Australian Genomics

International Horizon Scanning:

Technology Outlines of Disruptive Genomic Technologies

June 30 2025

Working Group John Christodoulou; Sally Dunwoodie; Paul Fennessy; Daniel MacArthur;

Coordinator: Michael C Quinn

Australian Genomics

Table of Contents

Long-read sequencing

1.1 Technology Overview

Long read sequencing refers to a technique that can sequence fragments in the 100,000 base pair range depending on the quality of sample preparation. Comparatively, the most frequently/commonly used next-generation sequencing in recent times has been short-read sequencing, which can sequence fragments of 50 to 300 base pairs.

Long-read sequencing is important in diagnostic settings such as repeat sequences, other complex genomic rearrangements, and phasing variants. However, it requires different sequencing hardware and bioinformatic pipelines.

As outlined by Oehler et al., (2023) (see also Figure 1):

> "Long-read DNA sequencing technologies have been rapidly evolving in recent years, and their ability to assess large and complex regions of the genome makes them ideal for clinical applications in molecular diagnosis and therapy selection, thereby providing a valuable tool for precision medicine."

PacBio and Oxford Nanopore are active in this space; refer Figure 1 (below) that compares sequencing methodology. Illumina representatives have shared that their comparable platform is Illumina Complete long read sequencing technology.

1.2 Potential Healthcare Applications

Improved diagnostics in rare disease and cancer (e.g. Huntington's disease). Recent studies have found a 10% increase in diagnostic rate, including novel variant discovery (Sinha et al., 2025), compared to current practice.

May shorten diagnostic path. For example, Erdmann et al., (2023) found causative repeat expansions in 28 of 100 clinically undiagnosed ataxia patients, using long-read sequencing.

1.3 Evidence and Readiness

Regulatory status (e.g. FDA, TGA, EMA, HC Canada): FDA has approved Azenta's clinical long-read whole genome sequencing using PacBio's Revio sequencer)[1]. No TGA approval at this time.

Clinical validation: Studies demonstrate long read sequencing is better than short-read sequencing with diagnostic yield improvements for unresolved rare disease cases (e.g. Erdmann et al., 2023 for Ataxia).

Methodology well characterised and published: (e.g. see Erdmann et al., 2023, application for Ataxia patients).

National Adoption: Victoria has state government funding for pilot implementation at VCGS (personal communication, Seb Lunke, VCGS) using Oxford Nanopore Technology.

Adoption by international genomic initiatives:

- **Genomics England** is integrating long read sequencing into pilot studies[2].
- **Broad Institute** e.g. Long Read Lab[3].
- Investigated for use in the **All of Us program** (see Mahmoud et al, 2024).

1.4 Market and Industry Engagement

Key players: Oxford Nanopore Technologies (ONT), Pacific Biosciences (PacBio). Other Life Science companies such as **Illumina** (Complete technology) have competing technologies. Some studies have done direct comparisons of sensitivity (e.g. Mahmoud et al., 2024).

[1] Azenta Obtains Regulatory Approval for Clinical Long-Read Whole Genome Sequencing Test (prnewswire.com)
[2] (https://re-docs.genomicsengland.co.uk/ont/)
[3] Long Read Lab | Broad Institute)

1.5 Cost and Economic Considerations

Infrastructure and test cost:

- Platform cost of Oxford Nanopore MinION Mk1D is $US2,999[4], PacBio Revlo Sequencer is $US779,000[5].
- Consumable costs are more expensive than for short-read sequencing[6]. For example, flow cell consumables are typically more expensive, and more computation power is required (Marx et al., 2023). flow cells: 24 pack flow cell pack for $US14,400.[7] Test cost is estimated at < $20 per sample (Hall et al., 2024).

Potential cost savings:
Reducing length of diagnostic journey, resulting in fewer unnecessary tests/procedures, fewer hospital admissions *vis a vis* unnecessary tests and symptom management, shorter time to diagnosis and treatment.

- Decreasing need for multiple rounds of testing (and/or reanalysis) when short-read sequencing is inconclusive. Would also reduce the need for other clinical investigations (e.g. imaging, etc).

1.6 Implementation Challenges and Barriers

Regulatory considerations: Not approved for use in Australia at this time.

Data analysis and interpretation: Requires specialized bioinformatics pipelines and trained personnel.

Infrastructure: Purchasing of long-read sequencing unit and more expensive consumables. Likely requires significant computational power and data storage and safe, ethical storage for long-read data processing.

Workforce concerns: training of technical diagnostic laboratory and bioinformatics staff and likely new variant calling pipelines. Automation of laboratory procedures may address some of the concerns[8].

Awareness and education of clinical staff (i.e. clinical geneticists and genetic counsellors) regarding technology.

1.7 Strategic Priority for Australia

Long read sequencing technologies generally align with Genomics Australia's proposed priorities of improved rare disease diagnostics (see Department of Health and Aged Care (DOHAC) update 22 Feb 2025)[9]. The technology has been identified at the state and territory level; for example, VCGS has been awarded funding through the Victorian Medical Research Acceleration Fund that may lead to development of feasibility data[10]. Pilot projects could assess its cost-effectiveness in the Australian health system before widespread adoption and reimbursement.

[4] Nanopore store: Price List
[5] PacBio Announces Record Orders, Including Orders for 76 Revio Systems Received in the Fourth Quarter of 2022 - PacBio
[6] Long-Read Sequencing vs Short-Read Sequencing: A Comparison
[7] Nanopore store: Price List
[8] Long-Read Sequencing Automation Gains Traction but Bottlenecks Remain | GenomeWeb
[9] https://www.health.gov.au/our-work/establishing-genomics-australia
[10] VMRAF grant - Murdoch Children's Research Institute

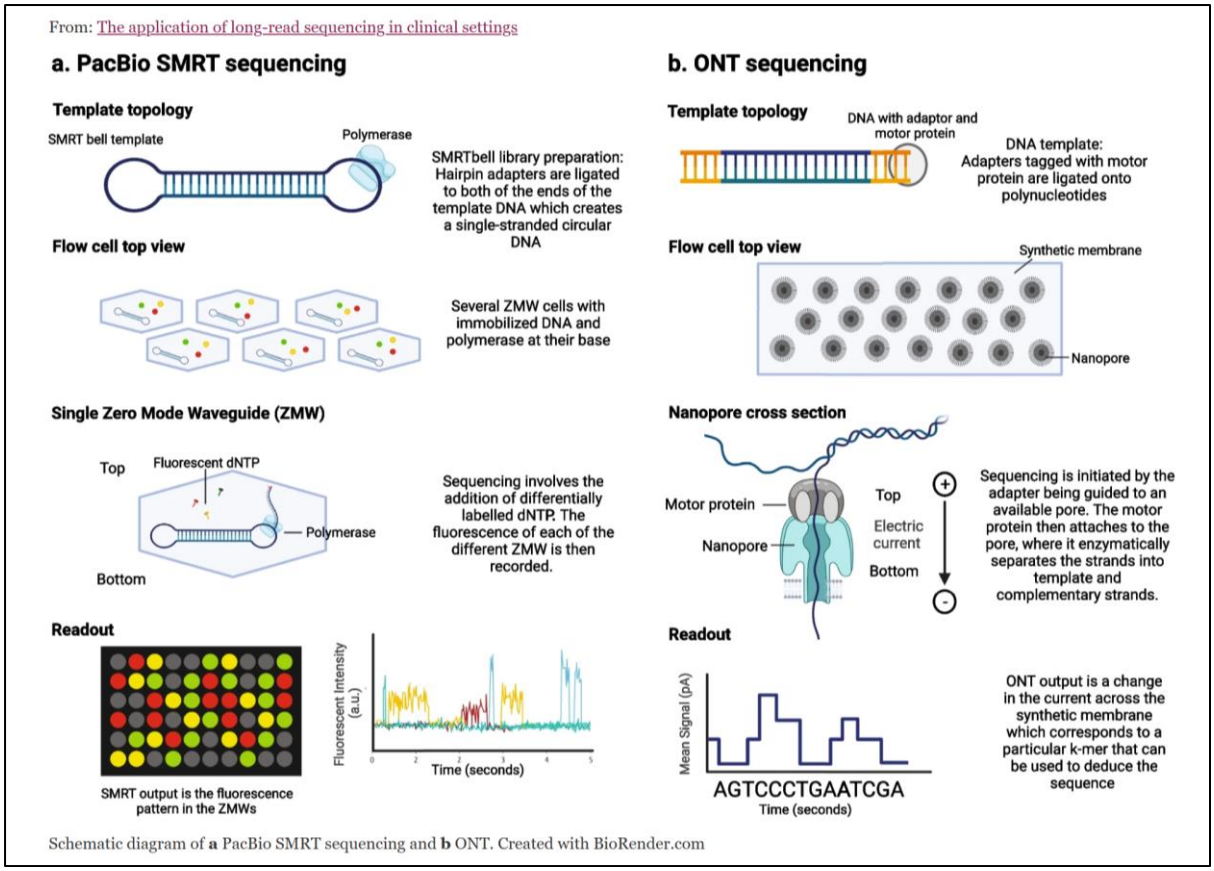


Figure 1: Schematic diagram of a. PacBio SMRT sequencing and b. ONT (Oehler et al., 2023, Figure 1, The application of long-read sequencing in clinical settings - PMC).

2 Spatial Genomics

2.1 Technology Overview

Spatial genomics in the context of clinical care is a rapidly evolving technique which combines both genomic sequencing with a spatial context. This permits a more complete interpretation of gene location of the cell or tissue a gene is expressed in to allow for better disease diagnosis and treatment. Techniques involved include in situ hybridization and DNA barcoding technology (Mulholland & Leedham., 2024; Bressan et al., 2023).

As outlined in Williams et al. (2022):

> "Although technologies for counting and profiling transcripts in tissue have existed for decades, it was only in 2021 that spatial transcriptomics was named 'Method of the Year 2020' by Nature Methods. The field continues to grow fast, driven by numerous factors including the reduced cost of next-generation sequencing, initiatives such as the Human Cell Atlas, and the BRAIN Initiative Cell Census Consortium, increases in computing capacity, and improvements in microscopy and imaging."

Spatial Genomics is an emerging technology that combines gene expression (see example in Figure 2) and the spatial context of tissues. Positional information (i.e. spatial) allows for more insight into tumour micro-environments (noting considerable tumour heterogeneity that can occur), and relating this to spatial factors in, for example, neurological diseases, and developmental biology.

2.2 Potential Healthcare Applications

Oncology:

- More complete tumour characterization – preserving tumour architecture addresses tumour heterogeneity and clonal evolution directly (Zhao et al., 2022)
- Enhanced biomarker discovery; e.g. in pancreatic adenocarcinoma samples, spatial techniques allow for identification of paracrine and autocrine signalling (Lyubetskaya et al., 2022).

Neurology:

- Spatial transcriptomics has been used to study Alzheimer's disease, permitting gene co-expression networks to be investigated in amyloid plaques (Chen et al., 2020).

Clinical trials and Therapies:

- Aids in risk stratification of patients for clinical trials and disease-appropriate therapies (Mulholland & Leedham., 2024). The ability to stratify patients for selection in clinical trials (using spatial techniques) has been predicted to save up to US$20 billion (Locke & Hoyt, 2023).

2.3 Evidence and Readiness

Regulatory status:

- Not TGA approved.
- SimBioSys Gains has FDA Approval for Spatial Omics Platform in Breast Cancer[11].

Clinical validation:

- Still primarily used in research, as reflected in examples below.
- Studies show spatial transcriptomics outperforms RNA sequencing in identifying tumour subtypes. (see An et al., 2024).
- Pilot studies, for example in breast cancer, demonstrate feasibility for clinical use (Yu et al., 2022).
- **Broad Institute** is incorporating spatial genomics in cancer research programs (e.g. collaboration between Broad and Illumina using Illumina Connected Multiomics[12]).
- **GA4GH** is developing data standards for **spatial transcriptomics** (e.g. see Jackson and Pachter 2023).

[11] https://www.precisionmedicineonline.com/precision-oncology/simbiosys-gains-fda-approval-spatial-omics-platform-breast-cancer-seeks
[12] Broad Institute and Illumina announce collaboration on Spatial Flagship Project

2.4 Market and Industry Engagement

Key players:

- **NanoString GeoMx DSP** (digital spatial profiling)[13].
- **10x Genomics Visium** ("unbiased spatial transcriptomics")[14].
- **BGI STOmics stereo-seq[15].**
- **Illumina –** uses Illumina Connected multiomics platform**[16].**

Industry developments:

- Rapid advancements in single-cell and spatial multiomics integration.
- There are "turnkey" solutions on offer. Greater commercial adoption will strengthen accessibility (Bressan et al., 2023).

2.5 Cost and Economic Considerations

Infrastructure and test Cost:

- **NanoString GeoMx DSP**: US$300,000 for new system[17] [18].
- **10x Genomics Visium**: US$2,200-4,300 per sample[19]. Platform is compatible with Illumina sequencers such as NovaSeq 6000 and HiSeq 2500.
- **BGI STOmics stereo-seq: from US$7000 per sample[20]** . Platform is compatible with MGI DNBSEQ technology.
- **Illumina – uses Illumina Connected multiomics platform:** NovaSeq X ~US$1 million; MiSeq i100, US$49,000 (noting platforms may already be available for other NGS applications)[21].

Potential cost savings: this technology:

- May lead to more accurate cancer treatment.
- May require fewer tissue biopsies.
- May also address tumour heterogeneity issues.

2.6 Implementation Challenges and Barriers

Data complexity: Requires advanced bioinformatics expertise for large-scale spatial datasets.

Standardization: Lack of clinical guidelines for spatial genomics implementation in diagnostics.

Infrastructure: Requires high-resolution imaging systems, computational power, and data storage.

Workforce: upskilling of laboratory diagnostic and Bioinformatics staff – currently mainly in the research space.

2.7 Strategic Priority for Australia

VMRAF grant (VIC) – Project title: Using Intelligent Analytics and Spatial Genomics to Improve Immunotherapy Treatment Outcomes in Breast Cancer Patients (La Trobe University)[22]. Spatial Genomics could be integrated into national cancer genomics initiatives (e.g. Victorian Comprehensive Cancer Centre, ZERO2, ICCON, KConFab).

[13] GeoMx DSP Spatial Genomics Overview | NanoString
[14] Visium Spatial Platform - 10x Genomics
[15] STOmics Stereo-seq | Advanced Spatial Multi-omics Technology
[16] Illumina spatial
[17] NanoString GeoMx DSP Digital Spatial Profiler - AV | LabX.com
[18] https://nanostring.com/blog/the-birth-of-spatial-genomics/
[19] https://www.uth.edu/cgc/price.htm
[20] Limited Promotion: Unlock Research Potential with Advanced Sequencing
[21] Illumina launches compact, low-cost gene sequencing devices | Reuters
[22] https://djsir.vic.gov.au/medical-research/sector-support/Victorian-Medical-Research-Acceleration-Fund

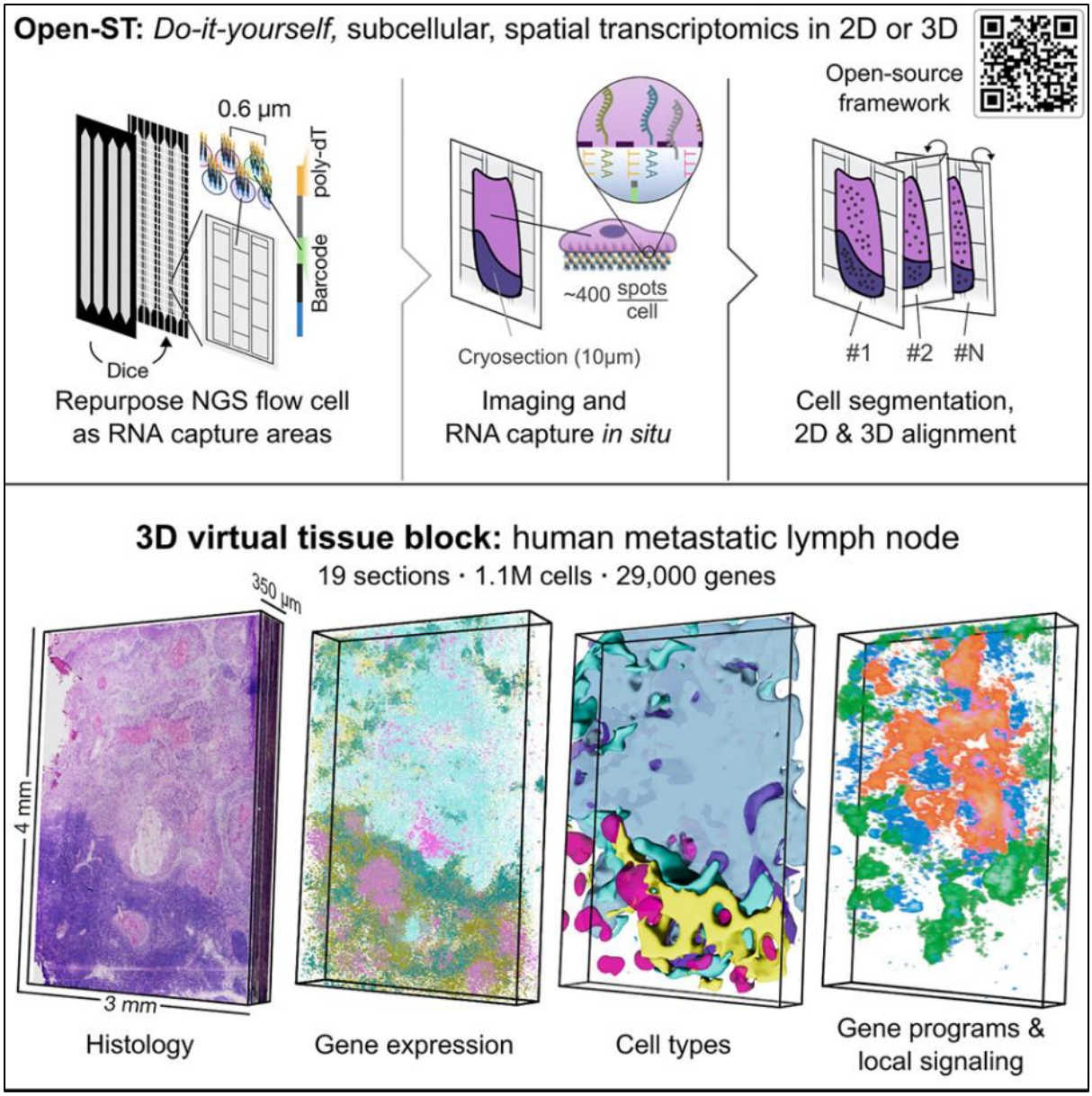


Figure 2. Graphical abstract (from Schott et al., 2024, Open-ST: High-resolution spatial transcriptomics in 3D. Open-ST: High-resolution spatial transcriptomics in 3D: Cell)

3 Sequencing in the field: use of low cost, highly portable NGS units for clinical applications

3.1 Technology Overview

'Sequencing in the field' can be described as bringing next generation sequencing (NGS) technology to remote locations, thus removing the need for central laboratory diagnostic infrastructure and alleviating concerns regarding equity of access for remote communities. The COVID-19 pandemic highlighted the need for such portability in remote locations, particularly for vulnerable populations. This concept has been around for more than a decade[23] but recently reduction in the cost of sequencers and connectivity in remote locations (e.g. Satellite systems) have increased potential viability. For example, the MinION, a portable palm-sized nanopore sequencing device (see Figure 3), has been available since 2014. The technology is compact, lightweight (e.g. weighs only 0.1kg) and has relatively fast sequencing turnaround times. This brings the technology to the area of need, with several applications, particularly in the infectious disease space (some may have indirect relevance to genomics). The MinION has been used in a range of settings including rainforests in Tanzania, Ecuador, Canadian High Arctic and International space stations (Mongan et al., 2019), aligning with the World Health Organisation[24] [25]

3.2 Potential Healthcare Applications

Infectious disease surveillance: Used in outbreak detection for pathogens such as **Ebola**, **SARS-CoV-2** in remote locations. (see Latorre-Perez, 2020).

Antimicrobial resistance (AMR) monitoring: Enables real-time tracking of resistant bacterial strains in hospitals and communities.

Cancer diagnostics: Potential for on-site mutation profiling (potentially germline and somatic), particularly in under-resourced areas.

Environmental health: Used in monitoring microbial communities in water and food safety applications (e.g. flood waters), potentially aiding in post natural disasters managing.

Health adjacent application: use in detecting biothreats, see Tyler et al (2023).

3.3 Evidence and Readiness

Regulatory Status Limited regulatory approvals for clinical applications, though used in research and public health surveillance. Not TGA approved.

Validation status:

- The **MinION** has been tested in real-world settings (e.g. the 2014 Ebola outbreak; Quick et al., 2016).
- Validated for microbial whole genome (WG) sequencing (Tyler et al., 2018).

3.4 Market and Industry Engagement

Key biotech and industry members: Oxford Nanopore Technologies[26] (MinION, Flongle), Illumina (iSeq for small-scale sequencing).

Commercial availability:

- The MinION is available commercially for US$2,999, significantly reducing costs compared to traditional sequencers. Technology has been available since 2014.

[23] https://www.otago.ac.nz/news/newsroom/revolutionary-handheld-dna-diagnostic-unit-allows-lab-quality-analysis-in-the-field
[24] WHO Strategy document. Global genomic surveillance strategy for pathogens with pandemic and epidemic potential, 2022-2032. https://www.who.int/initiatives/genomic-surveillance-strategy
[25] https://nanoporetech.com/news/news-oxford-nanopore-sequencing-technology-used-develop-assay-comprehensive-variant
[26] https://nanoporetech.com

- The Flongle adapter (i.e. a flow cell dongle) enables even lower-cost, disposable sequencing for single-use diagnostics[27].
- Illumina iSeq 100 desktop sequencer costs approximately US$20,000[28].

Technical challenges:

- Lower accuracy of nano technologies compared to core NGS sequencers (Zhang et al., 2024).
- Sensitivity issues of MinION vs. more traditional PCR (e.g. in context of testing for rabies virus in Kenya; see Gigante et al., 2020).
- Need for real-time data/analytical processing capabilities in field settings. However, can be used offline with whole genome sequencing (WGS) projects and software (e.g. MinION in context of Ebola surveillance; Quick et al., 2016).
- Training required of local personnel.

Infrastructure needs:

- the recommended or optimal number of units to cover a specified area/region/state/etc., and for a specified purpose, is unclear.
- Dependence on computing power, may create a bottleneck[29].
- **Workforce Training requirements** for healthcare workers in non-genomic settings.
- **Scalability concerns –** how might this technology be implemented in Australian rural/remote settings? As outlined by Wasswa et al**.** (2022): "*development of field laboratory packages by the manufacturer and* project *engineers would encourage the use of technology with minimal laboratory infrastructure. For example, equipment and consumables packaged within self-contained systems that also work as temporary bench tops in the field would greatly enhance the accessibility of MinION technology in remote regions of the world."*

3.5 Cost and Economic Considerations

Cost of implementation:

- **Device**: US$2,999[30] (MinION Mk1D).
- **Consumables**: Flow cells from US$600[31], making it accessible for small labs and field use.
- **Data storage and analysis**: Computational costs vary depending on location; may require satellite **network** infrastructure for sending data results (e.g. Starlink Mini[32]). Note, combined with a laptop, base-calling software may be run offline, but may require a local basecaller installed e.g. Guppy for ONT[33].

Potential cost savings:

- **Faster outbreak response** for infectious diseases, potentially leading to fewer hospitalisations.
- **Decentralization of genomics** lowers reliance on central sequencing labs, particularly true in the 'hub and spoke' model of some Australian states and territories, and dependence on centralized state and **territory** pathology providers.

3.6 Implementation challenges and barriers

Data accuracy: higher error rates in Nanopore based sequencing compared to short read NGS requires further benchmarking.

Sample integrity: DNA and RNA extraction outside of diagnostic laboratory conditions can present technical challenges.

Connectivity issues: may require satellite connectivity for data connectivity and data transfer.

Workforce training: of healthcare workers in rural and remote settings.

---

[27] https://nanoporetech.com/document/requirements/flongle-spec
[28] Illumina iSeq 100
[29] Sequencing • PANDORA
[30] Nanopore store: Store home
[31] Nanopore store: Flow cells
[32] Starlink | Roam
[33] Guppy protocol | Oxford Nanopore Technologies

3.7 Strategic Priority for Australia

Potential for early adoption: Australia's remote and rural healthcare needs make portable sequencing highly relevant**.** This also relates to the National Health Genomics Policy Framework commitment to cultural safe and appropriate service delivery to Aboriginal and Torres Strait Islanders who may live in rural, remote and very remote areas[34]. Casauria et al., (2024) encouraged the need to continue to assess access and equity issues regarding genetic test availability – the ability of portable NGS units to be employed under certain conditions would address these issues.

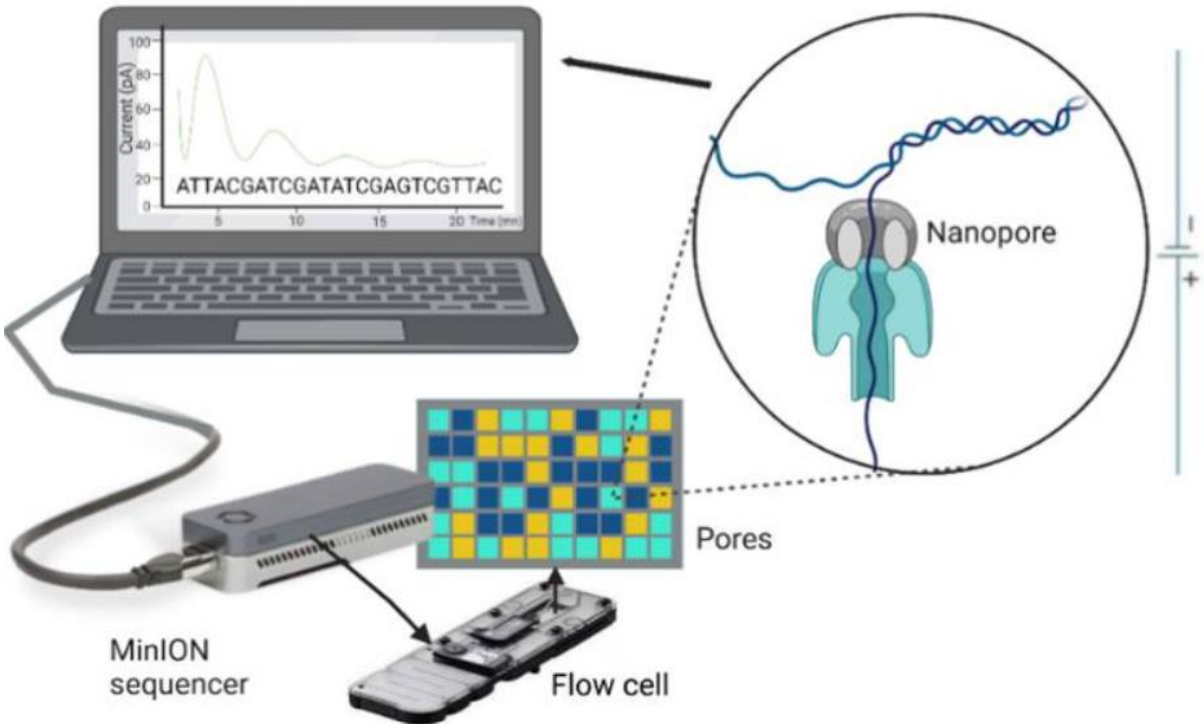


Figure 3: Schematic diagram indicating the composition of the MinION device, flow cell, nanopore, real-time computer access, and process management. Green is active, blue is inactive, and yellow are recovery pores on the nanopore membrane. (Wasswa et al., (2022), Figure 1, MinION Whole-Genome Sequencing in Resource-Limited Settings: Challenges and Opportunities - PMC)

[34] National Health Genomics Policy Framework 2018–2021

4 Genome-wide CRISPR Screening for Functional Genomics

4.1 Technology Overview

The CRISPR-Cas9 (and related) technology (or related tools) can be used for various applications, including genomic screening using a functional genomics approach (Aregger et al., 2019, see also Figure 4), drug sensitivity testing or drug resistance studies (Aregger et al., 2019). As the technology becomes more accessible and scalable there is significant promise to advance genomic precision medicine.

From Li et al., 2023:

> "Large-scale functional genomics screening is a powerful approach to systematically probe gene function. Its implementation in human cells has been substantially facilitated by the advent of new CRISPR-based technologies. Adapted from a bacterial innate immune system, CRISPR-Cas9 and its derivatives are robust and versatile tools for gene editing and manipulation in human cells. Attributed to the programmable and multiplexable nature of CRISPR-based technologies, they have been widely applied to introduce massively parallel genetic perturbations in large-scale functional genomics screens. Currently, three types of CRISPR-based perturbations are commonly used in such screens: (1) CRISPR knockout (CRISPRn), which utilizes the Cas9 nuclease to disrupt a target gene by introducing frameshift indels; (2) CRISPR interference (CRISPRi), which utilizes a catalytically dead Cas9 (dCas9) fused with a transcriptional repressor domain to silence the transcription of a target gene; and (3) CRISPR activation (CRISPRa), which utilizes dCas9 fused with transcriptional activator domains to activate the transcription of a target gene. Compared with CRISPRn, CRISPRi does not induce DNA double-strand breaks and thus is less toxic to cells that are sensitive to DNA damage, such as hPSCs."

4.2 Potential Healthcare Applications

Cancer Research: Using lung cancer as an example, Shen et al., (2022) summarizes CRISPR knockout (to achieve loss of function mutations), interference (using dCas9, a nuclease dead version of the protein) and activation (by fusing transcriptional activators) can be used to overcome chemotherapy resistance, overcoming radiation resistance, boosting immunotherapy, and identifying novel targets (Shen et al., 2022).

Metabolic disorders: CRSIPR screens have been utilized in a variety of metabolic disorders. For example, in Type 2 diabetes, a CRIPSR loss of function screen identified genes (such as CALCOCO2) regulating insulin secretion (Rottner et al., 2023). In the context of obesity, D-Lynes et al., 2023 used a genome-wide loss of function screen to investigate regulators of glucose metabolism in brown adipocytes.

Drug discovery: CRISPR screens can be used to identify markers relating to differential drug response. For example, a genome-wide activation library was used to identify genes relating to the drug metformin (diabetes drug with anti-tumour properties) resistance in prostate cancer cells (Chen et al., 2021).

4.3 Evidence and Readiness

Regulatory and Ethical Considerations:

Ethical Considerations: As gene editing progresses toward clinical applications, ethical concerns in relation to affecting the germline and any unintended consequences. (Ayanoglu et al., 2020).

Limited regulatory approval[35]

FDA, EMA and Health Canada approval circa 2023 for Casgevy, a CRISPR therapy to treat sickle-cell disease.[36] [37] [38].

