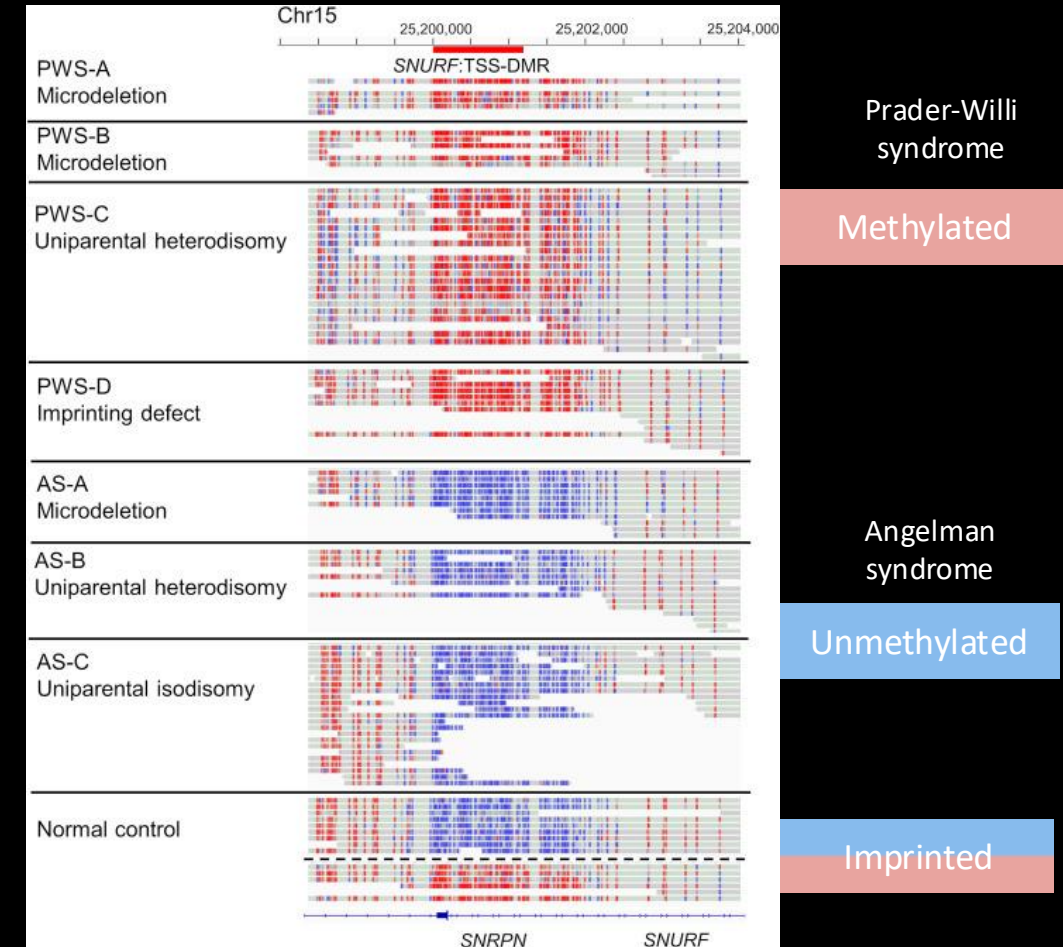




Disease diagnosis using nanopore sequencing

Analyzing differential methylation in Prader-Willi syndrome and Angelman syndrome

- Prader-Willi syndrome and Angelman syndrome are caused by aberrant genomic imprinting on chromosome 15q11.2, specifically in CpG island of *SNRPN* gene promoter region
 - PWS only has methylated alleles and AS only unmethylated alleles
- Detection of phased methylation differentiates between the diseases
- Correctly delineate the underlying pathogenesis (i.e. deletion, uniparental isodisomy, uniparental heterodisomy, and imprinting defect)
 - Research enabling better understanding of disease mechanism, with potential to replace the need for additional tests

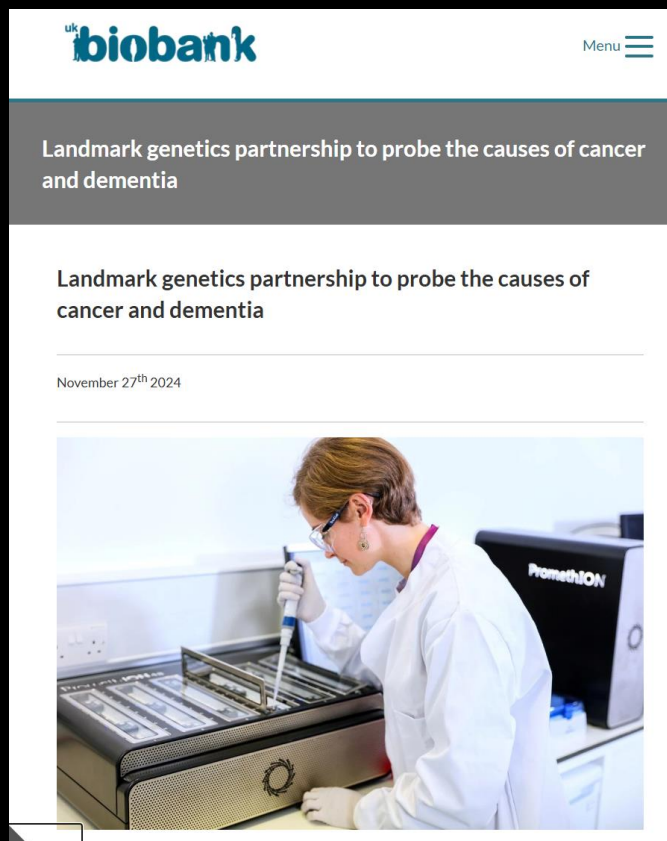


Yamada et al., *ESHJ* <https://doi.org/10.1016/j.ejmg.2022.104690> (2023)



Delivering the world's largest *comprehensive* epigenetic program

Along side a groundbreaking genetic variation catalog in a public dataset



- ✓ 50,000 nanopore genomes with complete epigenetics
- ✓ Discover & interpret novel genetic and epigenetic variation at population scale
- ✓ Samples across neurological indications, cancer, family trios, longitudinal, metabolic disorders & an overlap with Olink protein data
- ✓ Sequencing in collaboration with Amgen's **deCODE Genetics**
- ✓ First data release July 2026!



Delivered with scale & consistency

- New High Throughput Barcoding (HTB) protocol
- Additional Variation (SVs, indels, SNV, repeat expansions)
- 28M Phased CpG sites captured