[35] https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/australia-therapeutic-stem-cell/
[36] https://www.nature.com/articles/d41587-023-00016-6
[37] https://innovativegenomics.org/news/crispr-clinical-trials-2024/
[38] Summary Basis of Decision for Casgevy - Drug and Health Products Portal

Validation Status:

- Preclinical studies and large-scale functional genomics efforts have demonstrated the effectiveness of genome wide CRISPR screens (see Li et al., 2023). Ten clinical trials actively recruiting using CRISPR functional screens (clinicaltrials.gov).

International Genomic Initiatives:

- **Broad Institute**: see collaborative efforts[39].
- **Genome Canada**: for example, COVID19[40].
- **Australian Functional Genomics Network**[41].

4.4 Market and Industry Engagement

Key Industry Participants:

- CRISPR Therapeutics, Beam Therapeutics.

Technology providers:

- Illumina, 10x Genomics, PacBio.

4.5 Implementation Challenges and Barriers

Technical:

- Incomplete knockout or knockdown efficiency in animal models.
- Challenges in screening non-coding regions and gene regulatory elements.
- Off target effects (see Guo et al., 2023).

Infrastructure and Training:

- Requires specialized sequencing facilities, bioinformatics pipelines, and expertise in functional genomics analysis. Strategic funding of groups such as the Australia Functional Genomics Network (https://www.functionalgenomics.org.au/) Local Australian Conferences on Crispr have been organized[42].

4.6 Cost and Economic Considerations

Estimated Costs: High cost introduces major issues regarding equity and patient access to such treatments in healthcare. Variable set up costs, for example Cancer Research Horizons, can offer a cell-line CRISPR screen at a relatively low price (GB4,000 pounds)[43] . Treatment cost per patient can be very high (e.g. US$2.2 million per patient for Casgevy; see Rueda et al., 2024).

Potential Cost Savings: Relatively speaking, could be more cost-effective compared to Zinc-finger nuclease (ZFN) and Transcription Activator-Like Effector Nuclease (TALEN) systems, which both require protein engineering[44]. If such therapies can demonstrate long-term effectiveness, could be cheaper than existing treatments.

4.7 Strategic Priority for Australia

This technology aligns with the Medical Research Future Fund generally, with funding of CRISPR technology projects[45]. Opportunities to leverage existing networks, e.g. Australian Functional Genomics Network. By uncovering the mechanisms of disease and clinically actionable targets across cancer and rare disease, the technology relates to areas prioritized in the Australian Cancer Plan[46] and National Strategic Action Plan for Rare Diseases. Technology has the potential to treat rare diseases that were previously considered untreatable

[39] here https://www.broadinstitute.org/research-highlights-crispr
[40] https://genomecanada.ca/project/integration-genomics-and-ai-accelerate-drug-discovery-against-covid-19/
[41] (https://www.functionalgenomics.org.au/)
[42] https://phenomicsaustralia.org.au/crispr-down-under-2025/
[43] Functional Genomics Centre | Cancer Research Horizons
[44] What are the pros and cons of CRISPR-Cas9? | IDT
[45] MRFF invests $8m into two nationally significant Monash-led mRNA projects - Monash University
[46] Australian Cancer Plan | Cancer Australia

– but at a significant cost, which raises concerns around access, operational capability and capacity and fiscal sustainability.

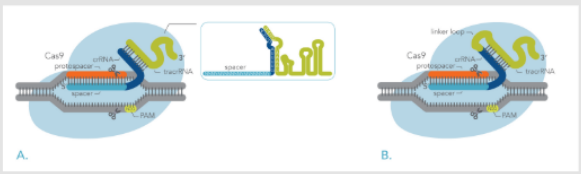


Figure 1. DNA cleavage by the CRISPR-Cas9 system. (A) Cas9 with two-part guide RNA. The guide RNA forms a complex with Cas9 endonuclease to guide targeted cleavage of genomic DNA. The cleavage site is specified by the spacer element of the crRNA. The crRNA spacer element recognizes 19 or 20 nt on the strand opposite from the NGG PAM (protospacer adjacent motif) site. The PAM site must be present immediately downstream of the protospacer for cleavage to occur. **(B)** Cas9 with single-guide RNA. The single-guide RNA (sgRNA) approach uses a fused crRNA and tracrRNA, but otherwise the entire Cas9 system works like the two-part guide RNA system shown in panel A.

Figure 4: DNA cleavage by the CRISPR-Cas9 system. (Thomas, 2023, Figure 1 What are the pros and cons of CRISPR-Cas9? | IDT)

5 Artificial intelligence (AI) and Drug Discovery in the context of Genomic Precision Medicine

5.1 Technology Overview

The power of AI is increasingly being used in a wide range of applications in relation to precision medicine. In the context of clinical genomics, AI in drug development can aid in drug target identification, patient stratification and clinical trial design (Niazi 2023).

As outlined in Paul et al., 2020:

> "Artificial Intelligence (AI) has recently started to gear-up its application in various sectors of the society with the pharmaceutical industry as a front-runner beneficiary. This review highlights the impactful use of AI in diverse areas of the pharmaceutical sectors viz., drug discovery and development, drug repurposing, improving pharmaceutical productivity, clinical trials, etc. to name a few, thus reducing the human workload as well as achieving targets in a short period. Crosstalk on the tools and techniques utilized in enforcing AI, ongoing challenges, and ways to overcome them, along with the future of AI in the pharmaceutical industry, is also discussed."

Although there may be ethical concerns and data security issues, AI will increasingly be applied to many aspects of healthcare, particularly drug development. Further work is needed to address ethical concerns and demonstrate the beneficial impact of AI on healthcare delivery and potential savings. Alliances between AI companies and Pharma are increasing (see also Table 1 below).

5.2 Potential Healthcare Applications

Predicting drug efficacy and toxicity: Machine learning models are being used to predict oncology drug efficacy and toxicity, thus increasing patient benefits (Badwan et al., 2023).

Drug repurposing: AI can speed up drug repurposing by identifying new uses of existing compounds for therapeutics, using data driven methods (Paul et al., 2020).

Personalized medicine: i.e. tailoring drug dosing for individual patient's genetic risk factors and/or germline profile (Tremmel et al., 2024).

Clinical trial optimization: for example, by predicting outcomes and reducing trial costs (Paul et al., 2020).

Discovery of new therapies: use of AI to rapidly identify novel drug targets (Blanco-Gonzalex et al., 2023).

5.3 Evidence and Readiness

Regulatory status: FDA has outlined draft guidance on the use of AI in the development of drug and biological products[47], [48].

The FDA has performed a general consultation on regulation AI within the therapeutic goods sector, including software as a medical device[49], which may streamline future applications**.**

Adoption in major genomic initiatives:

- **Broad Institute** collaborates with machine learning groups for large-scale drug screening (e.g. at the Schmidt Institute[50]).
- **Genome Canada** funds AI-powered drug repurposing projects (e.g. for COVID19 targets[51]).

[47] FDA issues first guidance on the use of AI in drug development - Drug Discovery World (DDW
[48] Using Artificial Intelligence & Machine Learning in the Development of Drug and Biological Products
[49] Consultation: Clarifying and strengthening the regulation of Artificial Intelligence (AI) | Therapeutic Goods Administration (TGA
[50] https://www.broadinstitute.org/news/new-machine-learning-techniques-boost-predictions-virtual-drug-screening-less-data
[51] https://genomecanada.ca/fourteen-ai-research-projects-join-fight-against-covid-19/

- Exscientia's AI-optimized precision oncology drug, **EXS21546**, is in Phase I clinical evaluation 2020[52] However, in 2023, Phase I/II trials were discontinued due to modelling indicating a high dose was needed for therapeutic effect.

5.4 Market and Industry Engagement

For key players in AI drug discovery, refer to Figure 5 and Table 1 below.

5.5 Implementation Challenges and Barriers

Data limitations: AI models rely on high-quality genomic and biomedical datasets, which are often incomplete or biased[53] .

Regulatory hurdles: Regulatory agencies globally are still adapting to AI-driven drug design methodologies[53].

High computational demand requires adequate infrastructure.

Workforce considerations: Need for skilled data scientists, bioinformaticians, collaborations between research and big pharma. In Australian setting, also highlights need for more clinical trial data for Aboriginal and Torres Strait Islanders.

Public Perception of AI generally: A recent study by Gillespie et al., (2025) indicated that Australia ranked the lowest in a by country comparison (n=47 countries) of positive AI emotion (Figure 15), indicating ongoing risk-aversion in AI by society generally.

5.6 Cost and Economic Considerations

Comparator and Investment in AI-powered drug discovery:

- Traditional drug discovery typically takes more than a decade and costs US$2 - $2.8 billion[54] (Paul et al., 2021) per successful drug candidate.
- Expected investment by pharma in AI would be US$5 billion by 2024 (Paul et al., 2021).

5.7 Strategic Priority for Australia

This technology application broadly aligns with the Medical Research Future Fund and National Science and Research Priorities. There is a need for continued academic / pharmaceutical and clinical collaborations to accelerate innovation (e.g. UNSW and Algorae Pharmaceuticals[55]). The National Health and Medical Research Strategy is currently being developed and provides an opportunity and identify any gaps and to address workforce issues in the health and medical research sector. The National Digital Health Strategy (2023-2028) also identifies a plan to be ready for emerging data sources and technology, including genomics and artificial intelligence[56].

[52] Exscientia pares down 'rapidly emerging pipeline'
[53] Nature editorial. (2023). AI's potential to accelerate drug discovery needs a reality check. *Nature*, 622, 217. DOI: 10.1038/d41586-023-03172-6
[54] Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products | FDA
[55] https://www.itnews.com.au/news/unsw-using-ai-to-help-with-drug-development-601002
[56] National Digital Health Strategy

Figure 5. Pharmaceutical key players that utilize AI (Paul et al., (2021), Figure 4, Artificial intelligence in drug discovery and development - PMC).

Table 1. Selected recent financings of companies applying AI in drug discovery[57].

Company	Date	Headline
Schrödinger	February 2020	Drug discovery software company closes $232 million IPO backed by Bill Gates and David Shaw.
Insitro	May 2020	Insitro raises $143 million in Series B funding, to help drive its machine learning-based drug discovery approaches further.
AbCellera	May 2020	AbCellera raises $105 million in Series B funding round to expand its antibody drug discovery platform.
Relay Therapeutics	July 2020	Relay Therapeutics, which focuses on understanding protein motion to design drug candidates, closes $400 million IPO.
Atomwise	August 2020	Sanabil Investments co-leads $123 million Series B funding round for Atomwise to support the development of its molecule identification software.
Recursion Pharmaceuticals	September 2020	Recursion Pharmaceuticals, which is applying machine learning to cellular imaging data, raises $239 million in Series D financing round led by Bayer's investment department Leaps. Other investors include Casdin Capital, Samsara BioCapital, Baillie Gifford and Lux Capital.
XtalPi	September 2020	More than a dozen investment companies raise $318 million in Series C round for start-up XtalPi, which is applying quantum physics with AI to discover drug candidates.
AbCellera	December 2020	AbCellera closes its IPO at $556 million.
Cellarity	February 2021	Cellarity raises $123 million in Series B funding for its drug discovery approach based on modulating cellular behaviors.
Valo Health	March 2021	Valo Health, which is developing its Opal computational drug discovery and development platform, raises $110 million to add to its $190 million raised in January 2021 for its Series B funding round.
Insitro	March 2021	Insitro raises $400 million in Series C financing led by Canada Pension Plan Investment Board.
Exscientia	March 2021	Exscientia completes $100 million Series C financing, with investors including Evotec, Bristol Myers Squibb and GT Healthcare.
Recursion Pharmaceuticals	April 2021	Recursion completes $436 million IPO.
Exscientia	April 2021	Exscientia secures additional $225 million in a series D round led by SoftBank Vision Fund 2.

[57] Tapping into the drug discovery potential of AI

6 Pharmacogenomics in Mental Health

6.1 Technology Overview

Pharmacogenomics in mental health involves using genetic information to guide the prescription of psychiatric medications, with the goal of targeting appropriate medication and dosage leading to improving efficacy and reducing adverse effects.

According to Hughes (2023): "Pharmacogenomics is a field of precision medicine which seeks to apply knowledge of human genetic variation to inform and individualise medicine use. Improved health outcomes from pharmacogenomics are achieved through prevention of adverse drug reactions and gains in drug efficacy."

Mental health was identified by Hughes (2023) as a potential exemplar of pharmacogenomics, particularly psychiatry, because it has a growing evidence base of medicines with actionable genetic variants, that is, variants that if present lead to meaningful drug or dosage decisions. In addition:

- Psychiatry has less objective phenotypic markers than other therapeutic areas such as cardiovascular disease.
- Mental health has a significant disease burden and increasing prevalence.
- Patients interact with multiple health professionals in both hospital and primary healthcare systems - exposing greater numbers of practitioners to pharmacogenomics more quickly.
- Depression has many drug treatment options and testing has the potential to aid the decisions.

This field has progressed from research to clinical implementation, with commercial tests available and growing integration into psychiatric practice. However, large-scale adoption remains variable (Figure 6).

6.2 Potential Healthcare Applications

In the context of mental health, pharmacogenomics has been researched in depression, anxiety, schizophrenia, bipolar and ADHA. Pharmacogenomics can also be applied to other diseases including drug selection and dosing in oncology (e.g. fluoropyrimidines), pain management and HIV treatment. We focus here on Mental Health, which is the readiest for implementation in terms of evidence and readiness.

6.3 Evidence and Readiness

Regulatory Approvals:
The TGA categorises all tests in the same class - moderate to high risk (Class 3 in-vitro medical devices). (Hughes 2023)

FDA has included pharmacogenomic warnings on certain psychiatric drugs (e.g., CYP2D6 interactions with SSRIs). As outlined by Hughes 2023:

- *The US FDA and other national drug agencies have assumed regulatory authority for pharmacogenomics, mandating pharmacogenomic data in product labels and drug registration applications, regulating laboratory developed tests and more.*
- *The FDA now has 209 and the EMA 94 drug labels with pharmacogenomics prescribing information.*
- *Labelling recommendations are not consistent (or harmonised) across agencies.*
- *Some regulators are moving to include pharmacogenomic data to improve genetic understanding of adverse events.*
- *Differing standards exist for regulating laboratory developed tests such as pharmacogenomics, and direct-to-consumer tests.*

Recognition in International Horizon Scanning or related Genomic Initiatives:

- **All of Us Research Program** – see review of Pharmacogenetics in Empey et al., (2025).

- **CADTH performed a horizon scan of Pharmacogenomic testing in psychiatric disorders (Young et al.**, 2023). Selected for inclusion on the 2023 CADTH watchlist[58]. As outlined by Young et al., (2023):

  > *"As the evidence regarding the use of pharmacogenomic testing for psychiatric disorders continues to evolve, implementors of this technology should consider issues related to clinician education and training, privacy and confidentiality of health data, and the potential for testing to exacerbate existing health inequities. Should pharmacogenomic testing be widely adopted, it has potential applicability in a high volume of treatment decisions. Health systems may need to consider expanding testing capacities by augmenting existing laboratory infrastructure, including testing equipment and personnel to conduct and interpret pharmacogenomic tests."*

- **Public perception of pharmacogenomics**: a recent study by Genomics England indicates good acceptability of pharmacogenomics as a tool in healthcare. For example, their survey of public acceptance found that 89% of the public indicated that they would undergo a pharmacogenomics test (Magavern et al., 2025) and 85% of UK adults believed that the NHS should make pharmacogenomics tests available to those that regularly took medication (Magavern et al., 2025).

6.4 Market and Industry Engagement

Commercial Tests: Companies like **GeneSight[59] (Myriad Genetics)**, MyDNA, and **PharmGKB[60]** offer clinically validated pharmacogenomic testing panels and GeneSight pharmacogenomic test for depression (Myriad Genetics.

6.5 Implementation Challenges and Barriers

Regulatory & Ethical Concerns: Data privacy, insurance discrimination, and informed consent issues remain challenges.

Healthcare System Readiness: Many psychiatrists and/or psychologists are not trained in genomic medicine, limiting adoption.

Reimbursement/Sustainability: RCPA has been advocating for greater accessibility to pharmacogenomic testing through the MBS[61].

Workforce Issues: Diagnostic laboratory readiness in terms of accreditation / training.

6.6 Cost and Economic Considerations

Cost of Testing: PGs test (Sonic) is priced at AU$197. MyDNA (based in Melbourne, VIC) offers a mental health medication test for $149. A Canadian study of 13 tests found a price range of CA$199 to $2,301 (median $499; Young and McDougal 2023).

Cost Savings: In Canada, direct (physician visits, medication) and indirect costs (loss of productivity) of Psychiatric disorders are predicted to have an economic impact of CA$50 billion a year.

An Australian systematic review in 2021 relating to pharmacogenomics and cost-effectiveness found in 10 of 18 studies that PG testing was likely to be cost effective; 7 reported that testing could lead to cost savings, and one reported testing was not cost-effective (noting these studies were all in the area of major depressive disorders; (Karamperis et al., 2021)).

6.7 Strategic Priority for Australia

The application of this approach aligns with the Mental Health Australia Strategy 2024-2029, including driving better mental health policies and systems[62]. The approach will also align with the Australian Commission on Safety and Quality in Health Care – Medication Safety Standards[63] by implementing safe and appropriate

---

[58] 2023 Watch List: Top 10 Precision Medicine Technologies and Issues
[59] GeneSight: Helping Patients with Depression Find the Right Antidepressant.
[60] https://www.pharmgkb.org/page/clinicianFAQ
[61] RCPA - Improving accessibility to pharmacogenomic testing
[62] mha_strategy_final.pdf
[63] Medication Safety Standard | Australian Commission on Safety and Quality in Health Care

prescription of drugs relating to genetic factors. Pharmacogenomic data would be particularly suitable for incorporation into an electronic medical record and My Health Record, given the range of primary care and allied health healthcare workers involved. Australian's investment in genomics, digital health and medication safety will likely aid in implementation of pharmacogenomics.

As summarised by Hughes (2023) regarding the current state of pharmacogenomics in Australia:

- A small but increasing number of tests are conducted (both publicly and privately funded) from an increasing number of service providers, including direct-to-consumer.
- Turnaround times for test results can be up to three weeks.
- Public funding for tests through the MBS is currently only for two drug/gene pairs.
- TGA categorises all tests in the same class - moderate to high risk (Class 3 in-vitro medical devices).
- There is little evidence of cost-effectiveness and clinical utility in local contexts.
- Australian genetic reference data is limited, and indigenous pharmacogenes are mostly unknown.
- Poor knowledge and awareness among practitioners mean the workforce is unprepared, and similarly, there is little public knowledge.
- Evidence-based models of service have not been developed.
- Standards-based data options are absent for storing and accessing reports, sharing across jurisdictions, or integrating with clinical decision support.
- Research activity is siloed in small trials and single-site hospital settings, resulting in little post-trial practice change.
- Clinical champions are few as is political will to break status quo.

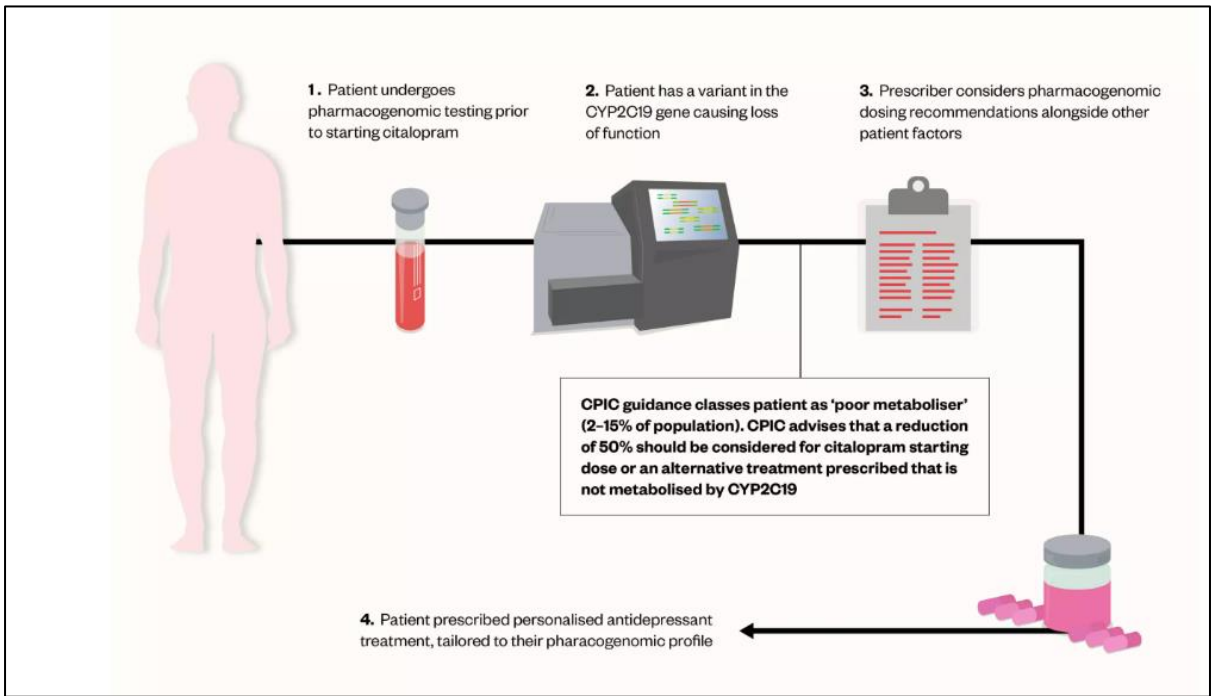


Figure 6. Example application of CPIC pharmacogenomic guidance for a patient with CYP2C19 variants prescribed citalopram (Berrou et al., (2023), Figure 2, Making the case for pharmacogenomics in the management of mental health conditions - The Pharmaceutical Journal).

7 *In Vivo* Base Editing and Prime Editing

7.1 Technology Overview

These are the next generation of CRISPR technology application. Unlike CRISPR-Cas9, *in vivo* base and prime editing can correct mutations without causing any breaks in double-stranded DNA (Newby & Liu et al., 2021). For example, base editors (such as Cytosine Base Editors) use enzymes to directly convert one DNA base to another. Prime editors (like PEmax) use a nickase Cas9 fused to a reverse transcriptase to make targeted edits that allow for a broader range of edits compared to CRISPR-Cas9 (Liu et al., 2024). These techniques are well suited for use with large size genes (Kantor et al., 2020). See also Figure 7 and Figure 8 for graphical depictions.

As outlined by Newby and Liu (2021):

> "Two classes of genome editing agents are particularly well-suited for directly correcting disease mutations because they can install programmable edits with relatively few uncontrolled indel outcomes (high product purity). These are:
>
> (1) base editors (BEs), which use a programmable DNA binding protein such as a catalytically impaired CRISPR-Cas protein or a TALE repeat array to direct an adenine or cytidine deaminase to modify a targeted window of single-stranded DNA, resulting in C•G to T•A or A•T to G•C conversions. Base editors can correct transition mutations, the largest single class of human disease-causing mutations, accounting for ~30% of known disease alleles; and
>
> (2) prime editors, which use a nuclease-impaired Cas protein to direct a reverse transcriptase that can replace or insert any desired sequence based on the information encoded in the co-delivered prime editor guide RNA (pegRNA). Prime editors are highly versatile and have been demonstrated to be capable of installing any base-to-base change as well as insertions of up to 44 base pairs and deletions of up to 80 base pairs. In theory, these features could permit prime editors to correct >89% of known human disease-causing mutations, excluding only those that involve aneuploidy, chromosomal rearrangement, or large duplications, insertions, or deletions."

7.2 Potential Healthcare Applications

Genetic Disease Therapy: e.g. cystic fibrosis, sickle cell disease (single point mutations). These can be targeted by base editing. For example, Anazlone et al. (2019) used prime editing in human cells ex vivo to correct genetic causes of sickle call and Tay-Sachs disease). Mbakam et al. (2023) used prime editing in cultured human cells on mutations of the DMD gene on chromosome 1 that causes Duchenne muscular dystrophy.

Cancer Therapy: can target both oncogenes and tumour suppressor genes. For example, Guerts et al. (2021) used prime editing to develop a model of TP53-mutant organoids in adult human stem-cell derived organoids.

7.3 Evidence and Readiness

In Australia, the Office of the Gene Technology Regulator has indicated that organisms modified by base or prime editors are not considered GMOs. "The legislative provisions referred to above do not exclude organisms modified using base editing or prime editing methods from regulation as GMOs, because the provisions are specific to enzymes with nuclease activity. Base editing and prime editing use disabled CRISPR/Cas9 coupled with other enzymatic domains to modify genes or genetic material, e.g. cytidine deaminase or adenosine deaminase[64]. "

Base Editing: Clinical trials for base editing in sickle cell disease and beta-thalassemia are in progress (e.g. Beam Therapeutics). See also Table 2.

Prime Editing: FDA approved Prime Medicine (application PM359) for phase 1 and phase 2 clinical trial in patients with chronic granulomatosis disease (CGD). See also Table 2.

[64] Overview - status of gene editing and other new technologies

European Medicines Agency (EMA) EU-IN identified base and prime editing as part of their Genome editing Horizon Scanning report[65].

7.4 Market and Industry Engagement

Beam Therapeutics[66]
Prime Medicine[67]
CRISPR Therapeutics[68]
Intellia Therapeutics[69]

7.5 Implementation Challenges and Barriers

Off-target Effects: This refers to unintended genetic modifications in non-targeted areas (Kantor et al., 2020).

Delivery Methods: Viral vectors, nanoparticles, and other delivery systems are being explored (Wang et al., 2020; Duan et al., 2021)

Ethical Considerations: As gene editing progresses toward clinical applications, ethical concerns in relation to affecting the germline and any unintended consequences. (Ayanoglu et al., 2020).

7.6 Cost and Economic Considerations

Preclinical and early research costs are high and challenging to quantify, with ethical and equity issues being raised[70].

Companies are offering Prime editing from AU$774 for prime editing mRNA[71].

Genscript offers base editor ABE8e for AU$310[72].

7.7 Strategic Priority for Australia

Using genome-wide CRISPR screening for identification of new therapeutic targets and biomarkers in cancer and rare disease would align with the *Australian Cancer Plan* and the *National Strategic Action Plan for Rare Diseases*. In relation to biotechnology company and industry involvement, this technology relates to the *National Reconstruction Fund*[73] and the *Biotechnology Blueprint*[74] (AusBiotech). CRISPR-based therapies are also expected to be funded in due course through PBS and/or National Health Reform Agreement mechanisms.

[65] Genome Editing EU-IN Horizon Scanning Report
[66] Breaking new ground to advance science with the potential to change lives | Beam Therapeutics
[67] Prime Medicine | Delivering on the promise of Prime Editing
[68] Home | CRISPR Therapeutics).
[69] Intellia Therapeutics - Revolutionize the course of medicine
[70] https://thebulletin.org/2024/10/crispr-therapies-can-treat-disease-but-cost-millions-an-equity-based-approach-could-bring-them-to-more-people/
[71] Prime editing mRNA — Messenger Bio
[72] Next-Generation Base & Prime Editors | Off-the-Shelf Gene Editing Nucleases | GenScript
[73] Home page | National Reconstruction Fund Corporation
[74] Biotechnology Blueprint - AusBiotech Ltd

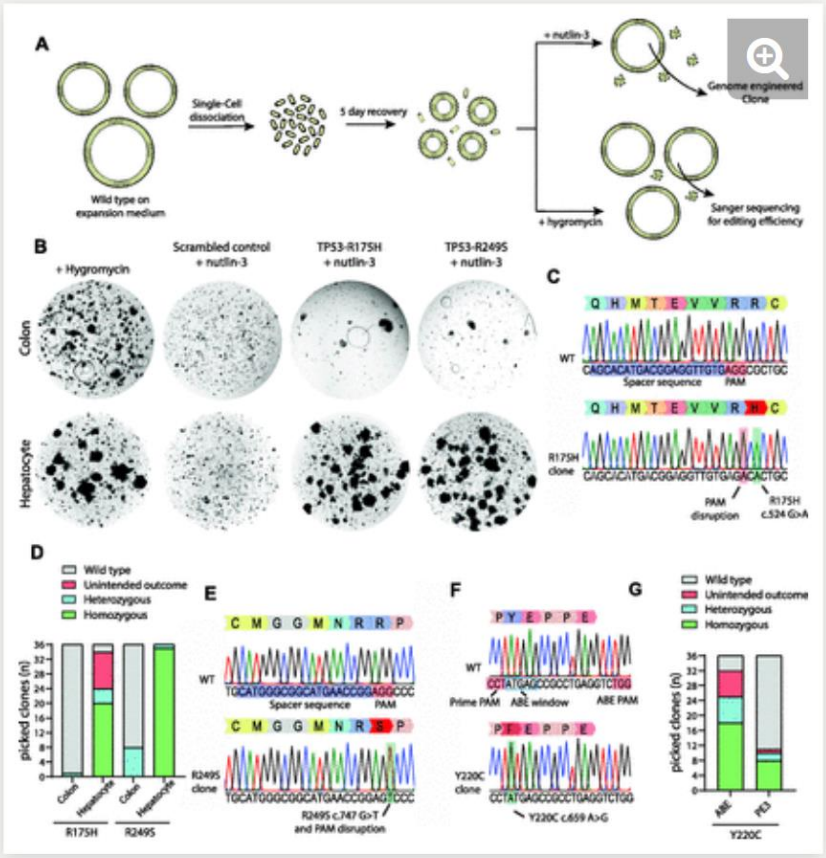
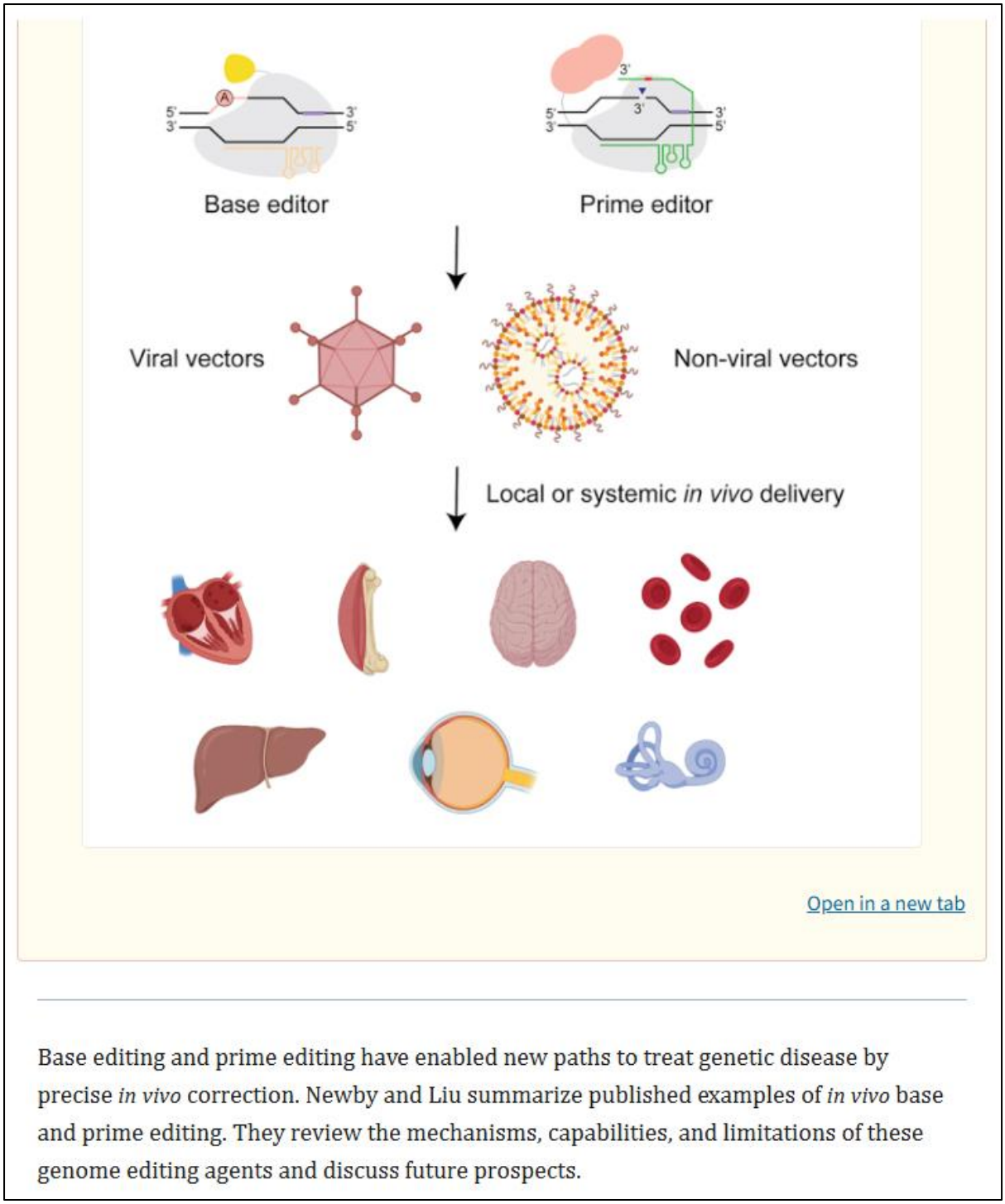


Figure 2.

Download figure | Open in new tab | Download PowerPoint

Prime editing enables generation of oncogenic mutations in organoids.
(A) Strategy to generate *TP53*-mutated human organoids. **(B)** Bright-field images of prime-editing experiments targeting the *TP53*-R175H and *TP53*-R249S mutations compared with a negative scrambled sgRNA control and hygromycin resistance. **(C)** Sanger sequencing trace of selected clonal organoids harboring the *TP53*-R175H mutation compared with WT. **(D)** Prime-editing efficiency on *TP53*-R175H and *TP53*-R249S as determined by Sanger sequencing on hygromycin-resistant clones. **(E)** Sanger sequencing trace of selected clonal organoids harboring the *TP53*-R249S mutation compared with WT. **(F)** Sanger sequencing trace of selected clonal organoids harboring the *TP53*-Y220C mutation compared with WT. **(G)** Adenine base editing versus prime-editing efficiency on the *TP53*-Y220C mutation as determined by Sanger sequencing of hygromycin-selected clones. Protospacer adjacent motifs are shown in red and guide-RNA sequences are shown in blue.

Figure 7. Prime editing enables generation of oncogenic mutations in organoids (Geurts et al., (2021), Figure 2, Evaluating CRISPR-based prime editing for cancer modelling and CFTR repair in organoids - PMC).



Base editing and prime editing have enabled new paths to treat genetic disease by precise *in vivo* correction. Newby and Liu summarize published examples of *in vivo* base and prime editing. They review the mechanisms, capabilities, and limitations of these genome editing agents and discuss future prospects.

Figure 8. Graphical abstract (Newby and Liu (2021), In vivo somatic cell base editing and prime editing - PMC).

Table 2. Comparison of advantages and disadvantages of CRISPR/Cas9, base editing and prime editing systems (Godbout et al., 2023, Table 1, Prime Editing for Human Gene Therapy: Where Are We Now? - PMC).

Comparison of advantages and disadvantages of CRISPR/Cas9, base editing, and prime editing systems.

	CRISPR/Cas9	Base Editing	Prime Editing
Off-target effects	Significant off-target effects • Possibility of non-specific indels at DSB site [21]; • DNA donor template can lead to plasmid integration in the genome; • Possible genome-wide off-targets.	Little or no off-target effects • No DSB; • Bystander base edits within a narrow window of 4–10 nt [22]; • Genome-wide off-targets studies need to be made.	Little or no off-target effects • No DSB; • No bystander edits; • Genome-wide off-targets studies need to be made.
Flexibility	• Can introduce insertions, deletions, and all types of substitutions.	• Can introduce C > T, G > A, A > G, T > C and C > G substitutions only. • The consideration of bystander edits makes base editing more stringent on the possible sites [22].	• Can introduce insertions, deletions, and all types of substitutions. • Less stringent PAM requirements [23].
Programmability [1]	Only if a DNA donor template is given	Yes	Yes
Efficient in vivo delivery	Currently possible	Currently possible (but more difficult than CRISPR/Cas9 because of its larger size)	Need to be improved (too big for conventional vehicles)

[1] Possibility to determine the issue of editing.

Feedback

8 Exosome-Based Biomarkers in Liquid Biopsy

8.1 Technology Overview

Exosomes carry bioactive molecules (e.g. nucleic acids, proteins) and are effective liquid biopsy biomarkers with applications to a range of disease diagnostics and prognosis.

As outlined by Li et al. (2022) (see also Figure 9, digital abstract):

> "Exosomes are membrane-defined extracellular vesicles (EVs) approximately 40–160 nm in diameter that are found in all body fluids including blood, urine, and saliva. They act as important vehicles for intercellular communication between both local and distant cells and can serve as circulating biomarkers for disease diagnosis and prognosis. Exosomes play a key role in tumour metastasis, are abundant in biofluids, and stabilize biomarkers they carry, and thus can improve cancer detection, treatment monitoring, and cancer staging/prognosis. Despite their clinical potential, lack of sensitive/specific biomarkers and sensitive isolation/enrichment and analytical technologies has posed a barrier to clinical translation of exosomes."

A range of clinical trials are being conducted in this area (e.g. WHO clinical trial registry reports 11 clinical trials when using search terms exosome liquid biopsy[75]).

Several commercial platforms are available for exosome isolation and analysis (e.g. ExoDx by Bio-Techne).

8.2 Potential Healthcare Applications

- **Cancer diagnostics and monitoring –** allows for non-invasive tumour diagnosis (see also Yu et al., 2023). Due to the relative ease of sample compared to tissue biopsies, the test is safer for the patient and also multiple testing would allow for ease of disease monitoring such as recurrence.
- **Neurodegenerative diseases:** e.g. for Parkinson's Disease[76] [77].

8.3 Evidence and Readiness

Regulatory status as outlined by Li et al., 2022:

> "LB cancer tests approved by the Food and Drug Administration (FDA) analyse specific targets in the three best-characterized LB biomarker types: circulating tumour cells (CTCs), circulating tumor DNA (ctDNA), or cell-free RNA (cfRNA) released by apoptotic and necrotic tumor cells. The FDA has now approved several LB cancer tests, including four that detect ctDNA target sequences, five that detect cfDNA targets, and one CTC test. The FDA has cleared five liquid biopsy tests for solid tumors in "general tumor profiling" or as "companion diagnostics" intended to aid clinicians in identifying patients who may benefit from targeted drug therapies".

In Australia, recent MSAC applications have involved cfDNA testing from whole blood in breast cancer and NSCLC (e.g. MSAC application 1782 and 1798) (see Australian Genomics response[78]).

Identification by International Horizon Scanning: CADTH report in 2019 on cancer screening included Exosome based liquid biopsy[79].

8.4 Market and Industry Engagement

Commercial availability:

- **Exosome diagnostics, ExoDx Prostate test**: FDA approved, using Exosome[80]. Evidence that test is a predictor of outcomes for high-grade prostate cancer (Tutrone et al., 2024).

---

[75] https://trialsearch.who.int/
[76] https://shakeitup.org.au/brain-derived-exosome-biomarkers-as-a-liquid-biopsy-for-parkinsons-disease/
[77] https://www.creative-biolabs.com/exosome/neurological-diseases-diagnosis-applied-exosomes.htm
[78] Response-to-MSAC-Application-1782-Consultation-Survey.pdf
[79] An Overview of Liquid Biopsy for Screening and Early Detection of Cancer
[80] https://www.exosomedx.com/news-events/fda-grants-breakthrough-device-designation-bio-technes-exodx-prostate-intelliscore-epi

- **FoundationOne Liquid CDx:** FDA approved[81].
- **Guardant360 CDx:** FDA approved. Includes biomarkers for common cancer types – lung, breast, colorectal, prostate[82].
- Creative Biolabs – provide services related to discovery and research of exosome markers[83].

8.5 Implementation Challenges and Barriers

Regulatory and ethical concerns:

- FDA has approved the FoundationOne Liquid CDx and the Guardant360 CDx.
- No relevant registrations on the TGA registry.

Infrastructure requirements:

- Trained workforce re processing of samples.
- Capital equipment.
- Bioinformatics.
- Pathologists.

Accuracy issues:

- Test has a potential false-positive or false-negative result risk (e.g. due to tumour non-shedding), with the FDA recommending a tissue biopsy test to confirm a negative result from Guardant360 CDx and FoundationOne Liquid CDx)[84].

8.6 Cost and Economic Considerations

Test cost:

- FoundationOne CDx cost is AU$3,590[85].

Potential savings and efficiency gains:

- Non-invasive liquid biopsies can reduce the need for tissue biopsies (resulting in fewer hospital visits and diagnostic tests).
- With suitable training, technology could be implemented outside of specialised metro cancer centre hubs, including in rural/remote areas (noting follow up tissue biopsy for histological purposes may still be required, which can necessitate travel).
- Early disease detection can lead to early clinical decision-making and treatment.

8.7 Strategic Priority for Australia

Australia's Medical Research Future Fund (MRFF) has invested in liquid biopsy research (not specifically exosome[86]. Exosome-based biomarkers are being explored by AIBN. This project endeavours to create innovative nanotechnologies and nanofabrication strategies, resulting in a highly sensitive and robust nanoarchitectonics integrated automated platform for the molecular profiling of exosomes at a single-particle resolution[87].

[81] FoundationOne Liquid CDx | Foundation Medicine
[82] Guardant360®: Comprehensive Liquid Biopsy Test
[83] Exosome Profiling Services - Creative Biolabs
[84] The Evolution of Liquid Biopsy in Cancer Care - The ASCO Post
[85] solidtumour_menu_2023_sg_final-shg-mkt-0156-00.pdf
[86] https://www.petermac.org/about-us/news-and-events/news/details/peter-mac-awarded-3-million-mrff-genomics-grant
[87] https://aibn.uq.edu.au/project/nanoarchitectured-platform-molecular-profiling-exosomes-single-particle-resolution

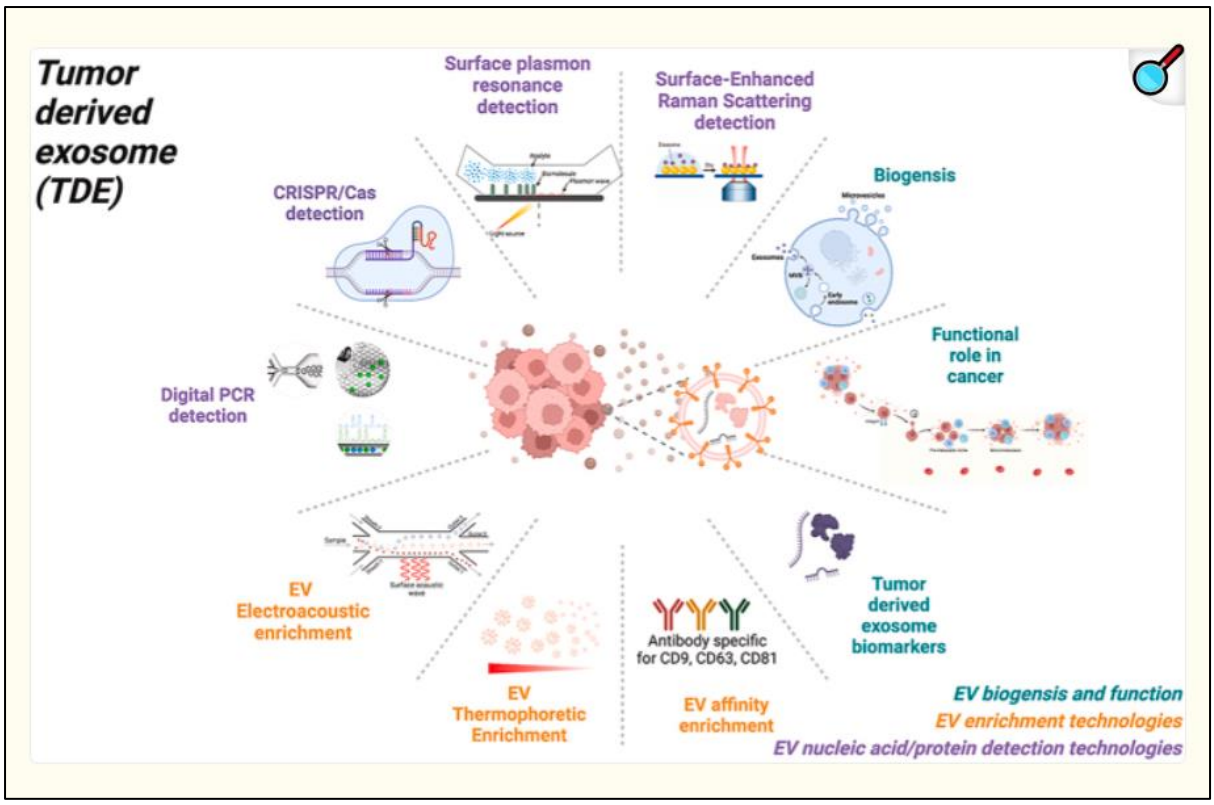


Figure 9. Digital abstract (Li et al., (2022), Advanced technologies for molecular diagnosis of cancer: State of pre-clinical tumour-derived exosome liquid biopsies - PMC).

9 Digital Twin

9.1 Technology Overview

In the context of genomics and healthcare, a digital twin is a dynamic, virtual representation of an individual that brings together a variety of data including genomics, physiology and other environmental information. This allows the simulation of various health trajectories and disease progression (Katsoulakis et al., 2024). (see also Figure 10 for a graphical depiction).

Disease progression can differ between different patients with very similar diagnoses or at different disease stages. Variation can depend upon both genetic factors (including both genetic risk factors and disease-causing variants) and environmental factors including exposure to pollution, lifestyle factors (e.g. diet) and inequitable health care (Li et al., 2025). Identifying factors that would predispose or protect against complex disease in a patient's lifetime would align with many health strategies around preventive and equitable health (for examples Australia's National Preventive Health Strategy 2021-2030). The use of digital twin models of genomic medicine may be important to achieving such goals.

As outlined by Boulos and Zhang (2021), a broad conceptualization is:

> "Conceptually, a digital twin is a digital replica or representation of a physical object, process, or service, but also much more than that. It is a virtual model (data plus algorithms) with special features not found in traditional models and simulations, one that dynamically pairs the physical and digital worlds, and leverages modern technologies, such as smart sensor technology, data analytics, and artificial intelligence (AI) to detect and prevent system failures, improve system performance, and explore innovative opportunities."

The technology is currently in early adoption, with proof-of-concept studies demonstrating its feasibility in oncology and rare diseases.

In the context of precision medicine, Domenico et al., 2025 (see also Figure 11) defined the digital twin model as "A digital twin is an in-silico framework that replicates a biological cell, sub-system, organ, or a whole organism, with a transparent predictive model of their relevant causal mechanisms and response to interventions.".

9.2 Potential Healthcare Applications

Personalized treatment simulations: drug selection and dosing (Bjornsson et al., 2019).

Oncology: Simulating tumour evolution (Kemkar et al., 2024).

In silico clinical trials (Moingeon et al., 2023).

9.3 Evidence and Readiness

Regulatory status. As outlined in Li et al, 2025:

> "The FDA has implemented pre-qualification programs to speed up the regulatory processes of digital tools. Additionally, protecting the privacy and rights of an individual's DT is crucial, especially as it incorporates sensitive, multiscale data. The analyses for example federated data analysis with evolving computational approaches that protect privacy even in population-based studies. A white paper from the US National Academy of Science recently recommended that the potential of digital twins to "accelerate scientific discovery and revolutionize health care" would merit an integrated agenda to harmonize research across sectors and focus efforts on realistic applications."

9.4 Market and Industry Engagement

Key industry players:

- ExactCure (merged with Quantum Genomics[88], see https://www.rootsanalysis.com/key-insights/5-leading-digital-twin-companies.html).

[88] https://www.rootsanalysis.com/key-insights/5-leading-digital-twin-companies.html

9.5 Implementation Challenges and Barriers

Regulatory and ethical concerns:

- Lack of regulatory frameworks for AI in healthcare, in general, and AI-driven digital twins, specifically.
- Limited numbers of clinical trials in this area specific to genomics[89] .

Technical limitations:

- High computational demands for real-time AI-driven simulations.
- Integration of high detail genomics multi-omics data with electronic health records (EHRs) remains a challenge (see later report).

Workforce Issues:

- Need for education of concept in context of genomics for health practitioners, data scientists and bioinformaticians and how to interact with the models. Could contribute to being a learning tool to further leverage mainstreaming of genomics into other medical specialties. Digital twin technology could be integrated into clinical decision support tools.

9.6 Cost and Economic Considerations

Cost of development:

- Developing digital twin models requires significant investment – estimated between US$50,000 and $500,000 at a high level (https://www.toobler.com/blog/digital-twin-cost-development).
- "The global digital twins in healthcare market size are estimated to grow from US$1.9 billion in 2024 to US$33.4 billion in 2035[90] .

Potential savings and efficiency gains:

- Reducing costs by using in silico clinical trials.
- Provide more effective treatment options and preventative health measures during the lifetime of a patient.

9.7 Strategic Priority for Australia

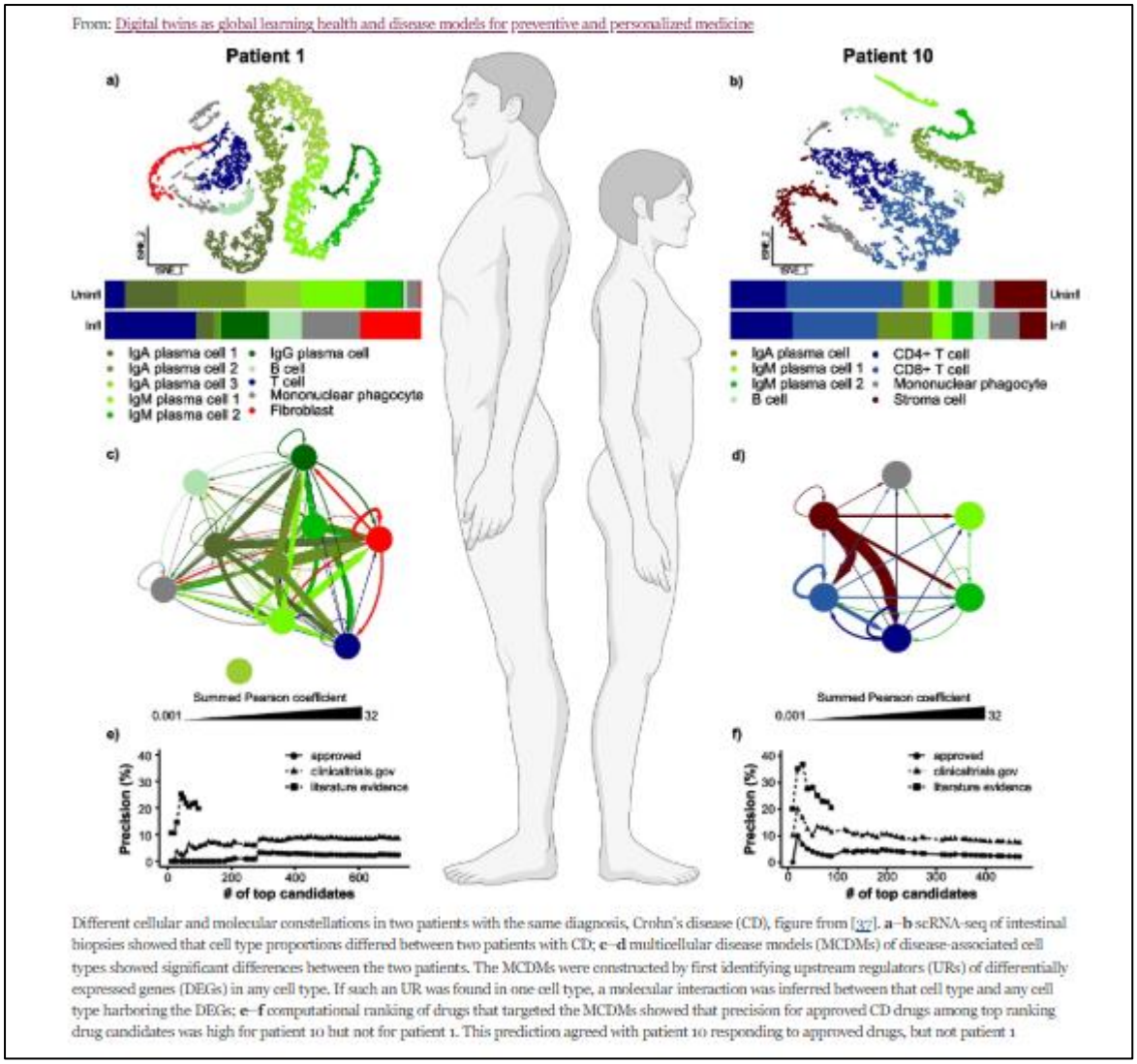
Digital Twin in genomic medicine aligns generally with the *National Digital Health Strategy* (2023-2028). One of the specific areas indicated (pg 49) relates to the use of Digital Twin:

- "Plan for emerging data sources and technology such as artificial intelligence, spatial data, genomics: Australian governments, researchers, industry and healthcare providers will actively prepare for and embrace scientific innovations and cutting-edge technologies like AI, machine learning, quantum technology and big data analytics. These advancements will support greater system efficiencies, quality improvement and early intervention and prevention, while observing the necessary regulatory and ethical frameworks."

Research groups at CSIRO are investigating digital twin applications more broadly (i.e. non-medical)[91]. Omics-based digital twin applications are being developed in Australia in the context of paediatric precision medicine (WIcksamasinghe et al., 2024)

The ability to simulate different disease types in difference genetic backgrounds for disease prevention, aligns with the *National Preventive Health Strategy*[92].

[89] https://ctv.veeva.com/study/integrating-whole-genome-sequencing-and-digital-twins-into-the-management-of-hypercholesterolemia-in
[90] https://www.rootsanalysis.com/reports/digital-twins-in-healthcare-market.html
[91] Digital Twin - CSIRO
[92] https://www.health.gov.au/resources/publications/national-preventive-health-strategy-2021-2030?language=en



Different cellular and molecular constellations in two patients with the same diagnosis, Crohn's disease (CD), figure from [37]. **a**–**b** scRNA-seq of intestinal biopsies showed that cell type proportions differed between two patients with CD; **c**–**d** multicellular disease models (MCDMs) of disease-associated cell types showed significant differences between the two patients. The MCDMs were constructed by first identifying upstream regulators (URs) of differentially expressed genes (DEGs) in any cell type. If such an UR was found in one cell type, a molecular interaction was inferred between that cell type and any cell type harboring the DEGs; **e**–**f** computational ranking of drugs that targeted the MCDMs showed that precision for approved CD drugs among top ranking drug candidates was high for patient 10 but not for patient 1. This prediction agreed with patient 10 responding to approved drugs, but not patient 1

Figure 10. Digital Twin summary (from Li et al., (2025), Figure 2, Digital twins as global learning health and disease models for preventive and personalized medicine - PMC).

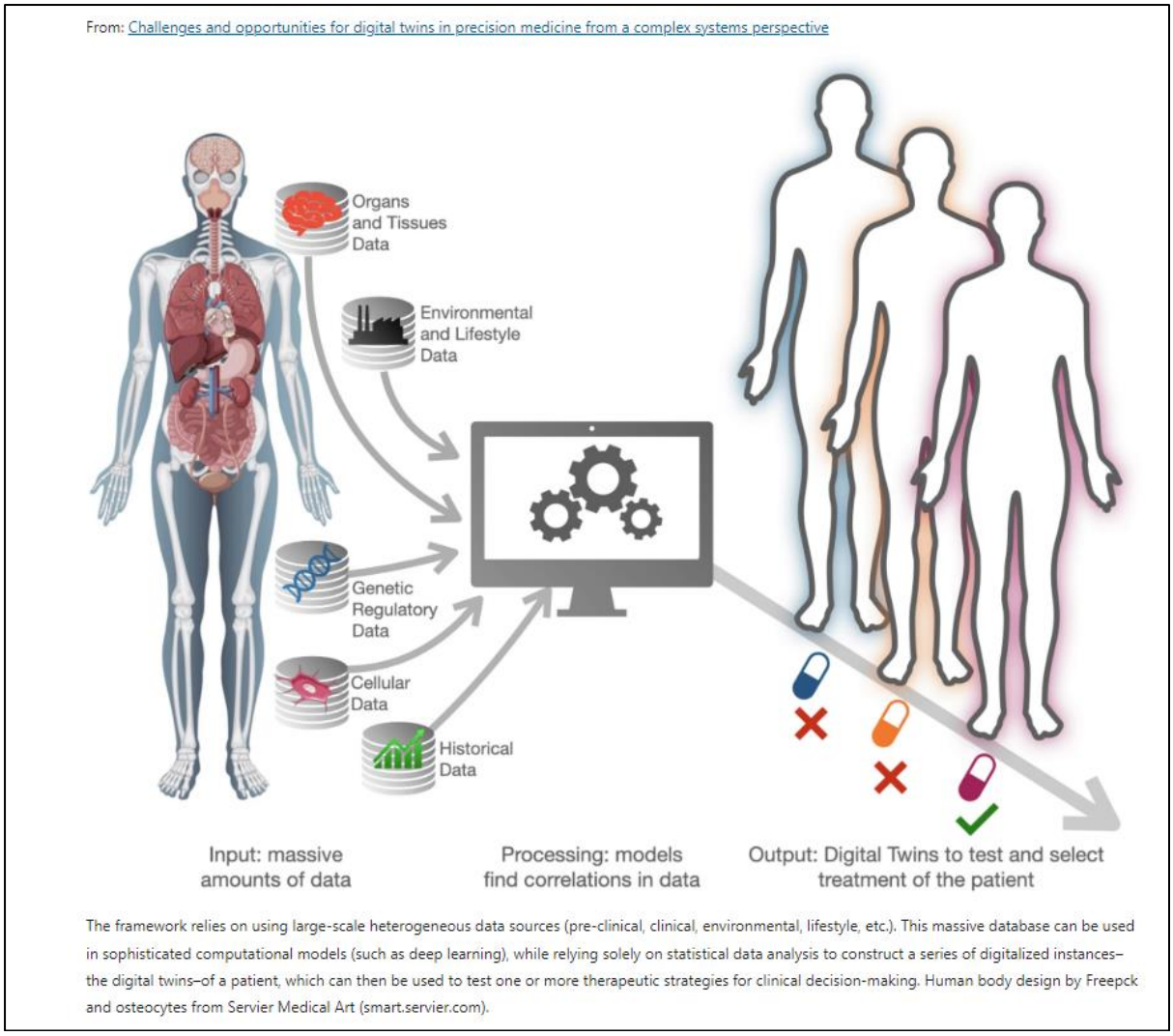


Figure 11. Precision medicine standard approach for digital twins (De Domenico et al., (2025), Figure 1, Challenges and opportunities for digital twins in precision medicine from a complex systems perspective - PMC).

10 Epigenetic Therapies for Cancer and Aging

10.1 Technology Overview

Epigenetic therapy involves using drugs or other interventions to modify gene expression patterns, potentially treating diseases by targeting epigenetic mechanisms like DNA methylation and histone modifications. Unlike genetic mutations, these changes are often reversible, offering a chance to restore normal cellular function.

As outlined by Dai et al., (2024) (see also Figure 12):

> "Epigenetics governs a chromatin state regulatory system through five key mechanisms: DNA modification, histone modification, RNA modification, chromatin remodelling, and non-coding RNA regulation. These mechanisms and their associated enzymes convey genetic information independently of DNA base sequences, playing essential roles in organismal development and homeostasis. Conversely, disruptions in epigenetic landscapes critically influence the pathogenesis of various human diseases. This understanding has laid a robust theoretical groundwork for developing drugs that target epigenetics-modifying enzymes in pathological conditions. Over the past two decades, a growing array of small molecule drugs targeting epigenetic enzymes such as DNA methyltransferase, histone deacetylase, isocitrate dehydrogenase, and enhancer of zeste homolog 2, have been thoroughly investigated and implemented as therapeutic options, particularly in oncology. Additionally, numerous epigenetics-targeted drugs are undergoing clinical trials, offering promising prospects for clinical benefits."

A recent study investigating epigenetics of older breast cancer survivors by Rentscher et al (2023) concluded that: "*Older breast cancer survivors, particularly those exposed to chemotherapy, showed greater epigenetic aging than controls that may relate to worse outcomes. If replicated, measurement of biological aging could complement geriatric assessments to guide cancer care for older women.*"

10.2 Potential Healthcare Applications

Cancer Care: DNMT inhibitors and HDAC inhibitors in cancer care. **Combination Therapies:** Epigenetic drugs enhancing immune checkpoint inhibitors (e.g. PD-1/PD-L1 inhibitors). (see also Figure 12).

Aging and Cancer care: above study by Rentscher et al., (2023) found greater epigenetic aging in breast cancer chemotherapy survivors, compared to controls.

Other rare disease applications: HDAC inhibitors like butyrate have shown some proof-of-concept efficacy in certain settings, like **sickle cell disease and beta-thalassemia** (Feehley et al., 2023).

10.3 Evidence and Readiness

Regulatory status: Approved Epigenetic Drugs: e.g. Azacitidine by FDA and EMA (Gnysyka et al., 2013).

- While there are eight FDA-approved and marketed epigenetic therapies with six to treat hematologic malignancies and two approved for use in solid tumours (Table 3, see below), trials of current epigenetic therapies have shown greater toxicity than expected, likely due to low specificity. (Feehley et al., 2023).

Clinical Trials:

- WHO clinical trial registry: 8 trials for "epigenetics and aging", 15 trials for "epigenetics and cancer".

Adoption by Global Initiatives:

- WHO International Agency for Research on Cancer has a Epigenomics and Mechanisms branch https://www.iarc.who.int/branches-egm-research/ (see https://www.iarc.who.int/branches-egm-research/).

10.4 Market and Industry Engagement

Key Industry Players: AstraZeneca, Inherent Biosciences[93]

[93] https://www.labiotech.eu/best-biotech/epigenetics-companies

10.5 Implementation Challenges and Barriers

Regulatory & Ethical Considerations:

- Long-term effects of epigenetic modifications remain unknown (adverse side-effects)[94].
- Ethical concerns regarding epigenetic interventions in aging – relating to equity of access and fairness.

Workforce: Could be challenges to introduce Epigenetics into clinical care models, especially for non-genetic specialists.

10.6 Cost and Economic Considerations

Current Costs:

- FDA-approved epigenetic drugs: **Source price per treatment.**
- Development costs for novel therapies remain high.

Economic Impact:

- Potential **cost savings** by reducing chemotherapy resistance.
- **Aging research investments** could extend healthy lifespan, reducing healthcare costs.

10.7 Strategic Priority for Australia

In addition to the goals of the National Health Genomics Policy Framework refresh, the application of epigentic therapies in the context of genomic medicine will also broadly align with the Australian Cancer Plan (2023-2033)[95]. Specifically, it will relate to precision oncology and the need for targeted therapies. In terms of access to safe, affordable and effective therapies, epigenetic therapies also would relate to the policy framework provided by the National Medicines Policy Update[96] (2022).

[94] https://www.sciencedirect.com/science/article/abs/pii/S0344033823003886
[95] Australian Cancer Plan | Cancer Australia
[96] National Medicines Policy | Australian Government Department of Health and Aged Care

Table 3. Summary of epigenetic approaches and molecules (Feehley et al., (2023), Table 1. Drugging the epigenome in the age of precision medicine - PMC)).

Epigenetic effector class	Drug	Modality	Marketed/developed by	Status/uses
1st generation DNA methyltransferase inhibitor	5-Azacytidine (Onureg, Vidaza)	Small molecule	Bristol Myers Squibb	FDA approved for the treatment of myelodysplastic syndrome
	5-Aza-2′-deoxycytidine (decitabine; Inqovi)	Small molecule	Astex/Taiho	FDA approved for the treatment of myelodysplastic syndrome
	Pseudoisocytidine	Small molecule	Various	Clinical development discontinued for hepatotoxicity concerns
	5,6-Dihydro-5-azacytidine (DHAC)	Small molecule	Various	Clinical development discontinued for cardiotoxicity concerns
2nd generation DNA methyltransferase inhibitor	Guadecitabine (SGI-110)	Small molecule	Astex Pharmaceuticals	Development discontinued due to lack of Phase 3 efficacy
	Fluorocyclopentenylcytosine (RX-3117, TV-1360)	Small molecule	Rexhan Pharmaceuticals (Ocuphire Pharma)	Clinical development paused due to weak Phase 2a data
1st generation histone deacetylase inhibitors	Suberoylanilide hydroxamic acid (SAHA, vorinostat, Zolinza)	Small molecule	Merck	FDA approved for the treatment of cutaneous T cell lymphoma
	Romidepsin (Istodax)	Small molecule	Bristol Myers Squibb	FDA approved for the treatment of cutaneous T cell lymphoma; accelerated approval for peripheral T cell lymphoma withdrawn
	Sodium butyrate/butyric acid	Small molecule	Various	Research compound to explore HDAC inhibition in model systems
2nd generation histone deacetylase inhibitors	Belinostat (Beleodaq)	Small molecule	Acrotech Biopharma	FDA approved for peripheral T cell lymphoma
	Panobinostat (Farydak)	Small molecule	Secura Bio	FDA accelerated approval for peripheral T cell lymphoma withdrawn
	Entinostat	Small molecule	Syndax	Clinical development paused due to lack of Phase 3 efficacy
	Tucidinostat (Chidamide, Epidaza or Hiyasta)	Small molecule	Chipscreen Biosciences	CFDA approved for peripheral T cell lymphoma; PMDA approved for adult T cell leukemia-lymphoma
Histone methyltransferase inhibitors	Pinometostat	Small molecule	Epizyme (Ipsen)	Clinical development discontinued due to lack of efficacy
	Tazemetostat (Tazverik)	Small molecule	Epizyme (Ipsen)	FDA approved for relapsed/refractory follicular lymphoma and epithelioid sarcoma
	GSK3326595	Small molecule	GlaxoSmith Kline	Clinical development paused
Lysine demethylase inhibitors	Tranylcypromine	Small molecule	Various	FDA approved for depression
	Ladademstat (ORY-1001)	Small molecule	Oryzion Genomics	In clinical development for multiple tumor types
	GSK2879552	Small molecule	GlaxoSmith Kline	Clinical development discontinued due to unfavorable risk/benefit to patients
Bromodomain inhibitors	Molibresib	Small molecule	GlaxoSmithKline	Clinical development discontinued
	Pelabresib (CPI-06160)	Small molecule	Constellation Pharmaceuticals (MorphoSys)	Clinical development ongoing in myelofibrosis (Phase 3)
	Apabetalone (RVX-208)	Small molecule	Resverlogix	Clinical development ongoing in cardiovascular, infectious disease (COVID-19), and renal disease (Phase 3)
IDH inhibitor	Ivosidenib (Tibsovo)	Small molecule	Servier	FDA approved for the treatment of acute myeloid leukemia and cholangiocarcinoma
	Enasidenib (Idhifa)	Small molecule	Bristol Myers Squibb/Servier	Relapsed/refractory acute myeloid leukemia
Precision epigenomic modulators	OTX-2002	Epigenomic programming	Omega Therapeutics	IND cleared by FDA; clinical trial to begin in 2H2022
	ST-502	Zinc finger protein transcription factor	Sangamo Therapeutics	Preclinical development ongoing

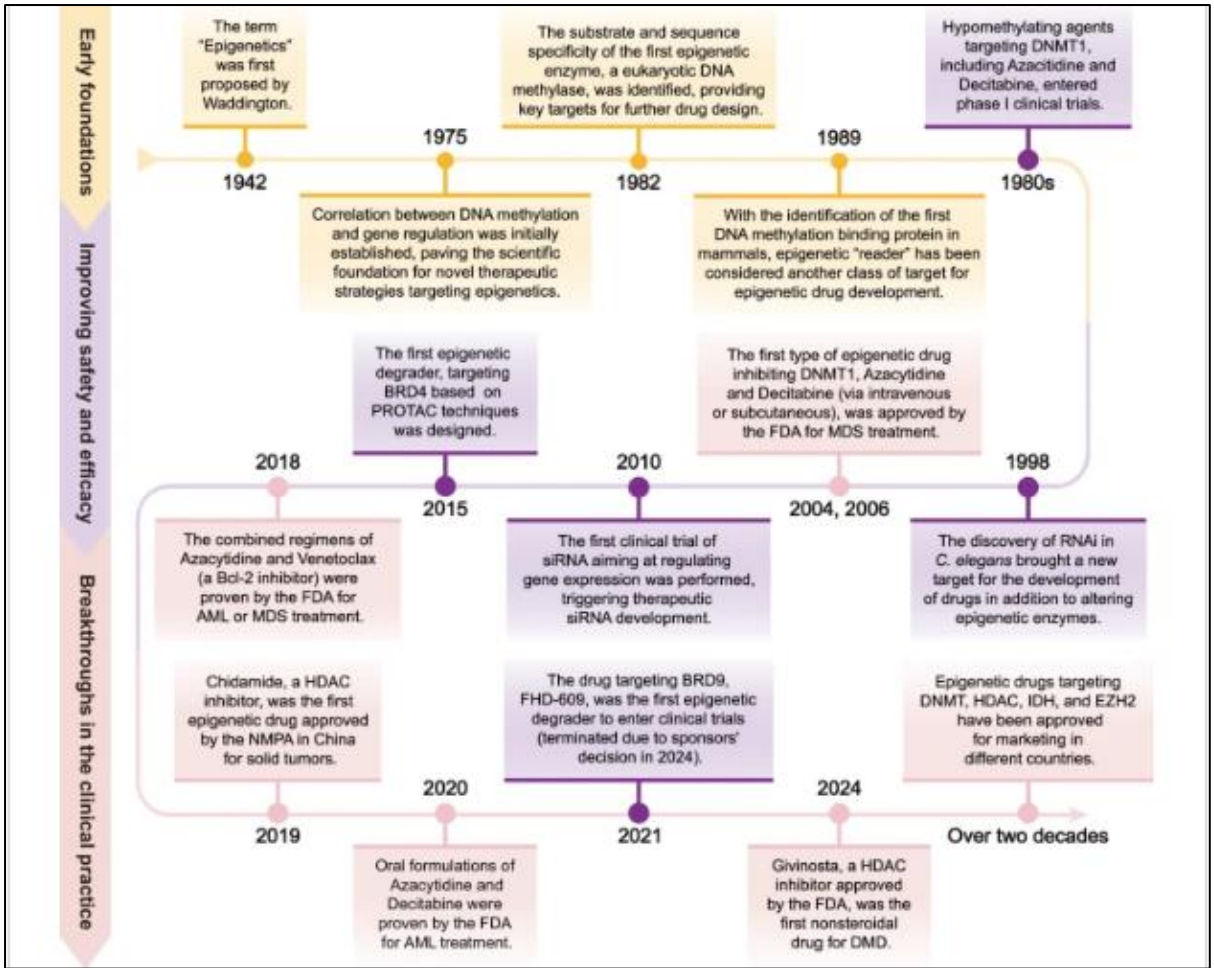


Figure 12. Timeline of major discoveries and advances in epigenetic research, Dai et al, (2025), Figure 2, Epigenetics-targeted drugs: current paradigms and future challenges - PMC.

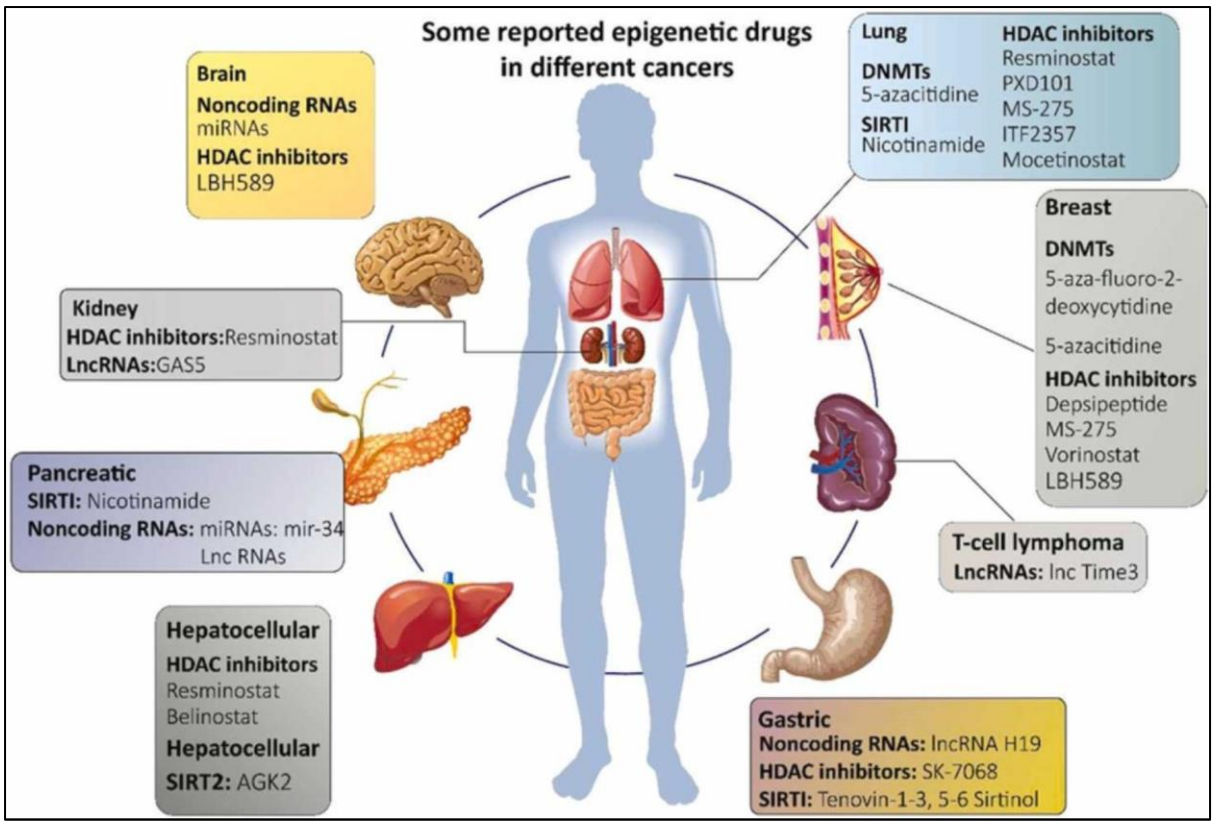


Figure 13. Some reported epigenetic drugs in cancer (Farani et al., (2023), graphical abstract, Epigenetic drugs as new emerging therapeutics: What is the scale's orientation of application and challenges? - ScienceDirect).

11 Single-Cell Sequencing

11.1 Technology Overview

This technology has been in existence since 2009 and was named the "Method of the Year in 2013" (Nature Methods editorial 2014). Over the last decade, clinical applications of the technique have proliferated.

Single-cell sequencing enables high-resolution analysis of genomic, transcriptomic, and epigenomic landscapes at the individual cell level. Proteomics is another possibility at the single cell level.

As outlined by Tang et al., (2019):

> "Single-cell sequencing technologies refer to the sequencing of a single-cell genome or transcriptome, to obtain genomic, transcriptome or other multi-omics information to reveal cell population differences and cellular evolutionary relationships. Traditional sequencing methods can only get the average of many cells, unable to analyze a small number of cells and lose cellular heterogeneity information. Compared with traditional sequencing technology, single-cell technologies have the advantages of detecting heterogeneity among individual cells, distinguishing a small number of cells, and delineating cell maps. In 2013, it was named "Nature Methods" as the annual technology. However, early single-cell sequencing limited its widespread use due to its high cost. But as the research progressed, many new single-cell sequencing methods were developed that reduced the cost threshold for single-cell sequencing. Nowadays, single-cell sequencing technology is increasingly used in various fields."

Note there is considerable overlap to other related technologies and applications including liquid biopsies, epigenetics, multiomics. For an overview of clinical applications refer to Jovic et al., 2022 (also Figure 14 below).

11.2 Potential Healthcare Applications

Many applications across various disease types – powerful tool for diagnostics and prognostics, including tumour heterogeneity.

Precision Oncology: aids in selected therapies based on single cell sequencing. For example, Peng et al., 2019 used single cell sequencing to indicate distinct tumour subpopulations in ductal pancreatic adenocarcinoma that relates to tumour invasiveness and therapy resistance. The technique will aid in pancreatic anticancer treatments such as targeted therapy and immunotherapy. Fustero-Torre et al., (2021) describe a computational method (Beyondcell) that permits identifying tumour subpopulations with distinct drug response in scRNA-seq tumour data, which aids in guidance of drug selection.

Tumour micro-environments: techniques such as NeighbourNet that investigate cell-specific co-expression networks to investigate tumour micro-environments[97].

Vaccine Development: single cell multiomics was used in establishing immune cell profiles of patients post COVID19 infection (Zhou et al., 2023).

Rare disease diagnosis: Single cell sequencing permits rare cells to be more accessible to analysis such as the diagnosis or rare somatic mutations that can only be determined by analysis of late-emerging subclones. The single-cell genomic resolution technique was used by Leung et al., (2017) in a study of metastatic colorectal cancer and is applicable in studies of somatic mosaicism in other diseases.

Stem cell characterization: Single cell sequencing allows for heterogeneity to be investigated in aspects of stem cell research, relating to multipotency; immunoregulatory functions; response to culture conditions and use in clinical trials (for example see review of mesenchymal stem cells and single cell sequencing in Zheng et al., (2020).

[97] NeighbourNet: Scalable cell-specific co-expression networks for granular regulatory pattern discovery – Lê Cao Lab

Type 2 Diabetes: Single-cell transcriptome profiling allowed for endocrine and exocrine cells of pancreatic islets, in healthy individuals and those with Type 2 Diabetes (Segerstolpe et al., 2016). Gene expression differences were also found to be correlated to patient BMI.

11.3 Evidence and Readiness

Regulatory status: technique has been used in FDA regulated clinical trials (e.g. Mission Bio's Tapestri platform[98]).

Clinical Trials: Multiple studies explore SCS in cancer. For example, on WHO clinical trial registry, (https://trialsearch.who.int/) 33 trials using search terms "single cell sequencing cancer".

Sanger's single cell sequencing centre[99]

Chan Zuckerberg initiative: supports Scale Bio's 100 million cell challenge[100].

Bioinformatics and software tools: available for data processing and visualization (e.g. Bioconductor packages Seurat (NYU, R package for scRNA-seq[101]).

11.4 Market and Industry Engagement

Selected industry technology providers:

- 10x Genomics (Chromium Xo single cell)[102].
- NanoString Technologies: CosMX SMI for spatial multiomics[103] .
- Illumina: recently acquired Fluent BioSciences[104].
- BD Bioscences BD Rhapsody Single-Cell Multiomics System[105].
- Oxford Nanopore Technologies: promethION 24[106] .
- Mission Bio: Tapestri platform workflow for sc solid tumour profiling[107].

11.5 Implementation Challenges and Barriers

Technical Complexity: Requires high-throughput sequencing, bioinformatics (and associated compute and data storage), and single-cell isolation technologies. Could be scalability issues in translation from research to clinic.

Cost and Infrastructure: Requires significant set up costs and computing power.

11.6 Cost and Economic Considerations

Sequencing Costs: US$1614 to $3228 per sample[108].

Clinical Adoption Barriers: Costly instrumentation and bioinformatics expertise required.

Potential Savings: There is a wide range of clinical applications (above) although no systematic review of potential health economics associated with scRNAseq.

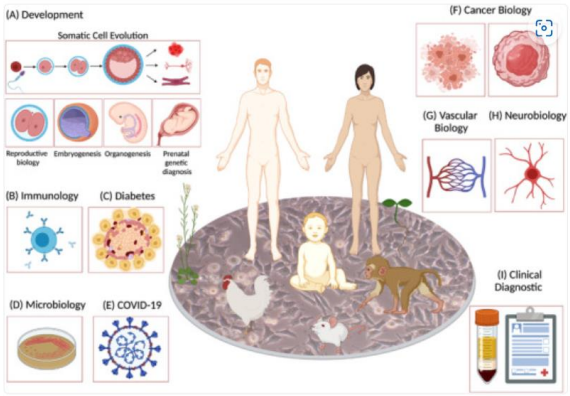
11.7 Strategic Priority for Australia

Fits within Genomics Australia's precision medicine agenda, including cancer.

---

[98] Servier leverages Mission Bio's Tapestri® Platform to uncover AML resistance mechanisms in pivotal TIBSOVO® (ivosidenib) clinical trial | Mission Bio
[99] https://www.sanger.ac.uk/collaboration/sanger-institute-ebi-single-cell-genomics-centre/
[100] https://www.news-medical.net/news/20240919/Chan-Zuckerberg-initiative-joins-Scale-Bios-e28098100-Million-Cell-Challengee28099-to-accelerate-single-cell-genomics-research.aspx
[101] GitHub - satijalab/seurat: R toolkit for single cell genomics
[102] Chromium Xo instrument – 10x Genomics
[103] CosMx SMI Overview - Single-Cell Imaging - NanoString
[104] Enabling single-cell sequencing for every laboratory
[105] Single-Cell Multiomics Systems | BD Biosciences
[106] Single-cell sequencing | Oxford Nanopore Technologies
[107] Mission Bio's Tapestri Solution for Solid Tumor Research
[108] Pricing – Sequencing Facility

Multiple centres with expertise in scRNAseq generation and analysis including (but not limited to) University of Queensland Genome Innovation Hub[109], The Walter and Eliza Hall Institute of Medical Research (Lewis et al., 2022) and the UNSW Ramaciotti Centre for Genomics[110], Garvan Institute of Medical Research[111].



Application of single-cell RNA sequencing technology. Single-cell RNA sequencing has been employed in different species (humans, animals, plants) to improve understanding of normal and disease models. A special note is placed on human health, and many single-cell RNA sequencing (scRNA-seq) methods are focused on understanding (A) development, (B) immunology, (C) diabetes, (D) microbiology, (E) SARS-CoV-2, (F) cancer biology, (G) vascular biology (H) neurobiology and (I) clinical diagnostics. Figure was created with BioRender with license for publication

Figure 14. Applications of single-cell RNA sequencing (Jovic et al., (2022), Figure 5, Single-cell RNA sequencing technologies and applications: A brief overview - PMC).

[109] Single-cell and short read sequencing - Genome Innovation Hub - University of Queensland
[110] Ramaciotti Centre for Genomics | School of Science - UNSW Sydney
[111] Computational Genomics Lab | Garvan Institute of Medical Research

12 RNA-Based Therapies (including small interfering (siRNA) and mRNA vaccines)

12.1 Technology Overview

RNA-based therapies, including small interfering RNA (siRNA) and messenger RNA (mRNA), are expanding beyond COVID-19 vaccines (with the pandemic bringing this area to wider public attention) into treatments for cancer, rare diseases, and genetic disorders. siRNA therapeutics use RNA interference (RNAi) to silence specific genes, while mRNA therapies enable cells to produce therapeutic proteins.

siRNA (From Zhu et al., 2022):

> "RNAi is an endogenous cellular process inducing double-stranded (ds) RNAs -triggered degradation of particular RNA targets, which provide an intrinsic defensive mechanism against invading viruses and transposable elements. siRNAs are short dsRNAs (20-24 nt) with distinct structures containing 5'-phosphate/3'-hydroxyl endings and two 3'-overhang ribonucleotides on each duplex strand. siRNAs can induce RNAi in mammalian cells. Therefore, researchers can use such simple gene silencing tools to investigate gene function and advance disease therapy. Mechanistically, the endoribonuclease Dicer cuts dsRNAs and isolates the guide and passenger strands within the RNA-induced silencing complex (RISC). The argonaute2 (AGO2) protein degrades the passenger siRNA strand, whereas the guide siRNA strand directly binds to the target RNA, causing AGO2-mediated cleavage. Besides degrading cytoplasmic RNAs, siRNAs can also trigger chromatin remodelling and histone modifications in the nucleus when they bind to the promoter regions, resulting in transcriptional silence."

mRNAs and mRNA vaccine (from Zhu et al., 2022):

> "The concept of mRNA-encoded drugs was discovered in the 1990s when direct injection of IVT mRNA into the mouse skeletal muscle showed encoded protein expression. Preclinical research on IVT mRNA promotes the clinical development of mRNA-based vaccination against cancer and infectious disease. Mechanistically, injected mRNA vaccines are delivered into the cytoplasm of the host cell (typically antigen-presenting cells (APCs)) and are translated into the targeted antigens. Subsequently, the major histocompatibility complexes (MHCs) present the expressed antigens to the surface of APCs to activate B cell/antibody-mediated humoral immunity and CD4+ T/CD8+ cytotoxic T-cell-mediated immunity. Besides, injected mRNA encoding immunostimulants (cytokines, chemokines, etc.) can promote APC maturation and activation, thus inducing a T-cell-mediated response and improving the immune tumour microenvironment."

12.2 Potential Healthcare Applications

Oncology:

- **mRNA cancer** vaccines: Autogene cevumeran (BioNTech/Genentech) is in phase 1 and phase II clinical trials for resected pancreatic ductal adenocarcinoma (PDAC)[112]).
- **mRNA vaccine:** Moderna's mRNA-4157/V940, in development with Merck. A recent Lancet study determined the drug in combination with pembrolizumab had longer recurrence free survival compared to pembrolizumab alone (Weber et al., 2024) (see also Figure 15).
- **Small interfering RNA (siRNA) therapies, for example** TKM-080301 to target advanced hepatocellular carcinoma (El Dika et al., 2018).

Rare Genetic Disorders

- **RNA editing technologies** that use engineered guide RNAs and ADARs e.g. Shape Therapeutics, using the RNAfix platform[113]**.**

[112] Three-year Phase 1 Follow-Up Data for mRNA-based Individualized Immunotherapy Candidate Show Persistence of Immune Response and Delayed Tumor Recurrence in Some Patients with Resected Pancreatic Cancer | BioNTech
[113] Home - ShapeTX

- **Antisense Oligonucleotides**
  - Nusinersen (Spinraza) that targets the *SMN2* gene (Spinal Muscular Atrophy) (Finkel et al., 2017), FDA approved 2016[114].
  - Etepllirsen (Exondys 51) that targets the *DMD* gene (Duchenne muscular dystrophy) (Mendel et al., 2013), FDA approved 2016[115].
- **siRNAs,** small interfering RNAs that can silence expression of specific genes**.**
  - GIvosiran (Givlaari) that targets ALAS1 mRNA (Acute hepatic porphyria (AHP)) (Kuter et al., 2023), FDA approved 2019**[116]**.
  - Lumasiran (Oxlumo) that targets HAO1 mRNA (Primary Hyperoxaluria type 1 (PH1), FDA approval 2022**[117]**.
- **mRNA Replacement therapy**
  - mRNA-3705 (Moderna), which targets Methylmalonyl-CoA mutase (MUT) (clinical condition is Methylmalonic acidemia (MMA). Encodes a functional MUT protein. Chosen for FDA START program[118].
- **Splicing modulators**
- Branaplam (LM1070) in a small-molecule splicing modulator developed by Novartis. Although initially investigated for treatment of SMA, more recent clinical trials focused on Huntington's Disease. However, there were some safety issues, with Novartis suspending dosing in the VIBRANT-HD clinical tria[l]119.

12.3 Evidence and Readiness

Regulatory Approvals: COVID-19 mRNA vaccines widely adopted.

Patisiran which treats polyneuropathy (siRNA) approved by FDA/EMA.

Clinical Trials: Multiple ongoing trials for RNA-based cancer vaccines.

For example, searching the WHO clinical trial registry, there are 64 trials for siRNA (for example in retinoblastoma NCT06424301 and brain tumours PRN-jRCTc030190174).

International Horizon scanning initiatives: CADTH through their drug pipeline scan identified inclisivan in 2024 as a siRNA[120]. The NIHR Vaccine Innovation Pathway plays a crucial role in accelerating vaccine development and associated clinical trials[121]. PCORI has identified mRNA-based vaccines for RSV and influenza (see Emerging Innovation brief[122].

12.4 Market and Industry Engagement

Key Players:

- Moderna: e.g. COVID19 mRNA vaccines.
- BioNTech[123].
- Alnylam Pharmaceuticals: RNAi therapeutics[124].
- Arrowhead Pharmaceuticals. TRiM tm Platform, for RNAi therapy[125].

---

[114] FDA approves first drug for spinal muscular atrophy | FDA
[115] FDA grants accelerated approval to first drug for Duchenne muscular dystrophy | FDA
[116] FDA approves givosiran for acute hepatic porphyria | FDA
[117] Alnylam Pharmaceuticals Press Release | Oct 06, 2022 | Alnylam Announces FDA Approval of Supplemental New Drug Application for OXLUMO® (lumasiran) in Advanced Prima
[118] Moderna's Investigational Therapeutic for Methylmalonic Acidemia (mRNA-3705) Selected by U.S. Food & Drug Administration for START Pilot Program
[119] Branaplam: VIBRANT-HD Study Update | Novartis
[120] Inclisiran (Leqvio)
[121] UK's first norovirus mRNA vaccine trial launched | NIHR
[122] Emerging Health Care Innovation Brief: Maternal Vaccine for RSV, Treating Post-COVID Cognitive Impairment (February 16-March 1, 2023) | PCORI
[123] BioNTech | mRNA: a drug class of its own
[124] How RNAi Works | Alnylam® Pharmaceuticals
[125] RNA Interference (RNAi) | Arrowhead Pharmaceuticals

Market Growth: RNA therapeutics expected to grow to 40 billion by 2034 (GlobeNewsWire 10 Feb 2025).[126]

12.5 Implementation Challenges and Barriers

Stability and Delivery: mRNA degradation (often challenging to work with, multiple feasibility issues compared to more stable DNA), and efficient cellular uptake remain challenges.

Manufacturing Scalability: Need for large-scale, cost-effective production of RNA molecules.

Workforce: requires expertise from researchers and clinical trial infrastructure. Possibility of a hub in Victoria (e.g. presence of Moderna facility in Melbourne).

12.6 Cost and Economic Considerations

Development Costs: A BMJ publication estimated the cost of mRNA vaccine development to be US$31.9 billion during the pandemic period (Lalani et al., 2023).

Pricing Trends: Current siRNA drugs are expensive, e.g. Patisiran costs between $451,430 and $677,145 per patient[127].

Potential Cost Savings: Faster, more scalable drug development.

12.7 Strategic Priority for Australia

- WHO lists RNA therapeutics as a transformative area in genomic medicine (for example see WHO report on mRNA vaccines[128].

There are opportunities for early adoption in Australia, for example,

- Moderna has a production site for RNA vaccines in VIC, developed in part due to COVID response. (see press release[129] This reflects the benefits of having onshore capability (and translational research capacity generally) in this area, especially in the context of preparation for any future pandemic response.

[126] RNA Based Therapeutic Market Size Expected to Reach USD
[127] Executive Summary - Pharmacoeconomic Review Report: Patisiran (Onpattro) - NCBI Bookshelf
[128] WHO mRNA vaccine report news
[129] https://www.health.gov.au/ministers/the-hon-mark-butler-mp/media/world-leading-moderna-vaccine-facility-opens-in-victoria

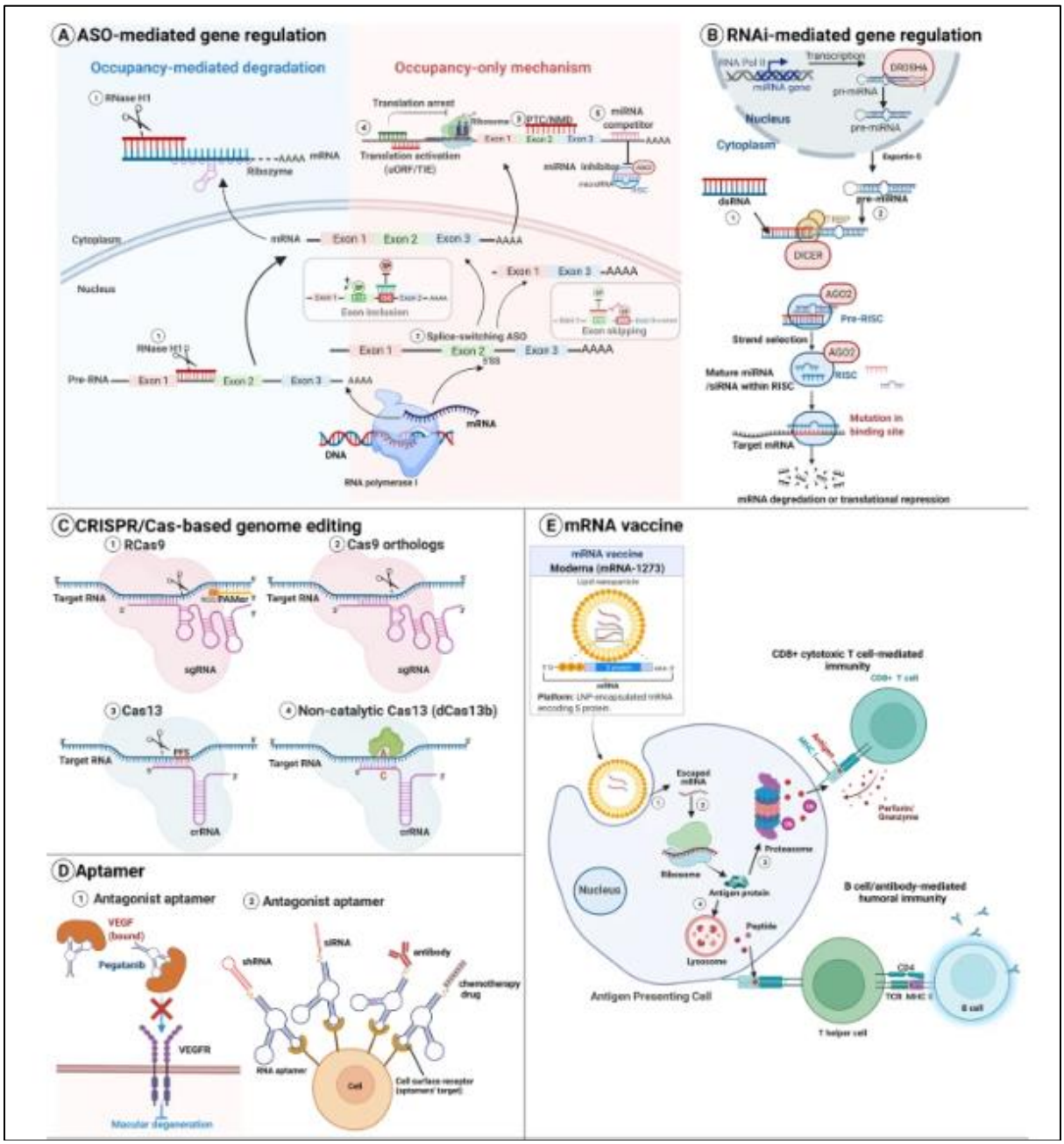


Figure 15. Types of RNA-based therapeutics and modes of action. (Zhu et al., (2022), Figure 2, RNA-based therapeutics: an overview and prospectus - PMC).

13 Multiomics Biomarker Discovery

13.1 Technology Overview

Multiomics biomarker discovery integrates various high-throughput data types, such as genomics, transcriptomics, proteomics, metabolomics, and epigenomics, to identify novel biomarkers and can be applied to a range of disease types.

As outlined by Chen et al, (2023):

> "Integration of different types of omics data can elucidate underlying pathogenic changes of the disease, which can then be verified in further molecular research. By integrating multi-omics, scientists can filter out novel associations between biomolecules and disease phenotypes, identify relevant signaling pathways, and establish detailed biomarkers of disease."

Australia has a good presence in this area, with training occurring nationally and internationally in the research field (e.g. Mixomics, University of Melbourne).

13.2 Potential Healthcare Applications

Early Diagnosis: Identification of molecular signatures for preclinical Alzheimer's disease and other neurodegenerative conditions. The approach has also been used in cancer studies – e.g. Multiomics approaches in biomarker discover in ovarian cancer diagnosis (Xiao et al., 2022, see also Figure 16).

Disease Progression Monitoring: Multiomics analysis helps track disease heterogeneity and patient-specific disease trajectories (Hasin et al., 2017).

Therapeutic Target Identification: Biomarkers from transcriptomics and proteomics can be used to develop targeted therapies (i.e. key pathway identification). For example, Wang et al., 2024 identified 1131 publications that utilized multiomics from 2007 – 2024.

13.3 Evidence and Readiness

Preclinical and Clinical Data: See Vacher et al., 2024 for characterization of Alzheimer's disease markers using mixomics.

Clinical trials: 111 studies featuring multiomics on the WHO International Clinical Trials Registry Platform (as of March 2025).

Large genomic datasets can be used for benchmarking, use of controls and validation studies (e.g. UK Biobank, see Garg et al, 2024).

International Horizon Scanning initiatives: The EMA New Approach Methodologies Horizon Scanning 2025 report identifies omics generally as crucial to precision medicine[130].

13.4 Implementation Challenges and Barriers

Technical Complexity: need for bioinformatics pipelines and cross-disciplinary expertise.

Standardization and Reproducibility: Multiomics data harmonization across different studies remains a challenge (e.g. data assumptions, benchmarking, standardization). (e.g. Bioconductor, MixOMICS).

13.5 Cost and Economic Considerations

Technology Costs: costs in data generation e.g. sequencing costs (between approx AU$1,000-AU$2,500 for each omics layer of genomics, transcriptomics, proteomics, metabolomics, epigenomics. Bioinformatics, Data analysis and biomarker discovery workflows are challenging to quantify and depend on disease type.

[130] New Approach Methodologies EU-IN Horizon Scanning Report

13.6 Strategic Priority for Australia

Australia could establish collaborative programs with international initiatives such as AMP-AD (see Reddy et al., 2024). Groups such as University of Melbourne Mixomics group (Le Cao) have had experience in this area for > 10 years and have ongoing international training programs[131]. Recent MRFF funding for OMIX3 multiomics platform[132]. An Annual Australian conference on multiomics is held[133].

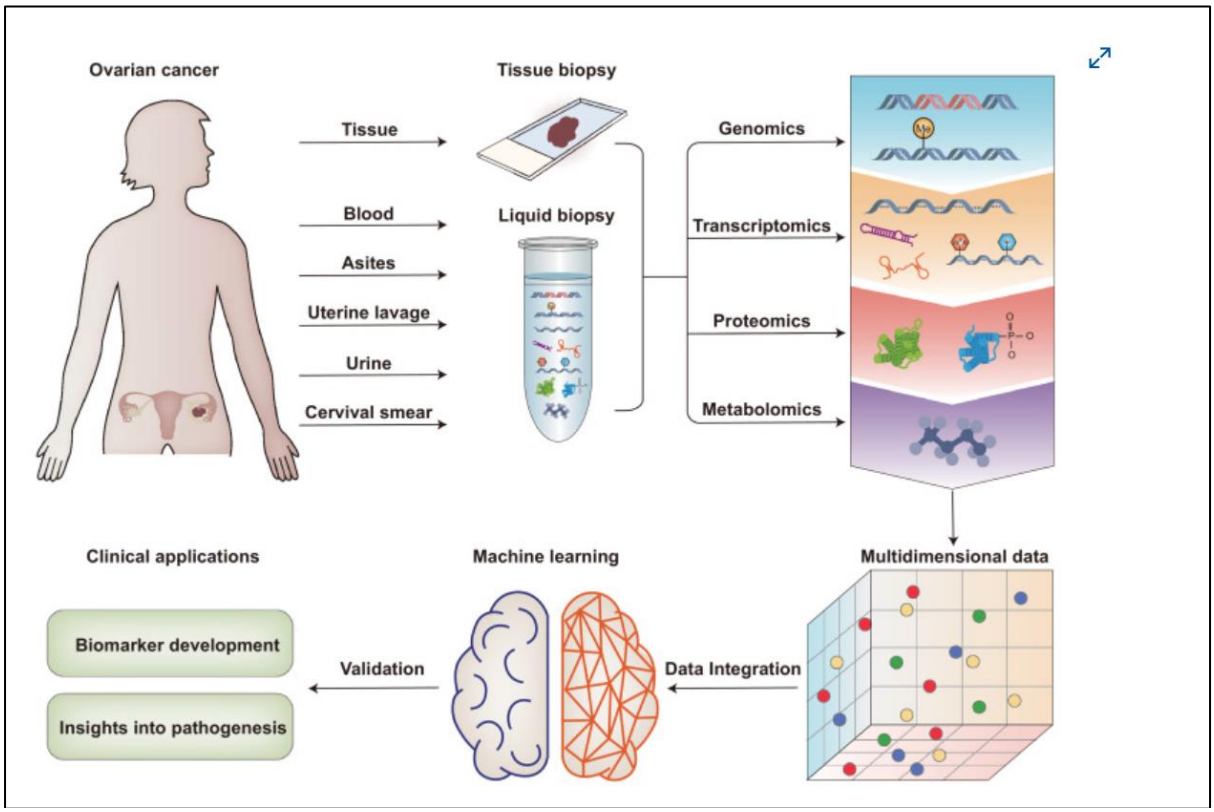


Figure 16. Schematic representation of multi-omics approaches towards biomarker discovery for early diagnosis in ovarian cancer (from Xiao et al., (2022), Figure 2, Multi-omics approaches for biomarker discovery in early ovarian cancer diagnosis - PMC).

[131] https://mixomics.org/category/news/workshop/
[132] https://www.biocommons.org.au/news/omix3-funding
[133] https://www.multiomics2024.org

14 Quantum computing

14.1 Technology Overview

Quantum computing (which has been a concept since the 1980s) harnesses the principles of quantum mechanics (such as quantum interference) to perform operations on data. Quantum bits can exist in multiple states at the same time (unlike classic bits) which permits quantum computers to solve problems more efficiently than 'classic compute' (see also Preskill 2018).

The technology has potential to impact on a wide variety of applications relevant to genomic precision medicine (see also Figure 17). For example:

> "The integration of quantum computing with genomics heralds a new era in DNA analysis, characterized by unprecedented speed and computational power. Quantum computing utilizes principles of quantum mechanics, such as superposition and entanglement, to perform calculations at speeds far beyond the capabilities of traditional computers. This revolutionary approach offers the potential to dramatically accelerate tasks in genomics such as sequence alignment, genetic mutation analysis, and complex trait mapping. The promise of quantum computing in genomics lies not only in enhancing the speed of genomic analyses but also in its potential to handle the vast complexities and the voluminous scale of genetic data more efficiently[134]. "

As indicated above, this technology could have far-reaching implications for genomics – anywhere that compute power is required. It could affect variant calling pipelines (see also AI in variant calling section), multiomic approaches where a lot of data is analysed simultaneously, and data storage (including encryption). The theory of quantum computing is derived from Shor's and Grover's Algorithms and applications of quantum computing can be related to both transformative capabilities and a threat to current data encryption systems[135].

We explore a few of the implementation challenges here – although it may be more than five years when the technology application hits the health system in a more mainstream way.

14.2 Potential Healthcare Applications

Key applications:

- **Variant calling pipelines and sequence alignments (see** Nałęcz-Charkiewicz et al., 2024**).**
- **Modelling complex gene expression**
- **Machine learning for genomic prediction**
- **Biomarker discovery**
  - Quantum computing allows more efficient exploration of multiomics data – for proof-of-concept research using quantum neural networks and CTLA4 activating pathways, see Nguyen 2024.
- **Drug discovery and Precision Medicine**
  - Faster compute would allow for increased efficiency in protein folding and protein-drug interactions[136].
  - Optimising clinical trials[116].
- **Genomic data storage and Secure Sharing of Genomic Data**[137]

- **Security Risk of Quantum Computing used against encrypted Healthcare data:**
  - Genomic data is implicitly and permanently identifiable.
  - Genomic data is often linked to other healthcare data (e.g. on electronic medical record systems).

[134] (https://medium.com/kinomoto-mag/quantum-computing-meets-genomics-the-dawn-of-hyper-fast-dna-analysis-03208c1428d8)
[135] Quantum Computing and The Future of Data Privacy - Certes
[136] How quantum computing is revolutionising drug development - Drug Discovery World (DDW
[137] https://medium.com/kinomoto-mag/quantum-computing-meets-genomics-the-dawn-of-hyper-fast-dna-analysis-03208c1428d8

- Data volume is likely to continue to increase as clinical genetic testing demands increase (e.g. increase in MBS item numbers relating to clinical genetic and genomic testing in the last 5 years[138]).
- Modern encryption methods[139] (e.g. Rivest-Shamir-Adleman (RSA) and Elliptic Curve cryptography (ECC), will be essentially obsolete once quantum computing is affordable and more available.
- High risk of "Harvest now, decrypt later" method.

- For a review of quantum encryption issues, privacy and the need for to integrate quantum safe solutions into existing infrastructure, see link[140].

14.3 Evidence and Readiness

Regulatory status:

- No related records on Australian Register of Therapeutic Goods (ARTG).
- Regulatory challenges could include issues around safe, ethical and equitable integration of quantum technologies into healthcare (see Stanford Law School policy guide on regulating quantum & AI in Healthcare, Kop, 2024). Broadly, the policy encourages 'proactive, flexible, and harmonized policy approaches'.

Adoption in international genomic initiatives (see also Figure 18)**:**

- Wellcome Institute using quantum computing to analyse pangenomes[141].
- Part of wider Wellcome Leap Q4Bio Challenge[142] "The Wellcome Leap Q4Bio Challenge is based on the premise that the early days of any new computational method will advance and benefit most from the co-development of applications, software, and hardware – allowing optimisations with not-yet-generalisable, early systems."
- Cleveland Clinic and IBM: establishing a quantum computing system for healthcare research[143].
- NIHR-IO conducted a report on emerging quantum technologies for use in healthcare[144].

14.4 Market and Industry Engagement

Key players:

- AWS Bracket; IBM; Microsoft; Google AI; Alibaba Group[145].
- Australian companies: Silicon Quantum Computing[146]; QuintessenceLabs[147]; Q-Ctrl[148].

Expected timeline:

- May be longer than five years to hit the sector. However, the possibility of quantum computing being used for potential threats against the health system may be within one to three years (for example Harvest now, Decrypt later threat), therefore policies and strategies should be put in place as soon as practical by relevant agencies.

[138] MSAC Applications for Genetic, Genomic and Screening Tests — Australian Genomics
[139] ECC vs RSA vs DSA - Encryption Differences | Sectigo® Official
[140] Quantum Computing and The Future of Data Privacy - Certes
[141] https://www.sanger.ac.uk/news_item/researchers-aim-to-analyse-pangenomes-using-quantum-computing/
[142] Q4Bio | Wellcome Leap: Unconventional Projects. Funded at Scale.
[143] How quantum computing is revolutionising drug development - Drug Discovery World (DDW)
[144] A Horizon Scan of Emerging Quantum Technologies for use in Healthcare - NIHR Innovation Observatory
[145] https://thequantuminsider.com/2023/12/29/quantum-computing-companies/
[146] Silicon Quantum Computing
[147] Home | Quantum Cybersecurity from QuintessenceLabs
[148] We make quantum technology useful | Q-CTRL

14.5 Implementation Challenges and Barriers

Technical limitations:

- Currently still at proof-of-concept stage, although some hybrid quantum/classical compute techniques are available[149].
- Challenging to establish / fund within health systems infrastructure.

Regulatory and ethical considerations:

- Potential equity issues if used in some states / territories but not others.
- Power of compute raises ethical issues e.g. may threaten encryption methods of data potentially exposing sensitive health information[150] .

Quantum Cryptography (PQC) or Quantum-Resistand Cryptology) and focuses on developing cryptographic algorithms and protocols that can withstand quantum computing applications[151] .

Specific to healthcare data security: Quantum computers will undoubtedly disrupt many facets of technology and business operations. Their impact on data encryption is one of the most pressing for healthcare organizations. As this technology becomes more accessible, it will both improve and threaten encryption practices[152].

As outlined by Thales: "Quantum computing is progressing rapidly; it won't be long before a quantum cyberattack will be possible. Quantum cyberattacks will be able to cripple large networks in a matter of minutes. Everything we rely on today to secure our connections and transactions will be threatened by quantum computers, compromising all keys, certificates, and data. Cybercriminals, armed with quantum power to break traditional encryption algorithms, can analyze massive amounts of data or hack critical infrastructure in seconds[153]."

14.6 Cost and Economics Considerations

Estimated cost of adoption:

- A$130 million has been invested in Australia for Quantum technologies[154]. A further $101.2 million was invested from the 2023 Australian federal budget[155].
- Current global market is $44.5 billion.

14.7 Strategic Priority for Australia

The ARC Centre of Excellence in Quantum Biotechnology (QUBIC)[156] is a $45 million research initiative to bring together quantum computing and life science. There has been a recent $36 million dollar Australian Government investment in the Critical Technologies Challenge Program (CTCP)[157]. The National Quantum Strategy, is the Australian Government's plan for growth and investment in the quantum industry in Australia[158]. Guidelines for quantum computing use in the context of secure genomic data processing, storage and analysis platforms should align with this strategy, including security issues.

[149] The Many Faces of Hybrid Classical-Quantum Computing - Part 1 - Quantum Computing Report
[150] https://www.wevolver.com/article/technical-and-ethical-issues-in-quantum-computing-the-quantum-challenge
[151] https://cpl.thalesgroup.com/encryption/post-quantum-crypto-agility
[152] medical design briefs
[153] Post-Quantum Crypto Agility
[154] https://iopscience.iop.org/article/10.1088/2058-9565/ab02b4/pdf
[155] https://www.industry.gov.au/publications/national-quantum-strategy; $101 million to help Aussie businesses adopt AI and quantum tech
[156] New research initiative aims to position Australia at the forefront of quantum biotechnology
[157] https://www.ausbiotech.org/news/new-grant-programme-for-quantum-technologies
[158] National Quantum Strategy

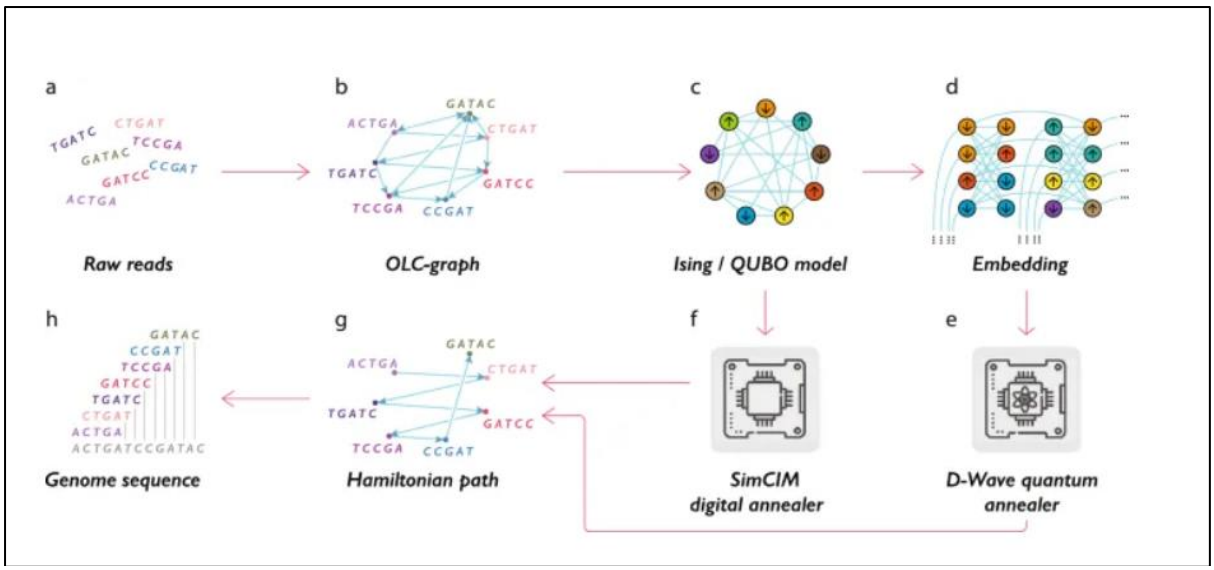


Figure 17. Quantum computing applications in Genomics. (https://medium.com/kinomoto-mag/quantum-computing-meets-genomics-the-dawn-of-hyper-fast-dna-analysis-03208c1428d8).

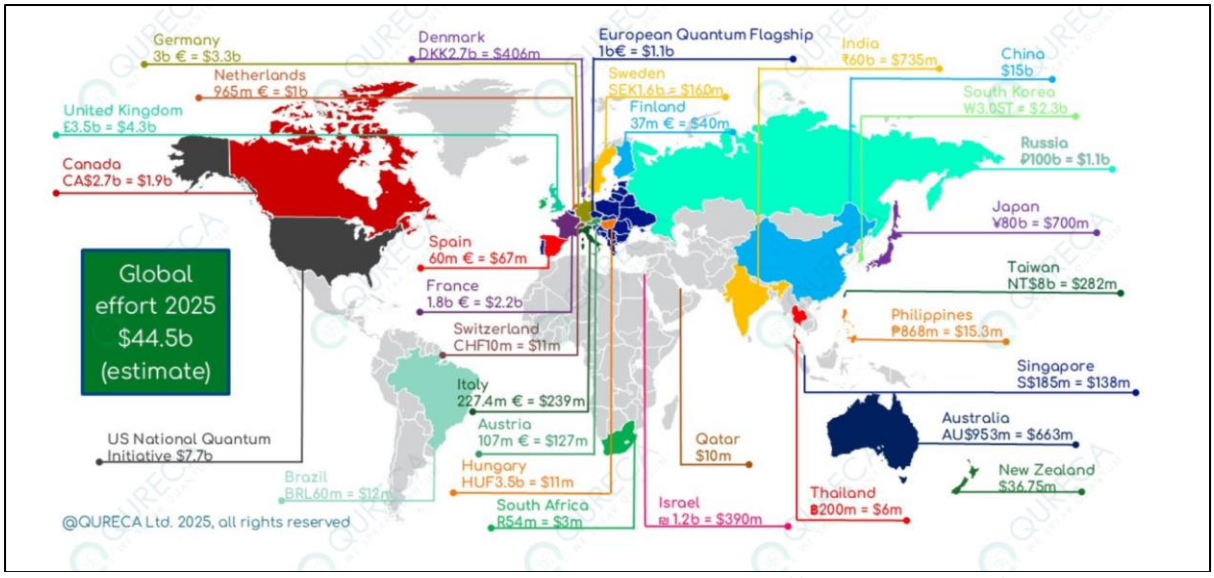


Figure 18. Global ecosystem of Quantum computing investments (https://www.qureca.com/quantum-initiatives-worldwide/).

15 Artificial Intelligence (AI) Driven Variant Interpretation

15.1 Technology Overview

Variant interpretation of genomic sequencing to determine pathogenic variants in rare disease and cancer is a time-consuming manual process, often involving multi-disciplinary teams of bioinformaticians, clinical geneticists and other specialists and allied health professionals. Artificial Intelligence is well suited for incorporation into variant calling, making use of Machine Learning algorithms and natural language processing. Tools that allow for efficient identification of clinically relevant variants, automated literature mining and variant classification may improve both the speed and accuracy of the process (Abdelwahab & Torkamaneh 2025).

For example, in 2018, DeepVariant was published – a SNP and small-indel variant caller that made use of deep neural networks (Poplin et al, 2018). It was found that AI-based variant calling tools outperformed conventional variant calling tools for SNVs and INDELs in most aspects for both long and short reads (Poplin et al, 2018). However, DeepVariant took high average memory across different sequencing platforms (Illumina, PacBIO and ONT).

15.2 Potential Healthcare Applications

- **Rare disease diagnosis:** AI models may improve diagnosis / aid in efficiencies of process. For example, tools such as Exomised and AMELIE use AI to match phenotype and genomic data to published literature (Birgmeier et al., 2020). Another example is Fabric Genomics that uses novel AI algorithms in identifying genetic causes of rare disease[159]. AI is also likely involved in Reanalysis programs, where genomic data from patients with no genetic diagnosis can be reinterrogated as phenotypes mature or new gene associations are discovered[160].
- **Cancer genomics:** potential better ability to identify driver mutations / pathways to target for treatment. This in turn facilitates targeted, precision medicine and better patient outcomes (for review see O'Connor & McVeigh 2025)
- **Variant prediction from phenotype data (e.g. tumour histology):** For example, Coudray et al., (2018), used histology images from lung cancer (from Cancer Genome Atlas) and a deep convolutional neural network to predict variants in tumour samples.
- **Variant reclassification** for example the LEAP (Learning from Evidence to Assess Pathogenicity) tool is proposed as a quality control using a machine learning algorithm to help classify variants (Lai et al., 2020).
- **Automated Clinical Report Generation**: Congenica uses proprietary automated processes for report generation of NGS data[161].
- **Population level genomics** e.g. GENCORE as an AI framework for reproductive carrier screening[162].
- **Pharmacogenomics** AI applications in interpreting drug-metabolizing gene variants (such as *CYP2D6* and codeine metabolism– see Silva et al., (2021), on the application of AI for chronic disease management using drug-gene pairings.

15.3 Evidence and Readiness

Sensitivity and Accuracy: Abdelwahab et al., (2023) investigated performance of conventional and AI variant callers and concluded that AI variant callers (e.g. DeepVariant) had greater specificity precision compared to conventional tools (e.g. GATK) for both short and long-read sequencing. AI callers also had better consistency across a variety of sequence data read types. However, the trade-off is a higher computation demand (refer to Figure 19 and 20).

---

[159] Fabric Genomics Launches GEM Algorithm to Accelerate Genetic Disease Diagnosis, Provide Comprehensive Clinical-Decision Support
[160] A national large-scale automated reanalysis program — Australian Genomics
[161] Automating Clinical Genomic Analysis & Reporting for Rapid NGS Results
[162] Generative AI Frameworks for Precision Carrier Screening

Regulatory approval: A growing number of AI algorithms have been approved by the FDA. These algorithms raise several regulatory and ethical challenges around the sourcing and privacy of the data used to train the algorithms, the transparency and generalizability of the underlying algorithms themselves, the regulatory process for refreshing these algorithms as further data become available, and the liability associated with prediction errors. Some of these issues can and should be addressed by open sharing of AI models in detail (including source codes, model weights, meta graphs, and so on) with the scientific and medical community to improve transparency. (Dias and Torkamani, 2019).

Policy around AI use in healthcare: As indicated by Kop (2024), there is a need for proactive, flexible and harmonized policy to allow for innovation in fields such as AI.

In Australia, the Australasian Institute of Digital Health is leading development of a National Policy Roadmap for Artificial Intelligence in Healthcare. The plan will drive national policy agenda for safe and ethical use of AI in healthcare[163]. Priority areas will include:

1. AI safety, quality, ethics and security – ensuring the safe use of AI in healthcare.
2. Workforce – enabling essential training and development of the healthcare and AI workforce.
3. Consumers – ensuring health AI literacy and sensitivities for collecting Indigenous information.
4. Industry – supporting industry to thrive and be competitive.
5. Research – guiding the research that will protect Australia's national interest.

International Horizon Scanning Initiatives: NIHR-IO did a general horizon scan on algorithms used in development of AI-enabled healthcare technologies[164]. AI-driven genomics being investigated by Genome England (also refer to AI in genomics podcast[165]).

15.4 Market and Industry Engagement

AI based variant calling tools: BCFTools, GATK4, Platypus, DNAscope, and DeepVariant (Abdelwahab et al., 2023).

Adoption timeline: AI-driven interpretation already used in some clinical settings (e.g. those that use GAT4K in their variant calling pipeline).

15.5 Implementation Challenges and Barriers

Regulatory and ethical concerns: Patient privacy and consent in AI-driven decision-making. This is particularly so given popularity in mainstreaming AI (i.e. AI chatbots using natural language processing) and concerns around data use of new technology such as DeepSeek[166].

A study by Harrison et al., (2024) assessed Australian perceptions of AI use in genomic medicine. Concerns included data security, risk of misdiagnosis, risk of discrimination and bigotry":

> "… findings suggest the public's view of AI in genomics is not substantially different from their view on the use of AI in other areas of medicine. However, the difference in our participants' views between MRI brain scans and genomic data suggest that for some, the type of data being analysed can affect the level of trust in AI use. This aligns with the findings of Middleton et al., who found in their research on collection and storage of genomic data that some participants described genomic data as being 'special' or 'different' compared to other forms of medical data. Further research is needed to clarify how the type of medical data may affect patient attitudes to AI analysis."

Requires stringent and consistent phenotype terminology: AI requires accurate phenotype information written in a standard format (e.g. FIHR, SNOMED or similar). Patient written clinical phenotypes have been shown to lead to inaccurate diagnosis results[167].

---

[163] https://digitalhealth.org.au/blog/australian-roadmap-for-artificial-intelligence-in-healthcare-to-be-launched-at-ai-care/
[164] I4I-AI-Report_July-2024.pdf
[165] https://www.genomicsengland.co.uk/podcasts/can-artificial-intelligence-accelerate-the-impact-of-genomics
[166] DeepSeek or deep risk? Keeping UNSW's (and your) data safe in the age of AI | Inside UNSW
[167] Leading AI models struggle to identify genetic conditions from patient-written descriptions | National Institutes of Health (NIH)

15.6 Cost and Economic Considerations

Cost of AI implementation: Already has been incorporated into some variant calling workflows both nationally and internationally.

Healthcare impact: Needs further study on how much it could increase diagnostic rates (or being introduced in a reanalysis capacity).

15.7 Strategic Priority for Australia

Harrison et al., (2024) indicates reasonable public support of use of AI, particularly in relation to diagnosis. Concerns were over data security, possibility of misdiagnosis, or any AI bias. Generally, aligns with precision medicine in Australia and preventative health.

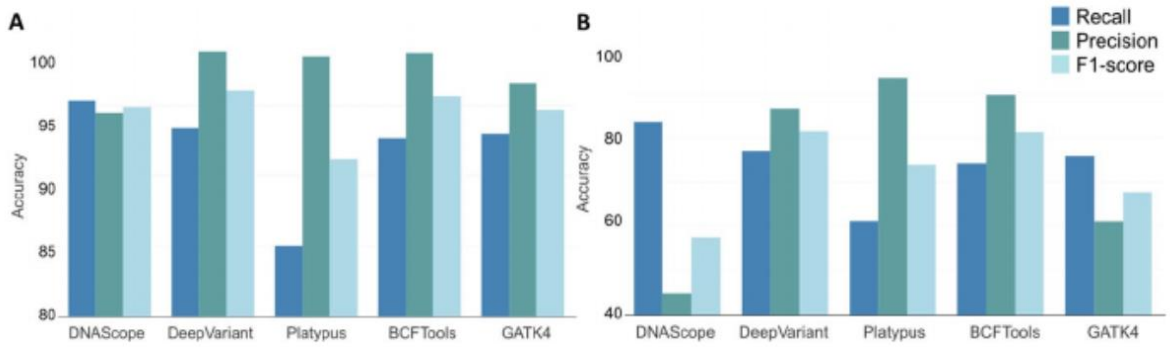
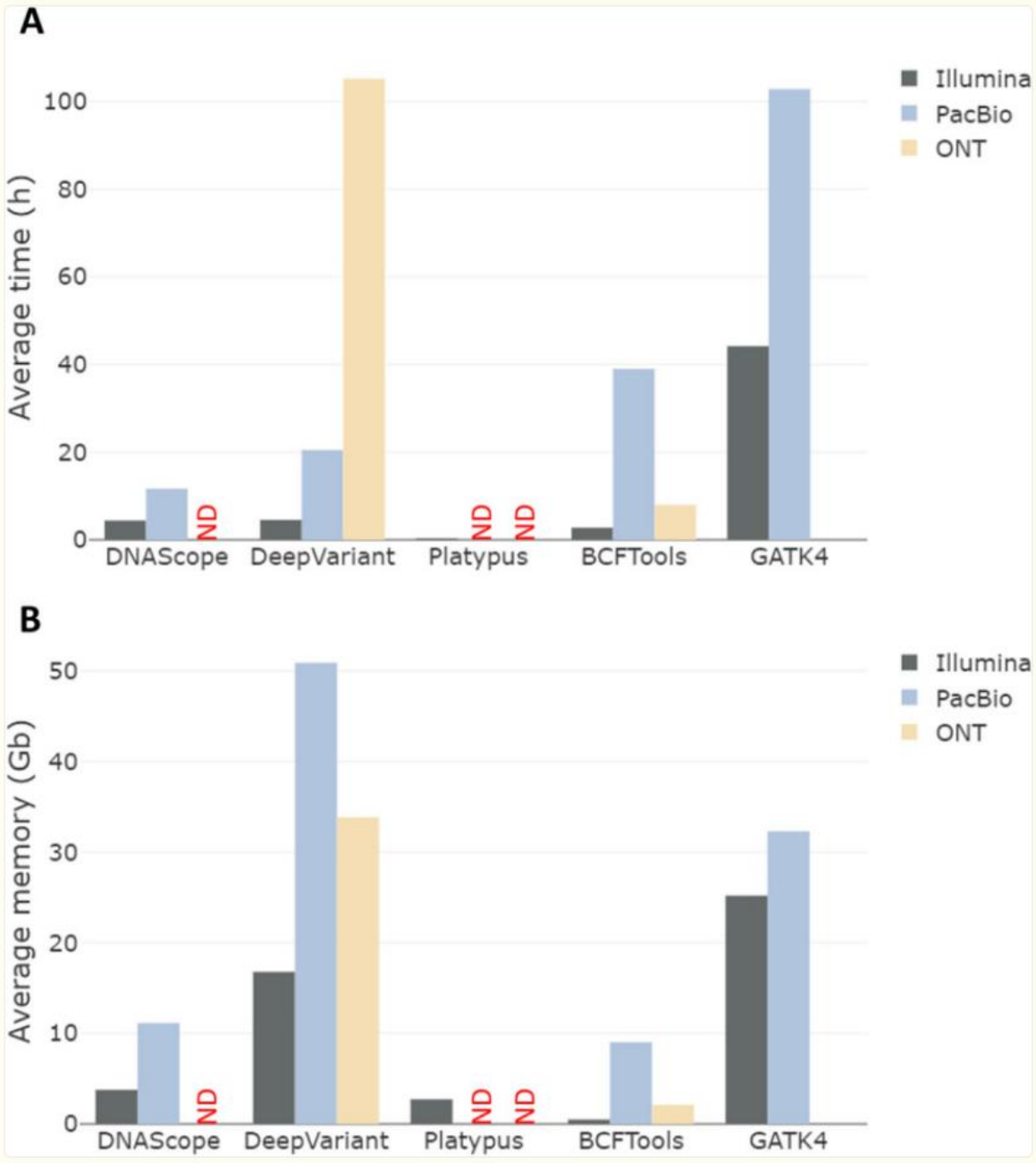


Figure 19. Average accuracy metrics of variants (SNVs (A) and INDELs (B)) called from Illumina data using give different variant callers (from Abdelwahab et al., 2023, Figure 1, Performance analysis of conventional and AI-based variant callers using short and long reads - PMC).

Fig. 4.



Open in a new tab

Average computational cost (time (**A**) and memory (**B**)) for variant calling using three different data types: Illumina, PacBio HiFi, and ONT. ND: not determined

Figure 20. Average computational cost (time(A) and memory (B)) for variant calling using three different data types: Illumina, PacBio HiFi, and ONT. ND: not determine (from Abdelwahab et al., (2023), Figure 4, Performance analysis of conventional and AI-based variant callers using short and long reads - PMC).

16 Microbiome based therapies for disease treatment and prevention

16.1 Technology Overview

Microbiome-based therapies aim to modulate the human microbiota to prevent or treat disease treatment, aided by recent advances in metagenomics. Therapies include live biotherapeutic products (LBPs), and fecal microbiota transplantation (FMT). Conditions targeted include inflammatory bowel disease, cancer and other metabolic disorders. Advances are being fuelled by advances in synthetic biology (e.g. engineered probiotics). Increasingly, the microbiome will be translated to clinical practice as another arm to disease prevention and treatment (refer also to Figure 21).

16.2 Potential Healthcare Applications

Infectious disease treatment / prevention: e.g. FMT, see Healthcare Infection Society Guidelines around DMT to treat recurrent or refractory *Clostridioides difficile* (Mullish et al., 2024).

Cancer treatment: Gut microbiota modulation enhances immunotherapy response (Routy et al., 2018).

Metabolic diseases: e.g. using microbiome signature in diagnosis? of non-alcoholic fatty liver disease and links to type 2 diabetes mellitus (Aron-Wisnewsky et al., 2020).

Technologies employed:

- **Fecal Microbiota Transplantation (FMT):** transfer of fecal matter from a healthy individual to restore microbiome balance.
- **Live Biotherapeutic Products (LBPs):** biologically active microbiomes, administered to restore microbiome balance.
- **Engineered microbial consortia: capable of modulating host immunity or metabolism.**
- **Phage therapy targeting the microbiome:** bacteriophage-based therapies (in contrast to chemical antibiotics) that are capable of selectively targeting disease-causing bacteria (Kortright et al., 2019).

16.3 Evidence and Readiness

FDA: microbiome-based therapies approved[168] and regulated as class 1 or class 2 biologicals[169].

ARTG: Faecal microbiota transplant (FMT Health 421990).

Clinical trials: 2546 clinical trials on WHO trial registry.

International initiatives: Human Microbiome Project (USA, NIH[170] https://hmpdacc.org/).

16.4 Market and Industry Engagement

Key players:

- Seres Therapeutics (USA)[171].
- Finch therapeutics (USA)[172].
- Synlogic (USA)[173] – synthetic biology and engineered probiotics.
- Enterome (France)[174].
- 4D Pharma (UK)[175].
- Biomebank (Australia)[176].

[168] https://www.nixonpeabody.com/insights/alerts/2023/05/15/fda-approves-microbiome-based-therapies
[169] Faecal microbiota transplant products regulation | Therapeutic Goods Administration (TGA)
[170] https://hmpdacc.org/)
[171] https://www.serestherapeutics.com/
[172] Home — Finch Therapeutics
[173] Home - Synlogic Therapeutics
[174] Enterome Secures €46M to Take Microbiome Therapies to Clinical Trials
[175] Revolutionary new medicines from the human gut microbiome
[176] BiomeBank - Restoring gut microbial ecology

- Microba (Australia)[177] A recent collaboration with Sonic Healthcare has expanded their market.

16.5 Implementation Challenges and Barriers

- Uncertainty for microbiome-based drugs beyond FMT.
- Personalized microbiome interventions require further validation (including in a range of populations).
- Ongoing evidence collection for implementation into mainstream clinical practice.

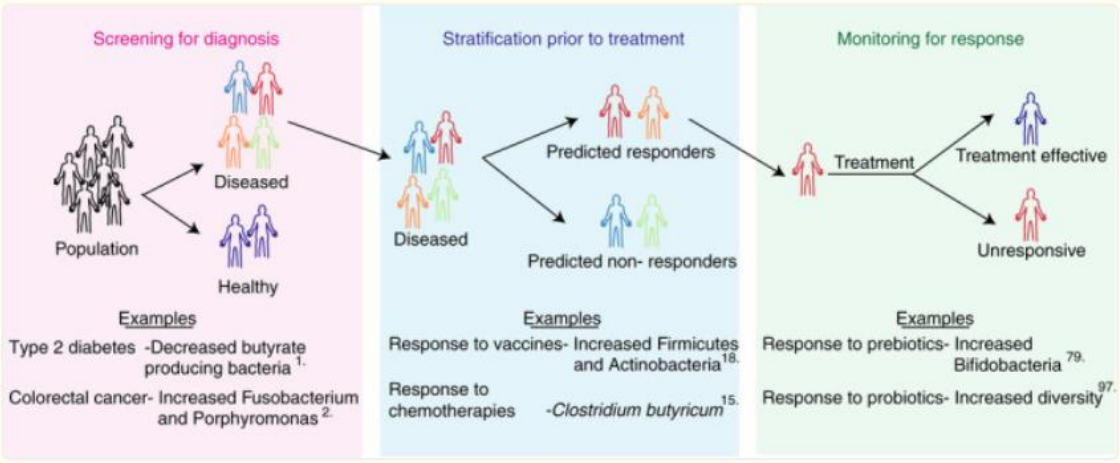
16.6 Cost and Economic Considerations

- FMT costing – between $5000 and $10,000 available only in limited Australian clinics[178].
- Potential for cost savings by reducing hospital stays and antibiotic resistance burdens.
- Microba test currently at AU$349 (see also partnership with Sonic Healthcare[179], however cost of diagnostic clinical testing for therapeutics not fully evaluated.

16.7 Strategic Priority for Australia

Australia is well placed in terms of integration of microbiome research, development and innovation into the public health system. For example, the National Microbial Genomics Framework (2025-2027) outlines a nationally consistent approach for microbial genomics integration[180] (interim Australian Centre for Disease Control). The Australian Consensus Statement on FMT outline guidelines for production and clinical use of FMT (Haifer et al., 2020). The Australian Microbiome Initiative also coordinate research efforts nationally[181]. Additionally, Australian innovation and expertise continues to evolve (e.g. Microba & Biomebank).

[177] Microba | Pioneering Microbiome Science for New Health Solutions
[178] FMT: The 'life-saving' treatment. Too soon for hospitals or not soon enough? | SBS The Feed
[179] Sonic Healthcare acquires strategic stake in Microba, establishes significant commercial partnershiphttps://microba.com/news/sonic-healthcare-acquires-strategic-stake-in-microba-establishes-significant-commercial-partnership/
[180] National Microbial Genomics Framework for Public Health 2025–2027
[181] Australian Microbiome – Australian Microbiome



Open in a new tab

Categorisation of microbiome-based biomarkers for disease. Microbiome-based biomarkers can be classed as tools for screening for diagnosis (pink box), stratification prior to treatment (blue box) and monitoring for response to treatment (green box).

Figure 21. Categorisation of microbiome-based biomarkers for disease. Microbiome-based biomarkers can be classed as tools for screening for diagnosis (pink box), stratification prior to treatment (blue box) and monitoring for response to treatment (green box) (From Gulliver et al, 2022, Figure 2, Review article: the future of microbiome-based therapeutics - PMC).

17 Organoid and Lab-Grown Tissue Models for Genomic Testing

17.1 Technology Overview

Organoids and lab-grown tissue models represent three-dimensional systems that are derived from stem cells of patient tissues. They replicate the structure and function of organs, thus offering a unique to interrogate. In the context of genomics, this includes response to therapies, investigate disease mechanisms and model specific mutations in a relevant tissue. The 3D structure better represents genomic heterogeneity and also tumour-heterogeneity in a cancer context. Examples of organoids include cardiac, brain and liver. Tissue models reduce over-reliance on animal models and alleviate and/or address ethical concerns around animal clinical testing.

As outlined by Yang 2023 (see also Figure 22):

> "Organoids are three-dimensional (3D) miniaturized versions of organs or tissues that are derived from cells with stem potential and can self-organize and differentiate into 3D cell masses, recapitulating the morphology and functions of their in vivo counterparts. Organoid culture is an emerging 3D culture technology, and organoids derived from various organs and tissues, such as the brain, lung, heart, liver, and kidney, have been generated. Compared with traditional bidimensional culture, organoid culture systems have the unique advantage of conserving parental gene expression and mutation characteristics, as well as long-term maintenance of the function and biological characteristics of the parental cells in vitro. All these features of organoids open new opportunities for drug discovery, large-scale drug screening, and precision medicine."

17.2 Potential Healthcare Applications

Cancer Genomics:

- Tumour-derived organoids from gastrointestinal cancer biopsies used to test drug response (Vlachogiannis et al., 2018).
- Patient-derived organoids can be utilized to assess chemotherapy response in metastatic colorectal cancer patients (Ooft et al., 2019).
- Used to assess tumour heterogeneity (living biobank concept, see Sachs et al., 2018 in Breast cancer example.

Cardiology: use of heart muscle organoids (Voges et al, 2023). Permits modelling of specific cardiac disease (e.g. arrhythmogenic cardiomyopathy) caused by specific mutations.

Rare Genetic Diseases: Patient-derived organoids to model rare disorders, for example Koc et al., (2025) used a cornea organoid model to study aniridia-associated keratopathy.

Functional Genomics and CRISPR screens: (see also HS Report 4). For example, Mukhare et al., (2025) described how CRISPR screens in human organoids (including pancreatic, ovarian, breast, colorectal, gastric, lung and melanoma tumoroid cell lines can investigate new tumour suppressors, drug screens and clonal evolution.

17.3 Evidence and Readiness

Regulatory Considerations: FDA Modernization Act 2.0: allows organoids to be used in some cases rather than animal models (see Zushin et al., 2023).

Clinical Trials: 141 studies for organoids, on WHO clinical trial registry.

International Horizon Scanning Initiatives: EMA New Approach Methodologies Horizon Scanning Report identified organoids as a complex *in vitro* model, using a Bibliometric Network Analysis[182].

[182] New Approach Methodologies EU-IN Horizon Scanning Report

17.4 Market and Industry Engagement

Biotech Startups & Pharma: Companies such as Hubrecht Organoid Technology[183].

Investment Trends: Attracting government funding and from investors[184].

17.5 Implementation Challenges and Barriers

Regulatory Hurdles: Changes to FDA Act will aid in evaluation.

Possible issues remain regarding standardization, scalability, ethical concerns and public acceptability.

Workforce: Highly specialised area, may be challenging to move through regulation and standardization.

17.6 Cost and Economic Considerations

Development Costs: High costs and expertise to set up, and cost per sample.

Cost savings: May aid in drug screening abilities and efficiency.

17.7 Strategic Priorities for Australia

Australia has established infrastructure, policy and facilities regarding organoid implementation into public healthcare. For example: in 2021, Phenomics Australia[185] established a nationally coordinated research service focussed on non-animal modelling, including 3D organoid systems; and ii) the Australian Organoid Facility[186] at the University of Queensland provides quality-assured organoids for basic, translational and contract research.

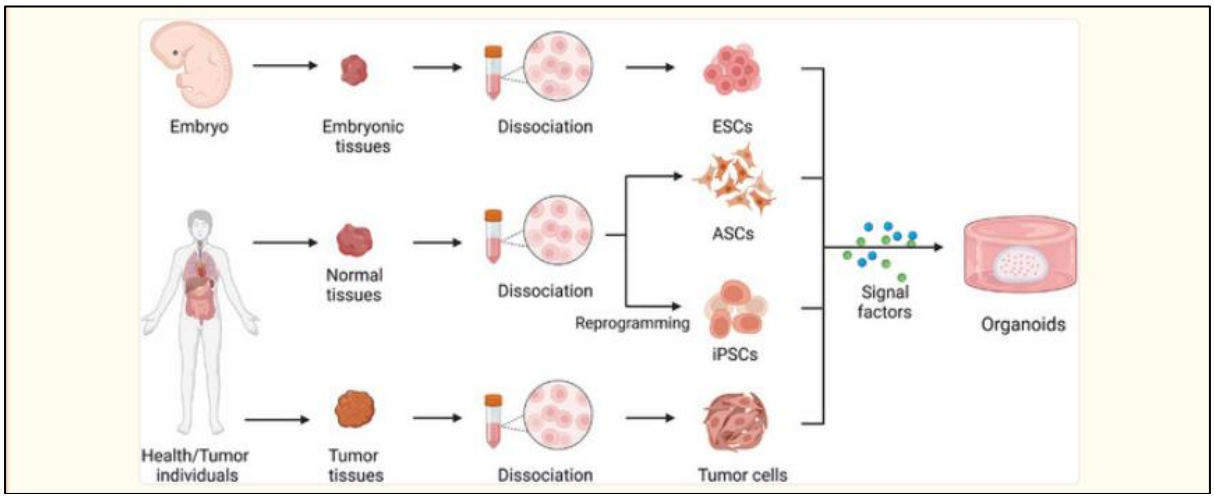


Figure 22. Strategies for formation of organoids in vitro. The cell sources for establishing organoids include embryonic stem cells (ESCs), adult stem cells (ASCs), induced pluripotent stem cells (iPSCs), and tumor cells. Resection and/or biopsy specimens from health / patient individuals are dissociated into single cell to form organoids by incubating with various signal factors (from Yang et al., (2023), Figure 1, Organoids: The current status and biomedical applications - PMC).

[183] Patient-derived organoids CRO | Drug discovery | Organoid development services - HUB Organoids
[184] https://www.sinaihealth.ca/news/sinai-healths-10m-funding-fuels-creation-of-lab-grown-organoids-for-disease-research-and-drug
[185] Phenomics Australia – Phenomics Australia
[186] Australian Organoid Facility (AOF) - Australian Institute for Bioengineering and Nanotechnology - University of Queensland

18 Direct RNA Sequencing for Disease Diagnosis

18.1 Technology Overview

Direct RNA sequencing is continuing to emerge as a tool in disease diagnosis and other healthcare applications by enabling high-throughput transcriptomic sequencing and profiling. The approach permits real-time analysis of full-length RNA molecules without the need for a reverse transcription (to cDNA) or amplification step. Therefore, the approach preserves native RNA modifications and splicing patterns to permit a more comprehensive assessment of disease relevant transcripts. This includes analysis of fusion genes, allele-specific expression and isoform differences. Combined with DNA sequencing approaches, direct RNA sequencing affords a more comprehensive picture of clinically relevant disease-causing mechanisms.

As outlined by Jain et al., (2022):

> "Nanopore direct RNA sequencing (DRS) reads continuous native RNA strands. Early adopters have used this technology to document nucleotide modifications and 3' polyadenosine tails on RNA strands without added chemistry steps. Individual strands ranging in length from 70 to 26,000 nucleotides have been sequenced. In our opinion, broader acceptance of nanopore DRS by molecular biologists and cell biologists will be accelerated by higher base call accuracy and lower RNA input requirements."

18.2 Potential Health Applications

Cancer Diagnosis: Identifying RNA signatures in tumour cells (e.g. fusion genes, allele-specific expression.

Infectious diseases: Direct RNA sequencing was pivotal in tracking SARS-CoV-2 variants (Viehweger et al., 2019)). For example, Herberg et al., (2016) discriminated between bacterial and viral infection in febrile children, using the host RNA signature, with high accuracy compared to clinical and microbiological diagnosis.

Rare diseases: e.g. RNA splicing, gene fusions and allele-specific expression in Mendelian diseases, which can be diagnostic in when whole exome or genome approaches are inconclusive (Kremer et al., 2017; Yepez et al., 2022, (see also Figure 23); Bournasoz et al., 2022).

18.3 Evidence and Readiness

Regulatory approval: limited FDA approval for direct applications.

FDA approved Foundation One for determination of fusions in tumours, using a tissue-based RNA sequencing test[187].

MBS reimbursements available – for example item 73433, neurotrophic receptor tyrosine kinase fusion determination using RNA in metastatic solid tumours[188].

18.4 Market and Industry Engagement

Commercial sequencer availability:
Oxford Nanopore Technologies
G4X
Thermo Fisher Scientific
PacBio

Service providers:
BGI Genomics
Novogene
Azenta Life Sciences
10x Genomics (Chromium platform, Visium for spatial transcriptomics
Strand Life Sciences

[187] Foundation Medicine Launches RNA Sequencing Test, FoundationOne®RNA, in the U.S. | Foundation Medicine
[188] Item 73433 | Medicare Benefits Schedule

18.5 Implementation Challenges and Barriers

Sample integrity. RNA is more challenging to handle compared to DNA, and requires further standardisation of sample extraction and quality (e.g. RIN score).
Accuracy: Long read sequencing allows for interpretation of isoforms and structural variants, however there are trade-offs in accuracy and low throughput.
Clinical validation: General lack of clinical guidelines.

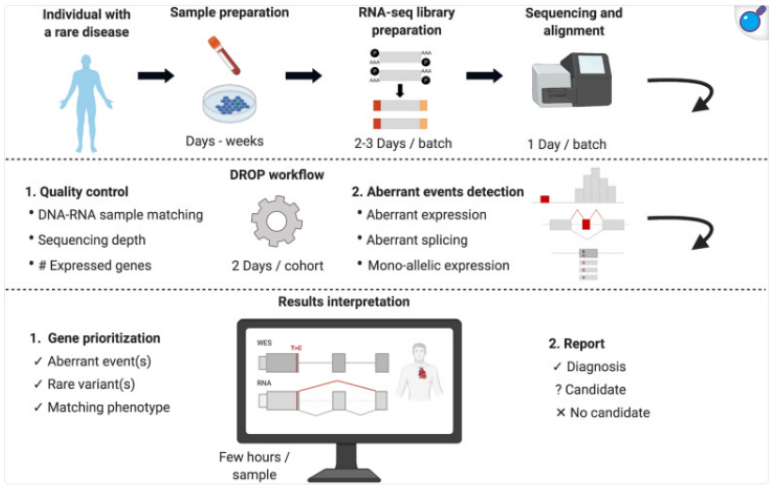
18.6 Cost and Economic Considerations

Equipment costs: Oxford Nanopore's platforms are relatively affordable (US$2,999), but advanced high-throughput systems can cost > $100,000 (e.g. Illumina MiSeq I100 Plus, $US49,000 - $US109,000)[189].

Per-sample costs: Lower than traditional RNA-seq due to reduced library preparation steps.

18.7 Strategic Priority for Australia

Strategic policy and investment recognise the transformative potential of RNA technologies such as direct RNA sequencing. For example, the Commonwealth Government released Australia's *RNA Blueprint* in 2024, which recognizes the importance of RNA-based therapeutics, diagnostics and associated manufacturing. Overarching goals included connecting and promoting the national RNA ecosystem and leading RNA regulation and guidance development[190]. Such a national approach could leverage existing RNA networks e.g. RNA4RD and Splice Accord and existing RNA manufacturing facilities such as the $96 million RNA research centre funded by the NSW Government at Macquarie University[191].



Experimental design of an RNA-seq based diagnostic study. First, individuals suspected of a Mendelian disorder are recruited for DNA sequencing. In addition, patient biopsy material is collected during the routine medical examination and prepared for RNA extraction. The sample preparation process can take from hours for biopsies to weeks for establishing a cell culture. RNA sequencing is then performed followed by alignment and quality control. The generated data go through DROP which consists of quality control steps and detection of aberrant RNA expression events. The results are then interpreted by sample, including the association of aberrant RNA expression events with rare variant(s) and the function of affected genes with the patient phenotype, which can lead to new diagnoses or candidates. Experience-based estimated durations are provided for each step

Figure 23. Experimental design of an RNA-seq based diagnostic study (Yepez et al., (2022), Figure 1, Clinical implementation of RNA sequencing for Mendelian disease diagnostics - PMC).

[189] Illumina Unveils MiSeq I100 Series Sequencing Systems To Advance Next Generation Sequencing For Labs; US List Price Is $49,000 & $109,000 For MiSeq I100 Plus; Available For Global Shipping In 2025
[190] Australia's RNA Blueprint | Department of Industry Science and Resources
[191] $96m RNA facility to be built at Macquarie University | This Week At Macquarie University

19 Integration of Genomics into Electronic Medical Records

19.1 Technology Overview

In Australia there are varying degrees of integration of electronic health records in health systems (i.e. moving from medical paper charts), in some cases only in the past 5 years. With genomics continuing to play a crucial role in healthcare, there may be a need to use genomic data more directly in medical records at the point of care (e.g. ieMR systems). As outlined by Carter et al., (2022), there is a lag in information systems to support genomic workflows from both a diagnostic laboratory and patient-facing provider perspective. Although many other applications may come into play in the future (e.g. pharmacogenomics, population level screening (e.g. reproductive carrier screening and newborn screening), microbiome factors etc), investigating this area for implementation would allow easier integration in the future (refer also Figure 24). This includes using SNOMED or FHIR data for interoperability and gene–phenotype associations.

As outlined by Robertson et al., 2024 (refer also to Figure 25):

> "EHRs are enabling health care to move from protocol-based medicine to precision medicine and helping bring about the next generation of evidence-based practice. Critical to this transformation are the clinical decision support systems (CDSSs). CDSSs are electronic systems that use the information in an EHR to support the treatment of a specific disease or group of related diseases. Using a patient's data in the EHR, a CDSS processes this information in real time and presents the results to clinicians, often with the context provided by the relevant clinical guidelines. The clinician is then able to filter these outputs through the lens of their clinical experience, and the nuance of the scenario, to provide an individual with a precise intervention based on their unique physiology, medical history, and current situation."

The adoption of other population level genomic screening (e.g. newborn screening) provides another opportunity to explore and plan for integration.

Note that other aspects identified in this project, such as AI more broadly, are likely to play key roles in harnessing the power of electronic medical records. For example, the ThinkRare algorithm may permit identification of patients with previously undetermined underlying genetic causes of disease[192].

19.2 Potential Healthcare Applications

- Disease Risk prediction (e.g. Polygenic Risk Score incorporation).
- Carrier Screening and reproductive planning.
- Pharmacogenomics and Medication Safety.
- Reanalysis: prompting of reanalysis as phenotype evolves, or new clinical information.
- Clinical workflow optimization e.g. automatic referral to specialist services or genetic counselling if certain thresholds are met via RMA-integrated genomics.
- Population health management: e.g. population level screening (see DNA screen).
- Family history and cascade testing: storing of family history consistent with privacy laws and streamlining of family contact.

19.3 Evidence and Readiness

- Emerge network (NIH) – Electronic Medical Records and Genomics network.
- EPIC software has been building a genomics model which is currently being employed in some Australian jurisdictions[193] [194].
- Points of consideration statement from ACMG (Gebe et al., 2020), this included the need for information to be available to other specialist clinicians, and the need to accommodate direct-to-consumer genetic testing.

[192] https://www.cheo.on.ca/en/news/world-first-ai-algorithm-developed-at-cheo-leads-to-rare-disease-diagnosis-for-families.aspx
[193] Epic | ...With the patient at the heart
[194] Epic Electronic Medical Records (EMR) : About Epic Electronic Medical Records (EMR)

- PennChart Genomics Initiative: *The PennChart Genomics Initiative (PGI) at the University of Pennsylvania is a multidisciplinary collaborative effort including Penn Medicine clinicians, researchers, pathologists, legal staff, and information services with input and efforts from Epic Systems Corporation (Wisconsin) and Ambry Genetics Corporation (California), a commercial genetic testing laboratory. (Lau-Min et al, 2020).*

19.4 Market and Industry Engagement

- Google Health e.g. Care Studio clinical software[195].
- Tempus startup[196]. A desktop platform for ordering, managing and receiving tests and patients results.
- Fabric Genomics[197].

19.5 Implementation Challenges and Barriers

Challenges and Barriers (refer also to Table 4)

- **Regulatory and ethical considerations:** use of genetic data by non-genetic specialists. Solutions of data sharing issues, and research vs clinical data / reporting.
- **Privacy concerns:** including how to store / secure family related data.
- **Resistance to change e.g.** Hospital and Health service units within a particular state or territory may be utilizing completely different electronic medical record systems, or withing the same system, with rolling upgrades and versioning issues, which would contribute to significant compatibility and standardization challenges.
- **Data volume and complexity –** also issues of interoperability between states, which is particularly important due to family and sibling data necessary for genetic interpretation of pedigrees**.**
- **Workforce:** training of staff and adoption issues.
- **Cost and infrastructure.**

Enablers

- Leverage existing **phenotype standardization (e.g. FHIR, SNOMED).**
- **National Genomic structures** (e.g. Genomics Australia).

19.6 Cost and Economic Considerations

- Very high infrastructure costs for changing / modifying ieMR system.
- Health economics of any cost savings would take considerable time / pilots to provide evidence base.

19.7 Australian Strategy

Integration of Genomics into electronic health record is a large task, however mapping out an approach and strategy in the immediate future will aid in implementation. There is a risk of not investing early in terms of the likely increase in genomic data, particularly at a population level (e.g. Reproductive carrier screening). Similarly, greater uptake of MBS funding for genomic testing may drive changes to ieMR[198]).

In order to ensure successful consultation and engagement in this area, we note the Importance of collaboration with Clinical Genetic provides, state, territory and Commonwealth government, Genomics and Genetic advocacy groups and Australian Institute of Digital Health (including State and Territory Digital Health Agencies. There is also an opportunity to align with the aspects of data sharing and interoperability of the proposed National Approach to Genomic Information Management (NAGIM[199] , which is a digital genomics framework including best practices on managing genomic information.

[195] Take a look at Conditions, our new feature in Care Studio
[196] tempus.com
[197] Clinical Genomics - Fabric Genomics
[198] MSAC Applications for Genetic, Genomic and Screening Tests — Australian Genomics
[199] Progress the implementation of the NAGIM Blueprint — Australian Genomics

Other relevant groups include the Australian Alliance for Artificial Intelligence for Health Care (AAAiH)[200]. and National Digital Health Strategy 2023-2028[201](Australian Digital Health Agency).

Other legislation and standards to be adhered to include The Privacy Act (1988), My Health Records Act (2012), National Pathology Accreditation Advisory Council (for genetic, genome and phenotype data). Genomic data integration must also align with clinical terminology standards such as SNOMED CT_AU[202], to ensure interoperability.

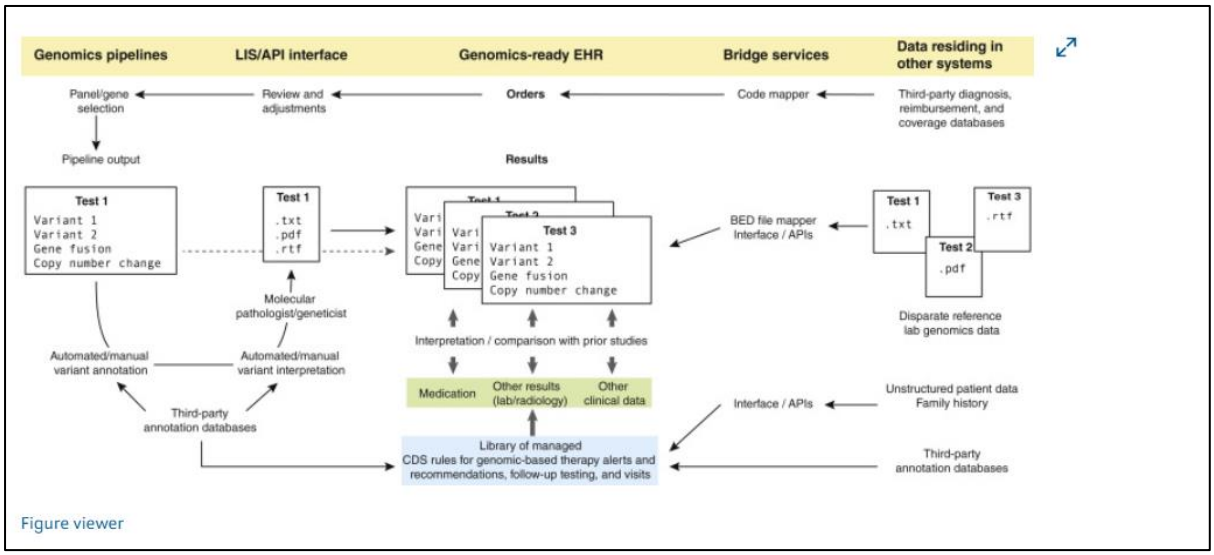


Figure 24. Workflow and data transformations required for a genomic-ready electronic health record (Carter et al., (2021), Figure 1, Electronic Health Records and Genomics - The Journal of Molecular Diagnostics).

[200] Ai Health Alliance | Innovation | Translation | Impact
[201] Discover the National Digital Health Strategy (2023 - 2028)
[202] SNOMED CT-AU and Australian Medicines Terminology May 2022 Release

Table 4. Summary of challenges of opportunities for use of electronic medical record in genomics (from Carter et al., (2021), Table 1, Electronic Health Records and Genomics - The Journal of Molecular Diagnostics).

Challenges	Opportunities
EHRs are not yet ready to send accurate, coded, and appropriately granular clinical history, signs, symptoms, family history, and other broad sets of data elements to laboratories without generating significant burden on providers.	Develop stakeholder consensus-derived and standardized methods to apply accurate concept codes to the clinical notes, signs, symptoms, and family histories as well as specimen locations, such that necessary information could be sent by the provider using an automated or semi-automated import into the electronic order for genomic testing.
EHRs lack sufficient information about genetic test orders and generally do not have discrete variant result data to facilitate appropriate test ordering and utilization. Absence of standardized genomic variant data structures from the LIS to the EHR.	Establish a consensus standard for minimum discrete data required to define a genomic variant in an EHR. Establish a consensus standard for minimum discrete data needed to define a genetic/genomic test order.
Interoperability standards for genomics are currently limited in several ways, including the use of syntax with limited hierarchy (HL7 version 2.x) and inadequate coding systems for genomic orders and results.	Before mandating changes to interoperability requirements, governments and regulators should carefully review the cost and burden to laboratories as well as the safety of existing coding standards that are currently inadequate for genomic data. Such work should occur after establishment of a consensus standard for minimum discrete data required to define a genomic variant.
Genomic reports between laboratories are variable in structure and content.	Develop recommendations for content and structure of genomic reports that support providing the established consensus standard for minimum discrete data required to define a genomic variant in an EHR.
Implementation of molecular pathology and genomics professional societies multi-organizational consensus standards and guidelines for variant nomenclature, hierarchical result structure, and genomic report formats has been modest.	Encourage laboratories and EHRs to support and implement molecular pathology and genomics professional societies multi-organizational consensus standards and guidelines for report content and structure to standardize structure and content between laboratories. Professional organizations should consider further developing consensus report structures that use sound principles of human factors engineering and usability.
There are no standards for how to display aggregated variant data over time and between sample sources, tests, and laboratories that keep clinical context and associated interpretation intact.	Standards for aggregation of genomic data over time and between sample sources, tests, and laboratories should be developed that keep clinical context and associated interpretation intact.
Consensus guidelines on best practice for requesting and providing reclassification of variants is not currently available.	Establish consensus guidelines on best practice for requesting and providing reclassification of variants.
Genomic reports are difficult for medical personnel and patients to understand, and in the United States, patients have the right to immediately access their genomic test reports on request.	Professional organizations should consider further developing consensus report structures that use sound principles of human factors engineering and usability that enable understanding by most patients.
Absence of national and international standards for CDS rules.	Establish evidence-based international recommendations for CDS in genomic test orders and in drug orders impacted by genomic results for safety and consistency in practice with a prerequisite minimum discrete genomic variant data consensus standard established.
Currently, textual data from genomic reports are exported and released to authorized parties, and analysis of such data is limited by its highly variable format and lack of structure.	Establish and integrate appropriate, safe, and functional international standards for interoperability and data retrieval.
Current technology lacks sufficient functionality to ensure that release of genomic data to appropriate health care organizations, research studies, or clinical repositories requires and receives informed consent from the patient or legal guardian, and/or institutional board review.	Develop technology and cybersecurity functions in EHRs that ensure that genomic data are released as authorized after informed consent from the patient along with tools to educate patients about informed consent.
Current coding and interoperability standards are not adequate for genomic data.	Develop safe, complete, and accurate standards for coding and interoperability of genomic data, per the future established minimum discrete variant data standard.

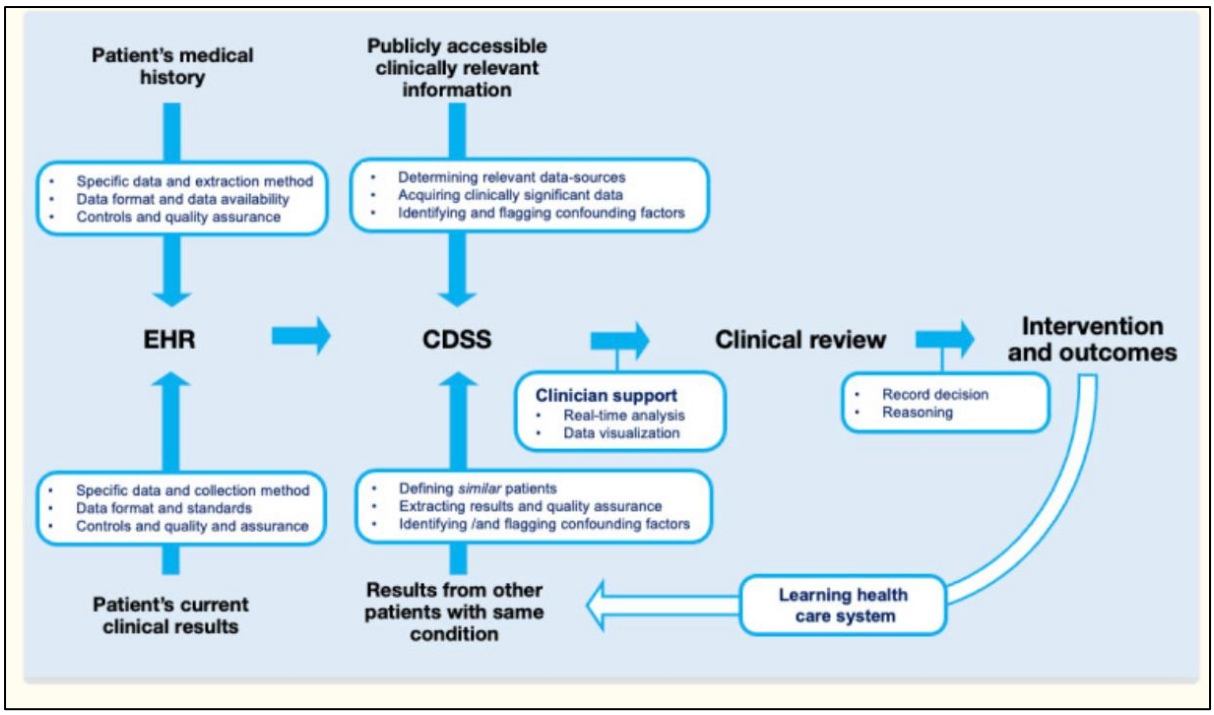


Figure 25. A simplified overview of a patient's journey through a modern digitally enabled health care system. (from Robertson et al., (2024), Figure 1, It Is in Our DNA: Bringing Electronic Health Records and Genomic Data Together for Precision Medicine - PMC).

Appendix 1: Methodology

International Horizon Scanning of Emerging Disruptive Health Genomics Technologies

Scan Sources

Material to review:

- Peer reviewed literature
- Policy/strategy/implementation papers
- Funding rounds by Australian and international initiatives
- Seed/pilot Funding by state health departments (e.g. VMRAF (VIC), ORI (QLD))
- Relevant conference programs (e.g. AGTA, HGSA, ESHG, ASHG)
- Clinical trial registries (WHO, NIH)

Initiatives/agencies/groups: Australia

- State and territory government representatives in genomic space (e.g. ORI Queensland Health)
- Australian Genomic Technologies Association representatives
- Life Sciences / Biotechnology representatives (e.g. DeCODE Science, Illumina, Oxford Nanopore Technologies, PacBio, BGI/ MGI, Twist BioScience, 10XGenomics)

Initiatives/agencies/groups: International:

- World Health Organization

UK

- Genomics England
- NIHR Innovation Observatory (Newcastle University) (https://www.io.nihr.ac.uk/)
- NICE (National Institute for Health and Care Excellence)

EUROPE

- International Consortia for Personalised Medicine
- Orphanet

USA

- PCORI (Patient Centred Outcomes Research Institute)
- GA4GH (Global Alliance for Genomics in Health)

- Broad Institute of MIT and Harvard
- Chan Zuckerberg Initiative
- Gates foundation

Canada

- Genome Canada
- National Research Council of Canada Industrial Research Assistance Program (NRC IRAP)
- Canadian Agency for Drugs and Technologies in Health (CADTH) Horizon Scanning Service

Singapore

- Precise Singapore

Scan Horizon

Technologies and/or Technology applications that were deemed to be hitting the health sector in the next 1-3 years.

Filtration Step

- Does the technology have the potential to impact the Australian healthcare system
- Likelihood of adoption by States and Territories
- Is the technology new or an established technology for a new indication

Technology prioritisation criteria

- Likelihood of adoption by States and Territories
- Alignment with Genomics Australia / National Health Genomics Policy Framework
- If a current unmet need is addressed
- Ease/challenge of implementation in health sector
- How likely technology application will hit sector in next 1-3 years
- Cost – both initial and to sustain (e.g. hospital / diagnostic infrastructure costs)
- Broader systems benefit e.g. lessening burden of journey to diagnosis; reduced length of hospital stay; reducing other hospital costs
- Opportunities for Disinvestment

References

Abdelwahab O, Belzile F, Torkamaneh D. Performance analysis of conventional and AI-based variant callers using short and long reads. BMC Bioinformatics. 2023 Dec 14;24(1):472. doi: 10.1186/s12859-023-05596-3. PMID: 38097928; PMCID: PMC10720095.

Abdelwahab O, Torkamaneh D. Artificial intelligence in variant calling: a review. Front Bioinform. 2025 Apr 23;5:1574359. doi: 10.3389/fbinf.2025.1574359. PMID: 40337525; PMCID: PMC12055765.

An J, Lu Y, Chen Y, Chen Y, Zhou Z, Chen J, Peng C, Huang R, Peng F. Spatial transcriptomics in breast cancer: providing insight into tumour heterogeneity and promoting individualized therapy. Front Immunol. 2024 Dec 19;15:1499301. doi: 10.3389/fimmu.2024.1499301. PMID: 39749323; PMCID: PMC11693744.

Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, Chen PJ, Wilson C, Newby GA, Raguram A, Liu DR. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature. 2019 Dec;576(7785):149-157. doi: 10.1038/s41586-019-1711-4. Epub 2019 Oct 21. PMID: 31634902; PMCID: PMC6907074.

Aregger M, Chandrashekhar M, Tong AHY, Chan K, Moffat J. Pooled Lentiviral CRISPR-Cas9 Screens for Functional Genomics in Mammalian Cells. Methods Mol Biol. 2019;1869:169-188. doi: 10.1007/978-1-4939-8805-1_15. PMID: 30324523.

Aron-Wisnewsky J, Vigliotti C, Witjes J, Le P, Holleboom AG, Verheij J, Nieuwdorp M, Clément K. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. Nat Rev Gastroenterol Hepatol. 2020 May;17(5):279-297. doi: 10.1038/s41575-020-0269-9. Epub 2020 Mar 9. PMID: 32152478.

Auerbach BJ, Hu J, Reilly MP, Li M. Applications of single-cell genomics and computational strategies to study common disease and population-level variation. Genome Res. 2021 Oct;31(10):1728-1741. doi: 10.1101/gr.275430.121. PMID: 34599006; PMCID: PMC8494214.

Ayanoğlu FB, Elçin AE, Elçin YM. Bioethical issues in genome editing by CRISPR-Cas9 technology. Turk J Biol. 2020 Apr 2;44(2):110-120. doi: 10.3906/biy-1912-52. PMID: 32256147; PMCID: PMC7129066.

Badwan BA, Liaropoulos G, Kyrodimos E, Skaltsas D, Tsirigos A, Gorgoulis VG. Machine learning approaches to predict drug efficacy and toxicity in oncology. Cell Rep Methods. 2023 Feb 21;3(2):100413. doi: 10.1016/j.crmeth.2023.100413. PMID: 36936080; PMCID: PMC10014302.

Berrou, P., Ramsunder A & Palmer, R., Making the case for pharmacogenomics in the management of mental health conditions2023. The Pharmaceutical Journal. Making the case for pharmacogenomics in the management of mental health conditions - The Pharmaceutical Journal.

Birgmeier J, Haeussler M, Deisseroth CA, Steinberg EH, Jagadeesh KA, Ratner AJ, Guturu H, Wenger AM, Diekhans ME, Stenson PD, Cooper DN, Ré C, Beggs AH, Bernstein JA, Bejerano G. AMELIE speeds Mendelian diagnosis by matching patient phenotype and genotype to primary literature. Sci Transl Med. 2020 May 20;12(544):eaau9113. doi: 10.1126/scitranslmed.aau9113. PMID: 32434849; PMCID: PMC9366928.

Björnsson B, Borrebaeck C, Elander N, Gasslander T, Gawel DR, Gustafsson M, Jörnsten R, Lee EJ, Li X, Lilja S, Martínez-Enguita D, Matussek A, Sandström P, Schäfer S, Stenmarker M, Sun XF, Sysoev O, Zhang H, Benson M; Swedish Digital Twin Consortium. Digital twins to personalize medicine. Genome Med. 2019 Dec 31;12(1):4. doi: 10.1186/s13073-019-0701-3. PMID: 31892363; PMCID: PMC6938608.

Blanco-González A, Cabezón A, Seco-González A, Conde-Torres D, Antelo-Riveiro P, Piñeiro Á, Garcia-Fandino R. The Role of AI in Drug Discovery: Challenges, Opportunities, and Strategies. Pharmaceuticals (Basel). 2023 Jun 18;16(6):891. doi: 10.3390/ph16060891. PMID: 37375838; PMCID: PMC10302890.

Bournazos AM, Riley LG, Bommireddipalli S, Ades L, Akesson LS, Al-Shinnag M, Alexander SI, Archibald AD, Balasubramaniam S, Berman Y, Beshay V, Boggs K, Bojadzieva J, Brown NJ, Bryen SJ, Buckley MF, Chong B, Davis MR, Dawes R, Delatycki M, Donaldson L, Downie L, Edwards C, Edwards M, Engel A, Ewans LJ, Faiz F, Fennell A, Field M, Freckmann ML, Gallacher L, Gear R, Goel H, Goh S, Goodwin L, Hanna B, Harraway J, Higgins M, Ho G, Hopper BK, Horton AE, Hunter MF, Huq AJ, Josephi-Taylor S, Joshi H, Kirk E, Krzesinski E, Kumar KR, Lemckert F, Leventer RJ, Lindsey-Temple SE, Lunke S, Ma A, Macaskill S, Mallawaarachchi A, Marty M, Marum JE, McCarthy HJ, Menezes MP, McLean A, Milnes D, Mohammad S, Mowat D, Niaz A, Palmer EE, Patel C, Patel SG, Phelan D, Pinner JR, Rajagopalan S, Regan M, Rodgers J, Rodrigues M, Roxburgh RH, Sachdev R, Roscioli T, Samarasekera R, Sandaradura SA, Savva E, Schindler T, Shah M, Sinnerbrink IB, Smith JM, Smith RJ, Springer A, Stark Z, Strom SP, Sue CM, Tan K, Tan TY, Tantsis E, Tchan MC, Thompson BA, Trainer AH, van Spaendonck-Zwarts K, Walsh R, Warwick L, White S, White SM, Williams MG, Wilson MJ, Wong WK, Wright DC, Yap P, Yeung A, Young H, Jones KJ, Bennetts B, Cooper ST; Australasian Consortium for RNA Diagnostics. Standardized practices for RNA diagnostics using clinically accessible specimens reclassifies 75% of putative splicing variants. Genet Med. 2022 Jan;24(1):130-145. doi: 10.1016/j.gim.2021.09.001. Epub 2021 Nov 30. PMID: 34906502.

Brad Hall, Sawsan Alyafei, Sathishkumar Ramaswamy, Shruti Sinha, Maha El Naofal, Fatma Rabea, Bryan J. Killinger, Gary J. Latham, Ahmad Abou Tayoun. 2024. A dual-mode targeted Nanopore sequencing assay for comprehensive SMN1 and SMN2 variant analysis. medRxiv 2024.02.22.24303180; doi: https://doi.org/10.1101/2024.02.22.24303180

Bressan D, Battistoni G, Hannon GJ. The dawn of spatial omics. Science. 2023 Aug 4;381(6657):eabq4964. doi: 10.1126/science.abq4964. Epub 2023 Aug 4. PMID: 37535749; PMCID: PMC7614974.

Carter AB, Abruzzo LV, Hirschhorn JW, Jones D, Jordan DC, Nassiri M, Ogino S, Patel NR, Suciu CG, Temple-Smolkin RL, Zehir A, Roy S. Electronic Health Records and Genomics: Perspectives from the Association for Molecular Pathology Electronic Health Record (EHR) Interoperability for Clinical Genomics Data Working Group. J Mol Diagn. 2022 Jan;24(1):1-17. doi: 10.1016/j.jmoldx.2021.09.009. Epub 2021 Oct 15. PMID: 34656760.

Casauria S, Collins F, White SM, Konings P, Wallis M, Pachter N, McGaughran J, Barnett C, Best S. Assessing the unmet needs of genomic testing in Australia: a geospatial exploration. Eur J Hum Genet. 2025 Apr;33(4):496-503. doi: 10.1038/s41431-024-01746-0. Epub 2024 Nov 27. PMID: 39592829; PMCID: PMC11986069.

Chen C, Wang J, Pan D, Wang X, Xu Y, Yan J, Wang L, Yang X, Yang M, Liu GP. Applications of multi-omics analysis in human diseases. MedComm (2020). 2023 Jul 31;4(4):e315. doi: 10.1002/mco2.315. PMID: 37533767; PMCID: PMC10390758.

Chen J, Huang Y, Tang Z, Li M, Ling X, Liao J, Zhou X, Fang S, Zhao H, Zhong W, Yuan X. Genome-Scale CRISPR-Cas9 Transcriptional Activation Screening in Metformin Resistance Related Gene of Prostate Cancer. Front Cell Dev Biol. 2021 Jan 26;8:616332. doi: 10.3389/fcell.2020.616332. PMID: 33575255; PMCID: PMC7870801.

Chen PJ, Liu DR. Prime editing for precise and highly versatile genome manipulation. Nat Rev Genet. 2023 Mar;24(3):161-177. doi: 10.1038/s41576-022-00541-1. Epub 2022 Nov 7. PMID: 36344749; PMCID: PMC10989687.

Chen WT, Lu A, Craessaerts K, Pavie B, Sala Frigerio C, Corthout N, Qian X, Laláková J, Kühnemund M, Voytyuk I, Wolfs L, Mancuso R, Salta E, Balusu S, Snellinx A, Munck S, Jurek A, Fernandez Navarro J, Saido TC, Huitinga I, Lundeberg J, Fiers M, De Strooper B. Spatial Transcriptomics and In Situ Sequencing to Study Alzheimer's Disease. Cell. 2020 Aug 20;182(4):976-991.e19. doi: 10.1016/j.cell.2020.06.038. Epub 2020 Jul 22. PMID: 32702314.

Coudray N, Ocampo PS, Sakellaropoulos T, Narula N, Snuderl M, Fenyö D, Moreira AL, Razavian N, Tsirigos A. Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning. Nat Med. 2018 Oct;24(10):1559-1567. doi: 10.1038/s41591-018-0177-5. Epub 2018 Sep 17. PMID: 30224757; PMCID: PMC9847512.

Dai W, Qiao X, Fang Y, Guo R, Bai P, Liu S, Li T, Jiang Y, Wei S, Na Z, Xiao X, Li D. Epigenetics-targeted drugs: current paradigms and future challenges. Signal Transduct Target Ther. 2024 Nov 26;9(1):332. doi: 10.1038/s41392-024-02039-0. PMID: 39592582; PMCID: PMC11627502. Ghasemi, S., Jeddi, F., & Moradi, S. (2023). "Epigenetic Therapeutics in Cancer: Advancing the Next Generation of Drugs." *Nature Reviews Drug Discovery*. DOI: 10.1038/s41573-023-00290.

De Domenico M, Allegri L, Caldarelli G, d'Andrea V, Di Camillo B, Rocha LM, Rozum J, Sbarbati R, Zambelli F. Challenges and opportunities for digital twins in precision medicine from a complex systems perspective. NPJ Digit Med. 2025 Jan 17;8(1):37. doi: 10.1038/s41746-024-01402-3. PMID: 39825012; PMCID: PMC11742446. Dias R, Torkamani A. Artificial intelligence in clinical and genomic diagnostics. Genome Med. 2019 Nov 19;11(1):70. doi: 10.1186/s13073-019-0689-8. PMID: 31744524; PMCID: PMC6865045.

Duan L, Ouyang K, Xu X, Xu L, Wen C, Zhou X, Qin Z, Xu Z, Sun W, Liang Y. Nanoparticle Delivery of CRISPR/Cas9 for Genome Editing. Front Genet. 2021 May 12;12:673286. doi: 10.3389/fgene.2021.673286. PMID: 34054927; PMCID: PMC8149999.

El Dika I, Lim HY, Yong WP, Lin CC, Yoon JH, Modiano M, Freilich B, Choi HJ, Chao TY, Kelley RK, Brown J, Knox J, Ryoo BY, Yau T, Abou-Alfa GK. An Open-Label, Multicenter, Phase I, Dose Escalation Study with Phase II Expansion Cohort to Determine the Safety, Pharmacokinetics, and Preliminary Antitumor Activity of Intravenous TKM-080301 in Subjects with Advanced Hepatocellular Carcinoma. Oncologist. 2019 Jun;24(6):747-e218. doi: 10.1634/theoncologist.2018-0838. Epub 2018 Dec 31. PMID: 30598500; PMCID: PMC6656521.

Emani PS, Warrell J, Anticevic A, Bekiranov S, Gandal M, McConnell MJ, Sapiro G, Aspuru-Guzik A, Baker JT, Bastiani M, Murray JD, Sotiropoulos SN, Taylor J, Senthil G, Lehner T, Gerstein MB, Harrow AW. Quantum computing at the frontiers of biological sciences. Nat Methods. 2021 Jul;18(7):701-709. doi: 10.1038/s41592-020-01004-3. PMID: 33398186; PMCID: PMC8254820.

Empey PE, Karnes JH, Johnson JA. Pharmacogenetics: Opportunities for the *All of Us* Research Program and Other Large Data Sets to Advance the Field. Annu Rev Pharmacol Toxicol. 2025 Jan;65(1):111-130. doi: 10.1146/annurev-pharmtox-061724-080718. PMID: 39847465.

Erdmann H, Schöberl F, Giurgiu M, Leal Silva RM, Scholz V, Scharf F, Wendlandt M, Kleinle S, Deschauer M, Nübling G, Heide W, Babacan SS, Schneider C, Neuhann T, Hahn K, Schoser B, Holinski-Feder E, Wolf DA, Abicht A. Parallel in-depth analysis of repeat expansions in ataxia patients by long-read sequencing. Brain. 2023 May 2;146(5):1831-1843. doi: 10.1093/brain/awac377. PMID: 36227727.

Farani MR, Sarlak M, Gholami A, Azaraian M, Binabaj MM, Kakavandi S, Tambuwala MM, Taheriazam A, Hashemi M, Ghasemi S. Epigenetic drugs as new emerging therapeutics: What is the scale's orientation of application and challenges? Pathol Res Pract. 2023 Aug;248:154688. doi: 10.1016/j.prp.2023.154688. Epub 2023 Jul 17. PMID: 37494800.

Feehley T, O'Donnell CW, Mendlein J, Karande M, McCauley T. Drugging the epigenome in the age of precision medicine. Clin Epigenetics. 2023 Jan 11;15(1):6. doi: 10.1186/s13148-022-01419-z. PMID: 36631803; PMCID: PMC9832256.

Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, Chiriboga CA, Saito K, Servais L, Tizzano E, Topaloglu H, Tulinius M, Montes J, Glanzman AM, Bishop K, Zhong ZJ, Gheuens S, Bennett CF, Schneider E, Farwell W, De Vivo DC; ENDEAR Study Group. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med. 2017 Nov 2;377(18):1723-1732. doi: 10.1056/NEJMoa1702752. PMID: 29091570.

Fujiwara M, Hashimoto H, Doi K, Kujiraoka M, Tanizawa Y, Ishida Y, Sasaki M, Nagasaki M. Secure secondary utilization system of genomic data using quantum secure cloud. Sci Rep. 2022 Nov 2;12(1):18530. doi: 10.1038/s41598-022-22804-x. PMID: 36323706; PMCID: PMC9630297.

Fustero-Torre C, Jiménez-Santos MJ, García-Martín S, Carretero-Puche C, García-Jimeno L, Ivanchuk V, Di Domenico T, Gómez-López G, Al-Shahrour F. Beyondcell: targeting cancer therapeutic heterogeneity in single-cell RNA-seq data. Genome Med. 2021 Dec 16;13(1):187. doi: 10.1186/s13073-021-01001-x. PMID: 34911571; PMCID: PMC8675493.

Garg M, Karpinski M, Matelska D, Middleton L, Burren OS, Hu F, Wheeler E, Smith KR, Fabre MA, Mitchell J, O'Neill A, Ashley EA, Harper AR, Wang Q, Dhindsa RS, Petrovski S, Vitsios D. Disease prediction with multi-omics and biomarkers empowers case-control genetic discoveries in the UK Biobank. Nat Genet. 2024 Sep;56(9):1821-1831. doi: 10.1038/s41588-024-01898-1. Epub 2024 Sep 11. PMID: 39261665; PMCID: PMC11390475.

Geurts MH, de Poel E, Pleguezuelos-Manzano C, Oka R, Carrillo L, Andersson-Rolf A, Boretto M, Brunsveld JE, van Boxtel R, Beekman JM, Clevers H. Evaluating CRISPR-based prime editing for cancer modeling and CFTR repair in organoids. Life Sci Alliance. 2021 Aug 9;4(10):e202000940. doi: 10.26508/lsa.202000940. PMID: 34373320; PMCID: PMC8356249.

Gigante CM, Yale G, Condori RE, Costa NC, Long NV, Minh PQ, Chuong VD, Tho ND, Thanh NT, Thin NX, Hanh NTH, Wambura G, Ade F, Mito O, Chuchu V, Muturi M, Mwatondo A, Hampson K, Thumbi SM, Thomae BG, de Paz VH, Meneses S, Munyua P, Moran D, Cadena L, Gibson A, Wallace RM, Pieracci E.G., Li Y. Portable Rabies Virus Sequencing in Canine Rabies Endemic Countries Using the Oxford Nanopore MinION. Viruses. 2020 Nov 4;12(11):1255. doi: 10.3390/v12111255. PMID: 33158200; PMCID: PMC7694271.

Gillespie, N., Lockey, S., Ward, T., Macdade, A., & Hassed, G. (2025). *Trust, attitudes and use of artificial intelligence: A global study 2025*. The University of Melbourne and KPMG. DOI 10.26188/28822919

Gnyszka A, Jastrzebski Z, Flis S. DNA methyltransferase inhibitors and their emerging role in epigenetic therapy of cancer. Anticancer Res. 2013 Aug;33(8):2989-96. PMID: 23898051.

Godbout K, Tremblay JP. Prime Editing for Human Gene Therapy: Where Are We Now? Cells. 2023 Feb 7;12(4):536. doi: 10.3390/cells12040536. PMID: 36831203; PMCID: PMC9954691.

Grebe TA, Khushf G, Chen M, Bailey D, Brenman LM, Williams MS, Seaver LH; ACMG Social, Ethical and Legal Issues Committee. The interface of genomic information with the electronic health record: a points to consider statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020 Sep;22(9):1431-1436. doi: 10.1038/s41436-020-0841-2. Epub 2020 Jun 1. PMID: 32475985.

Gulliver EL, Young RB, Chonwerawong M, D'Adamo GL, Thomason T, Widdop JT, Rutten EL, Rossetto Marcelino V, Bryant RV, Costello SP, O'Brien CL, Hold GL, Giles EM, Forster SC. Review article: the future of microbiome-based therapeutics. Aliment Pharmacol Ther. 2022 Jul;56(2):192-208. doi: 10.1111/apt.17049. Epub 2022 May 24. PMID: 35611465; PMCID: PMC9322325.

Guo C, Ma X, Gao F, Guo Y. Off-target effects in CRISPR/Cas9 gene editing. Front Bioeng Biotechnol. 2023 Mar 9;11:1143157. doi: 10.3389/fbioe.2023.1143157. PMID: 36970624; PMCID: PMC10034092.

Haifer C, Kelly CR, Paramsothy S, Andresen D, Papanicolas LE, McKew GL, Borody TJ, Kamm M, Costello SP, Andrews JM, Begun J, Chan HT, Connor S, Ghaly S, Johnson PD, Lemberg DA, Paramsothy R, Redmond A, Sheorey H, van der Poorten D, Leong RW. Australian consensus statements for the regulation, production and use of faecal microbiota transplantation in clinical practice. Gut. 2020 May;69(5):801-810. doi: 10.1136/gutjnl-2019-320260. Epub 2020 Feb 11. PMID: 32047093.

Happi Mbakam C, Rousseau J, Tremblay G, Yameogo P, Tremblay JP. Prime Editing Permits the Introduction of Specific Mutations in the Gene Responsible for Duchenne Muscular Dystrophy. Int J Mol Sci. 2022 May 31;23(11):6160. doi: 10.3390/ijms23116160. PMID: 35682838; PMCID: PMC9181224.

Harrison JE, Lynch F, Stark Z, Vears DF. Analysis of public perceptions on the use of artificial intelligence in genomic medicine. Hum Genomics. 2024 Nov 18;18(1):128. doi: 10.1186/s40246-024-00686-6. PMID: 39558426; PMCID: PMC11575060.

Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome Biol. 2017 May 5;18(1):83. doi: 10.1186/s13059-017-1215-1. PMID: 28476144; PMCID: PMC5418815.

Herberg JA, Kaforou M, Wright VJ, Shailes H, Eleftherohorinou H, Hoggart CJ, Cebey-López M, Carter MJ, Janes VA, Gormley S, Shimizu C, Tremoulet AH, Barendregt AM, Salas A, Kanegaye J, Pollard AJ, Faust SN, Patel S, Kuijpers T, Martinón-Torres F, Burns JC, Coin LJ, Levin M; IRIS Consortium. Diagnostic Test Accuracy of a 2-Transcript Host RNA Signature for Discriminating Bacterial vs Viral Infection in Febrile Children. JAMA. 2016 Aug 23-30;316(8):835-45. doi: 10.1001/jama.2016.11236. Erratum in: JAMA. 2017 Feb 7;317(5):538. doi: 10.1001/jama.2016.18601. PMID: 27552617; PMCID: PMC5997174.

Hughes 2023. Research Priorities for Australian pharmacogenomics. https://www.australiangenomics.org.au/wp-content/uploads/2022/11/Pharmacogenomics-Incubator-Project-Report_30Aug2022-.pdf.
Robertson AJ, Mallett AJ, Stark Z, Sullivan C. It Is in Our DNA: Bringing Electronic Health Records and Genomic Data Together for Precision Medicine. JMIR Bioinform Biotechnol. 2024 Jun 13;5:e55632. doi: 10.2196/55632. PMID: 38935958; PMCID: PMC11211701.

Jackson KC, Pachter L. A standard for sharing spatial transcriptomics data. Cell Genom. 2023 Aug 9;3(8):100374. doi: 10.1016/j.xgen.2023.100374. PMID: 37601972; PMCID: PMC10435375.

Jain, M., Abu-Shumays, R., Olsen, H.E. *et al.* Advances in nanopore direct RNA sequencing. *Nat Methods* **19**, 1160–1164 (2022). https://doi.org/10.1038/s41592-022-01633-w

Jovic D, Liang X, Zeng H, Lin L, Xu F, Luo Y. Single-cell RNA sequencing technologies and applications: A brief overview. Clin Transl Med. 2022 Mar;12(3):e694. doi: 10.1002/ctm2.694. PMID: 35352511; PMCID: PMC8964935.

Jovic D, Liang X, Zeng H, Lin L, Xu F, Luo Y. Single-cell RNA sequencing technologies and applications: A brief overview. Clin Transl Med. 2022 Mar;12(3):e694. doi: 10.1002/ctm2.694. PMID: 35352511; PMCID: PMC8964935.

Kamel Boulos MN, Zhang P. Digital Twins: From Personalised Medicine to Precision Public Health. J Pers Med. 2021 Jul 29;11(8):745. doi: 10.3390/jpm11080745. PMID: 34442389; PMCID: PMC8401029.
Kantor A, McClements ME, MacLaren RE. CRISPR-Cas9 DNA Base-Editing and Prime-Editing. Int J Mol Sci. 2020 Aug 28;21(17):6240. doi: 10.3390/ijms21176240. PMID: 32872311; PMCID: PMC7503568.

Karamperis K, Koromina M, Papantoniou P, Skokou M, Kanellakis F, Mitropoulos K, Vozikis A, Müller DJ, Patrinos GP, Mitropoulou C. Economic evaluation in psychiatric pharmacogenomics: a systematic review. Pharmacogenomics J. 2021 Aug;21(4):533-541. doi: 10.1038/s41397-021-00249-1. Epub 2021 Jul 2. PMID: 34215853.

Katsoulakis E, Wang Q, Wu H, Shahriyari L, Fletcher R, Liu J, Achenie L, Liu H, Jackson P, Xiao Y, Syeda-Mahmood T, Tuli R, Deng J. Digital twins for health: a scoping review. NPJ Digit Med. 2024 Mar 22;7(1):77. doi: 10.1038/s41746-024-01073-0. PMID: 38519626; PMCID: PMC10960047.

Kemkar S, Tao M, Ghosh A, Stamatakos G, Graf N, Poorey K, Balakrishnan U, Trask N, Radhakrishnan R. Towards verifiable cancer digital twins: tissue level modeling protocol for precision medicine. Front Physiol. 2024 Oct 23;15:1473125. doi: 10.3389/fphys.2024.1473125. PMID: 39507514; PMCID: PMC11537925.

Koc AC, Sari V, Kocak G, Recber T, Nemutlu E, Aberdam D, Güven S. Patient-derived cornea organoid model to study metabolomic characterization of rare disease: aniridia-associated keratopathy. BMC Ophthalmol. 2025 Jan 10;25(1):14. doi: 10.1186/s12886-024-03831-w. PMID: 39794714; PMCID: PMC11724546.

Kortright KE, Chan BK, Koff JL, Turner PE. Phage Therapy: A Renewed Approach to Combat Antibiotic-Resistant Bacteria. Cell Host Microbe. 2019 Feb 13;25(2):219-232. doi: 10.1016/j.chom.2019.01.014. PMID: 30763536.
Kremer LS, Bader DM, Mertes C, Kopajtich R, Pichler G, Iuso A, Haack TB, Graf E, Schwarzmayr T, Terrile C, Koňaříková E, Repp B, Kastenmüller G, Adamski J, Lichtner P, Leonhardt C, Funalot B, Donati A, Tiranti V,

Lombes A, Jardel C, Gläser D, Taylor RW, Ghezzi D, Mayr JA, Rötig A, Freisinger P, Distelmaier F, Strom TM, Meitinger T, Gagneur J, Prokisch H. Genetic diagnosis of Mendelian disorders via RNA sequencing. Nat Commun. 2017 Jun 12;8:15824. doi: 10.1038/ncomms15824. PMID: 28604674; PMCID: PMC5499207.

Kuter DJ, Bonkovsky HL, Monroy S, Ross G, Guillén-Navarro E, Cappellini MD, Minder AE, Hother-Nielsen O, Ventura P, Jia G, Sweetser MT, Thapar M; ENVISION Investigators. Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial. J Hepatol. 2023 Nov;79(5):1150-1158. doi: 10.1016/j.jhep.2023.06.013. Epub 2023 Jul 20. PMID: 37479139.

Lai C, Zimmer AD, O'Connor R, Kim S, Chan R, van den Akker J, Zhou AY, Topper S, Mishne G. LEAP: Using machine learning to support variant classification in a clinical setting. Hum Mutat. 2020 Jun;41(6):1079-1090. doi: 10.1002/humu.24011. Epub 2020 Apr 1. PMID: 32176384; PMCID: PMC7317941.

Lalani HS, Nagar S, Sarpatwari A, Barenie RE, Avorn J, Rome BN, Kesselheim AS. US public investment in development of mRNA covid-19 vaccines: retrospective cohort study. BMJ. 2023 Mar 1;380:e073747. doi: 10.1136/bmj-2022-073747. Erratum in: BMJ. 2023 Mar 14;380:p587. doi: 10.1136/bmj.p587. PMID: 36858453; PMCID: PMC9975718.

Latorre-Pérez A, Pascual J, Porcar M, Vilanova C. A lab in the field: applications of real-time, *in situ* metagenomic sequencing. Biol Methods Protoc. 2020 Aug 20;5(1):bpaa016. doi: 10.1093/biomethods/bpaa016. PMID: 33134552; PMCID: PMC7585387.

Lau-Min KS, Asher SB, Chen J, Domchek SM, Feldman M, Joffe S, Landgraf J, Speare V, Varughese LA, Tuteja S, VanZandbergen C, Ritchie MD, Nathanson KL. Real-world integration of genomic data into the electronic health record: the PennChart Genomics Initiative. Genet Med. 2021 Apr;23(4):603-605. doi: 10.1038/s41436-020-01056-y. Epub 2020 Dec 10. PMID: 33299147; PMCID: PMC8026392.

Leung ML, Davis A, Gao R, Casasent A, Wang Y, Sei E, Vilar E, Maru D, Kopetz S, Navin NE. Single-cell DNA sequencing reveals a late-dissemination model in metastatic colorectal cancer. Genome Res. 2017 Aug;27(8):1287-1299. doi: 10.1101/gr.209973.116. Epub 2017 May 25. PMID: 28546418; PMCID: PMC5538546.

Lewis SM, Asselin-Labat ML, Nguyen Q, Berthelet J, Tan X, Wimmer VC, Merino D, Rogers KL, Naik SH. Spatial omics and multiplexed imaging to explore cancer biology. Nat Methods. 2021 Sep;18(9):997-1012. doi: 10.1038/s41592-021-01203-6. Epub 2021 Aug 2. PMID: 34341583.

Li K, Ouyang M, Zhan J, Tian R. CRISPR-based functional genomics screening in human-pluripotent-stem-cell-derived cell types. Cell Genom. 2023 Apr 18;3(5):100300. doi: 10.1016/j.xgen.2023.100300. PMID: 37228745; PMCID: PMC10203043.

Li L, Zhang L, Montgomery KC, Jiang L, Lyon CJ, Hu TY. Advanced technologies for molecular diagnosis of cancer: State of pre-clinical tumor-derived exosome liquid biopsies. Mater Today Bio. 2022 Dec 29;18:100538. doi: 10.1016/j.mtbio.2022.100538. PMID: 36619206; PMCID: PMC9812720.

Li, X., Loscalzo, J., Mahmud, A.K.M.F. *et al.* Digital twins as global learning health and disease models for preventive and personalized medicine. *Genome Med* **17**, 11 (2025). https://doi.org/10.1186/s13073-025-01435-7

Liu Q, Huang R, Hsieh J, Zhu H, Tiwari M, Liu G, Jean D, ElZarrad MK, Fakhouri T, Berman S, Dunn B, Diamond MC, Huang SM. Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Tremmel R, Hübschmann D, Schaeffeler E, Pirmann S, Fröhling S, Schwab M. Innovation in cancer pharmacotherapy through integrative consideration of germline and tumor genomes. Pharmacol Rev. 2025 Jan;77(1):100014. doi: 10.1124/pharmrev.124.001049. Epub 2024 Nov 22. PMID: 39952686. Regulatory Submissions for Drug Development From 2016 to 2021. Clin Pharmacol Ther. 2023 Apr;113(4):771-774. doi: 10.1002/cpt.2668. Epub 2022 Jun 16. PMID: 35707940.

Lynes MD, Huang Q, Cora C, Su SC, Yi P, Tseng YH. A CRISPR Screen Identifies the E3 Ubiquitin Ligase Rfwd2 as a Negative Regulator of Glucose Uptake in Brown Adipocytes. Genes (Basel). 2023 Sep 26;14(10):1865. doi: 10.3390/genes14101865. PMID: 37895214; PMCID: PMC10606202.

Lyubetskaya A, Rabe B, Fisher A, Lewin A, Neuhaus I, Brett C, Brett T, Pereira E, Golhar R, Kebede S, Font-Tello A, Mosure K, Van Wittenberghe N, Mavrakis KJ, MacIsaac K, Chen BJ, Drokhlyansky E. Assessment of spatial transcriptomics for oncology discovery. Cell Rep Methods. 2022 Nov 15;2(11):100340. doi: 10.1016/j.crmeth.2022.100340. PMID: 36452860; PMCID: PMC9701619.

Magavern EF, Marengo G; Participant Panel at Genomics England; Sivathasan C, Mezzanzanica M, Wright AJ, Keen J, Sharma V, McDermott JH, Duckett C, McCormick D, Simmonds S, Walters E; National Centre for Social Research Team; Weinman J, Parry V, Newman WG, Caulfield MJ. A United Kingdom nationally representative survey of public attitudes towards pharmacogenomics. QJM. 2025 Feb 20:hcaf035. doi: 10.1093/qjmed/hcaf035. Epub ahead of print. PMID: 39971322.

Mahmoud M, Huang Y, Garimella K, Audano PA, Wan W, Prasad N, Handsaker RE, Hall S, Pionzio A, Schatz MC, Talkowski ME, Eichler EE, Levy SE, Sedlazeck FJ. Utility of long-read sequencing for All of Us. Nat Commun. 2024 Jan 29;15(1):837. doi: 10.1038/s41467-024-44804-3. PMID: 38281971; PMCID: PMC10822842.

Maruf AA, Fan M, Arnold PD, Müller DJ, Aitchison KJ, Bousman CA. Pharmacogenetic Testing Options Relevant to Psychiatry in Canada: Options de tests pharmacogénétiques pertinents en psychiatrie au Canada. Can J Psychiatry. 2020 Aug;65(8):521-530. doi: 10.1177/0706743720904820. Epub 2020 Feb 17. PMID: 32064906; PMCID: PMC7492886.

Marx V. Method of the year: long-read sequencing. Nat Methods. 2023 Jan;20(1):6-11. doi: 10.1038/s41592-022-01730-w. PMID: 36635542.

Mauritz Kop, *Regulating Quantum & AI in Healthcare: A Brief Policy Guide*, EU AI ALLIANCE, EUROPEAN COMMISSION, Dec. 7, 2024

Happi Mbakam C, Roustant J, Rousseau J, Yameogo P, Lu Y, Bigot A, Mamchaoui K, Mouly V, Lamothe G, Tremblay JP. Prime editing strategies to mediate exon skipping in *DMD* gene. Front Med (Lausanne). 2023 May 25;10:1128557. doi: 10.3389/fmed.2023.1128557. PMID: 37305116; PMCID: PMC10248452.

Mendell JR, Rodino-Klapac LR, Sahenk Z, Roush K, Bird L, Lowes LP, Alfano L, Gomez AM, Lewis S, Kota J, Malik V, Shontz K, Walker CM, Flanigan KM, Corridore M, Kean JR, Allen HD, Shilling C, Melia KR, Sazani P, Saoud JB, Kaye EM; Eteplirsen Study Group. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013 Nov;74(5):637-47. doi: 10.1002/ana.23982. Epub 2013 Sep 10. PMID: 23907995.

Method of the year 2013. Nat Methods. 2014 Jan;11(1):1. doi: 10.1038/nmeth.2801. PMID: 24524124.
Moingeon P, Chenel M, Rousseau C, Voisin E, Guedj M. Virtual patients, digital twins and causal disease models: Paving the ground for in silico clinical trials. Drug Discov Today. 2023 Jul;28(7):103605. doi: 10.1016/j.drudis.2023.103605. Epub 2023 May 3. PMID: 37146963.

Mongan AE, Tuda JSB, Runtuwene LR. Portable sequencer in the fight against infectious disease. J Hum Genet. 2020 Jan;65(1):35-40. doi: 10.1038/s10038-019-0675-4. Epub 2019 Oct 3. PMID: 31582773; PMCID: PMC6892364.

Mukhare R, Gandhi KA, Kadam A, Raja A, Singh A, Madhav M, Chaubal R, Pandey S, Gupta S. Integration of Organoids With CRISPR Screens: A Narrative Review. Biol Cell. 2025 Apr;117(4):e70006. doi: 10.1111/boc.70006. PMID: 40223602; PMCID: PMC11995251.

Mulholland EJ, Leedham SJ. Redefining clinical practice through spatial profiling: a revolution in tissue analysis. Ann R Coll Surg Engl. 2024 Apr;106(4):305-312. doi: 10.1308/rcsann.2023.0091. PMID: 38555868; PMCID: PMC10981989.

Mullish BH, Merrick B, Quraishi MN, Bak A, Green CA, Moore DJ, Porter RJ, Elumogo NT, Segal JP, Sharma N, Marsh B, Kontkowski G, Manzoor SE, Hart AL, Settle C, Keller JJ, Hawkey P, Iqbal TH, Goldenberg SD, Williams HRT. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridioides difficile* infection and other potential indications: second edition of joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. Gut. 2024 Jun 6;73(7):1052-1075. doi: 10.1136/gutjnl-2023-331550. PMID: 38609165.

Nałęcz-Charkiewicz K, Charkiewicz K, Nowak RM. Quantum computing in bioinformatics: a systematic review mapping. Brief Bioinform. 2024 Jul 25;25(5):bbae391. doi: 10.1093/bib/bbae391. PMID: 39140856; PMCID: PMC11323091.

Nature editorial. (2023). AI's potential to accelerate drug discovery needs a reality check. *Nature*, 622, 217. DOI: 10.1038/d41586-023-03172-6

Newby GA, Liu DR. In vivo somatic cell base editing and prime editing. Mol Ther. 2021 Nov 3;29(11):3107-3124. doi: 10.1016/j.ymthe.2021.09.002. Epub 2021 Sep 10. PMID: 34509669; PMCID: PMC8571176.

Nguyen PN. Biomarker discovery with quantum neural networks: a case-study in CTLA4-activation pathways. BMC Bioinformatics. 2024 Apr 12;25(1):149. doi: 10.1186/s12859-024-05755-0. PMID: 38609844; PMCID: PMC11265126.

Niazi SK. The Coming of Age of AI/ML in Drug Discovery, Development, Clinical Testing, and Manufacturing: The FDA Perspectives. Drug Des Devel Ther. 2023 Sep 6;17:2691-2725. doi: 10.2147/DDDT.S424991. PMID: 37701048; PMCID: PMC10493153.

O'Connor O, McVeigh TP. Increasing use of artificial intelligence in genomic medicine for cancer care- the promise and potential pitfalls. BJC Rep. 2025 Apr 1;3(1):20. doi: 10.1038/s44276-025-00135-4. PMID: 40169715; PMCID: PMC11962076.

Oehler JB, Wright H, Stark Z, Mallett AJ, Schmitz U. The application of long-read sequencing in clinical settings. Hum Genomics. 2023 Aug 8;17(1):73. doi: 10.1186/s40246-023-00522-3. PMID: 37553611; PMCID: PMC10410870.

Ooft SN, Weeber F, Dijkstra KK, McLean CM, Kaing S, van Werkhoven E, Schipper L, Hoes L, Vis DJ, van de Haar J, Prevoo W, Snaebjornsson P, van der Velden D, Klein M, Chalabi M, Boot H, van Leerdam M, Bloemendal HJ, Beerepoot LV, Wessels L, Cuppen E, Clevers H, Voest EE. Patient-derived organoids can predict response to chemotherapy in metastatic colorectal cancer patients. Sci Transl Med. 2019 Oct 9;11(513):eaay2574. doi: 10.1126/scitranslmed.aay2574. PMID: 31597751.

Paramsothy S, Kamm MA, Kaakoush NO, Walsh AJ, van den Bogaerde J, Samuel D, Leong RWL, Connor S, Ng W, Paramsothy R, Xuan W, Lin E, Mitchell HM, Borody TJ. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet. 2017 Mar 25;389(10075):1218-1228. doi: 10.1016/S0140-6736(17)30182-4. Epub 2017 Feb 15. PMID: 28214091.

Paul D, Sanap G, Shenoy S, Kalyane D, Kalia K, Tekade RK. Artificial intelligence in drug discovery and development. Drug Discov Today. 2021 Jan;26(1):80-93. doi: 10.1016/j.drudis.2020.10.010. Epub 2020 Oct 21. PMID: 33099022; PMCID: PMC7577280.

Peng J, Sun BF, Chen CY, Zhou JY, Chen YS, Chen H, Liu L, Huang D, Jiang J, Cui GS, Yang Y, Wang W, Guo D, Dai M, Guo J, Zhang T, Liao Q, Liu Y, Zhao YL, Han DL, Zhao Y, Yang YG, Wu W. Single-cell RNA-seq highlights intra-tumoral heterogeneity and malignant progression in pancreatic ductal adenocarcinoma. Cell Res. 2019 Sep;29(9):725-738. doi: 10.1038/s41422-019-0195-y. Epub 2019 Jul 4. Erratum in: Cell Res. 2019 Sep;29(9):777. doi: 10.1038/s41422-019-0212-1. PMID: 31273297; PMCID: PMC6796938.

Poplin R, Chang PC, Alexander D, Schwartz S, Colthurst T, Ku A, Newburger D, Dijamco J, Nguyen N, Afshar PT, Gross SS, Dorfman L, McLean CY, DePristo MA. A universal SNP and small-indel variant caller using deep neural networks. Nat Biotechnol. 2018 Nov;36(10):983-987. doi: 10.1038/nbt.4235. Epub 2018 Sep 24. PMID: 30247488.

Preskill, J. (2018). *Quantum computing in the NISQ era and beyond*. Quantum, 2, 79. https://doi.org/10.22331/q-2018-08-06-79

Quick J, et al. (2016). Real-time, portable genome sequencing for Ebola surveillance. *Nature*, 530(7589), 228-232.

Reddy JS, Heath L, Linden AV, Allen M, Lopes KP, Seifar F, Wang E, Ma Y, Poehlman WL, Quicksall ZS, Runnels A, Wang Y, Duong DM, Yin L, Xu K, Modeste ES, Shantaraman A, Dammer EB, Ping L, Oatman SR, Scanlan J, Ho C, Carrasquillo MM, Atik M, Yepez G, Mitchell AO, Nguyen TT, Chen X, Marquez DX, Reddy H, Xiao H, Seshadri S, Mayeux R, Prokop S, Lee EB, Serrano GE, Beach TG, Teich AF, Haroutunian V, Fox EJ, Gearing M, Wingo A, Wingo T, Lah JJ, Levey AI, Dickson DW, Barnes LL, De Jager P, Zhang B, Bennett D, Seyfried NT, Greenwood AK, Ertekin-Taner N. Bridging the gap: Multi-omics profiling of brain tissue in Alzheimer's disease and older controls in multi-ethnic populations. Alzheimers Dement. 2024 Oct;20(10):7174-7192. doi: 10.1002/alz.14208. Epub 2024 Aug 30. PMID: 39215503; PMCID: PMC11485084.

Rentscher KE, Bethea TN, Zhai W, Small BJ, Zhou X, Ahles TA, Ahn J, Breen EC, Cohen HJ, Extermann M, Graham DMA, Jim HSL, McDonald BC, Nakamura ZM, Patel SK, Root JC, Saykin AJ, Van Dyk K, Mandelblatt JS, Carroll JE. Epigenetic aging in older breast cancer survivors and noncancer controls: preliminary findings from the Thinking and Living with Cancer Study. Cancer. 2023 Sep 1;129(17):2741-2753. doi: 10.1002/cncr.34818. Epub 2023 Jun 1. PMID: 37259669; PMCID: PMC10659047.

RiskAnalytica, Smetanin P, Stiff D, et al. The life and economic impact of major mental illnesses in Canada. Ottawa (ON): Mental Health Commission of Canada; 2011: https://www.mentalhealthcommission.ca/wp-content/uploads/drupal/MHCC_Report_Base_Case_FINAL_ENG_0_0.pdf.

Rottner AK, Ye Y, Navarro-Guerrero E, Rajesh V, Pollner A, Bevacqua RJ, Yang J, Spigelman AF, Baronio R, Bautista A, Thomsen SK, Lyon J, Nawaz S, Smith N, Wesolowska-Andersen A, Fox JEM, Sun H, Kim SK, Ebner D, MacDonald PE, Gloyn AL. A genome-wide CRISPR screen identifies CALCOCO2 as a regulator of beta cell function influencing type 2 diabetes risk. Nat Genet. 2023 Jan;55(1):54-65. doi: 10.1038/s41588-022-01261-2. Epub 2022 Dec 21. PMID: 36543916; PMCID: PMC9839450.

Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, Fidelle M, Flament C, Poirier-Colame V, Opolon P, Klein C, Iribarren K, Mondragón L, Jacquelot N, Qu B, Ferrere G, Clémenson C, Mezquita L, Masip JR, Naltet C, Brosseau S, Kaderbhai C, Richard C, Rizvi H, Levenez F, Galleron N, Quinquis B, Pons N, Ryffel B, Minard-Colin V, Gonin P, Soria JC, Deutsch E, Loriot Y, Ghiringhelli F, Zalcman G, Goldwasser F, Escudier B, Hellmann MD, Eggermont A, Raoult D, Albiges L, Kroemer G, Zitvogel L. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018 Jan 5;359(6371):91-97. doi: 10.1126/science.aan3706. Epub 2017 Nov 2. PMID: 29097494.

Rueda J, de Miguel Beriain Í, Montoliu L. Affordable Pricing of CRISPR Treatments is a Pressing Ethical Imperative. CRISPR J. 2024 Oct;7(5):220-226. doi: 10.1089/crispr.2024.0042. Epub 2024 Oct 10. PMID: 39392045.

Sachs N, de Ligt J, Kopper O, Gogola E, Bounova G, Weeber F, Balgobind AV, Wind K, Gracanin A, Begthel H, Korving J, van Boxtel R, Duarte AA, Lelieveld D, van Hoeck A, Ernst RF, Blokzijl F, Nijman IJ, Hoogstraat M, van de Ven M, Egan DA, Zinzalla V, Moll J, Boj SF, Voest EE, Wessels L, van Diest PJ, Rottenberg S, Vries RGJ, Cuppen E, Clevers H. A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity. Cell. 2018 Jan 11;172(1-2):373-386.e10. doi: 10.1016/j.cell.2017.11.010. Epub 2017 Dec 7. PMID: 29224780.

Schott M, León-Periñán D, Splendiani E, Strenger L, Licha JR, Pentimalli TM, Schallenberg S, Alles J, Samut Tagliaferro S, Boltengagen A, Ehrig S, Abbiati S, Dommerich S, Pagani M, Ferretti E, Macino G, Karaiskos N, Rajewsky N. Open-ST: High-resolution spatial transcriptomics in 3D. Cell. 2024 Jul 25;187(15):3953-3972.e26. doi: 10.1016/j.cell.2024.05.055. Epub 2024 Jun 24. PMID: 38917789.

Segerstolpe Å, Palasantza A, Eliasson P, Andersson EM, Andréasson AC, Sun X, Picelli S, Sabirsh A, Clausen M, Bjursell MK, Smith DM, Kasper M, Ämmälä C, Sandberg R. Single-Cell Transcriptome Profiling of Human Pancreatic Islets in Health and Type 2 Diabetes. Cell Metab. 2016 Oct 11;24(4):593-607. doi: 10.1016/j.cmet.2016.08.020. Epub 2016 Sep 22. PMID: 27667667; PMCID: PMC5069352.

Shen W, Hu F, Lei P, Tang Y. Applications of CRISPR screening to lung cancer treatment. Front Cell Dev Biol. 2023 Dec 15;11:1295555. doi: 10.3389/fcell.2023.1295555. PMID: 38169973; PMCID: PMC10760454.

Silva P, Jacobs D, Kriak J, Abu-Baker A, Udeani G, Neal G, Ramos K. Implementation of Pharmacogenomics and Artificial Intelligence Tools for Chronic Disease Management in Primary Care Setting. J Pers Med. 2021 May 21;11(6):443. doi: 10.3390/jpm11060443. PMID: 34063850; PMCID: PMC8224063.
Sinha S, Rabea F, Ramaswamy S, Chekroun I, El Naofal M, Jain R, Alfalasi R, Halabi N, Yaslam S, Sheikh Hassani M, Shenbagam S, Taylor A, Uddin M, Almarri MA, Du Plessis S, Alsheikh-Ali A, Abou Tayoun A. Long read sequencing enhances pathogenic and novel variation discovery in patients with rare diseases. Nat Commun. 2025 Mar 14;16(1):2500. doi: 10.1038/s41467-025-57695-9. PMID: 40087273; PMCID: PMC11909103.
TechTarget (2024). Why is Genomic Data EHR Integration Important?

Tutrone R, Lowentritt B, Neuman B, Donovan MJ, Hallmark E, Cole TJ, Yao Y, Biesecker C, Kumar S, Verma V, Sant GR, Alter J, Skog J. Correction to: ExoDx prostate test as a predictor of outcomes of high-grade prostate cancer - an interim analysis. Prostate Cancer Prostatic Dis. 2024 Mar;27(1):161. doi: 10.1038/s41391-023-00681-3. Erratum for: Prostate Cancer Prostatic Dis. 2023 Sep;26(3):596-601. doi: 10.1038/s41391-023-00675-1. PMID: 37337052; PMCID: PMC10876471.

Tyler AD, Mataseje L, Urfano CJ, Schmidt L, Antonation KS, Mulvey MR, Corbett CR. Evaluation of Oxford Nanopore's MinION Sequencing Device for Microbial Whole Genome Sequencing Applications. Sci Rep. 2018 Jul 19;8(1):10931. doi: 10.1038/s41598-018-29334-5. PMID: 30026559; PMCID: PMC6053456.
Tyler AD, McAllister J, Stapleton H, Gauci P, Antonation K, Thirkettle-Watts D, Corbett CR. Field-based detection of bacteria using nanopore sequencing: Method evaluation for biothreat detection in complex samples. PLoS One. 2023 Nov 28;18(11):e0295028. doi: 10.1371/journal.pone.0295028. PMID: 38015952; PMCID: PMC10684088.

Vacher M, Canovas R, Laws SM, Doecke JD. A comprehensive multi-omics analysis reveals unique signatures to predict Alzheimer's disease. Front Bioinform. 2024 Jun 19;4:1390607. doi: 10.3389/fbinf.2024.1390607. PMID: 38962175; PMCID: PMC11219798.

Viehweger A, Krautwurst S, Lamkiewicz K, Madhugiri R, Ziebuhr J, Hölzer M, Marz M. Direct RNA nanopore sequencing of full-length coronavirus genomes provides novel insights into structural variants and enables modification analysis. Genome Res. 2019 Sep;29(9):1545-1554. doi: 10.1101/gr.247064.118. Epub 2019 Aug 22. PMID: 31439691; PMCID: PMC6724671.

Vlachogiannis G, Hedayat S, Vatsiou A, Jamin Y, Fernández-Mateos J, Khan K, Lampis A, Eason K, Huntingford I, Burke R, Rata M, Koh DM, Tunariu N, Collins D, Hulkki-Wilson S, Ragulan C, Spiteri I, Moorcraft SY, Chau I, Rao S, Watkins D, Fotiadis N, Bali M, Darvish-Damavandi M, Lote H, Eltahir Z, Smyth EC, Begum R, Clarke PA, Hahne JC, Dowsett M, de Bono J, Workman P, Sadanandam A, Fassan M, Sansom OJ, Eccles S, Starling N, Braconi C, Sottoriva A, Robinson SP, Cunningham D, Valeri N. Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. Science. 2018 Feb 23;359(6378):920-926. doi: 10.1126/science.aao2774. PMID: 29472484; PMCID: PMC6112415.

Voges HK, Mills RJ, Porrello ER, Hudson JE. Generation of vascularized human cardiac organoids for 3D in vitro modeling. STAR Protoc. 2023 Sep 15;4(3):102371. doi: 10.1016/j.xpro.2023.102371. Epub 2023 Jun 28. PMID: 37384522; PMCID: PMC10511847.

Wang D, Zhang F, Gao G. CRISPR-Based Therapeutic Genome Editing: Strategies and In Vivo Delivery by AAV Vectors. Cell. 2020 Apr 2;181(1):136-150. doi: 10.1016/j.cell.2020.03.023. PMID: 32243786; PMCID: PMC7236621.

Wasswa FB, Kassaza K, Nielsen K, Bazira J. MinION Whole-Genome Sequencing in Resource-Limited Settings: Challenges and Opportunities. Curr Clin Microbiol Rep. 2022;9(4):52-59. doi: 10.1007/s40588-022-00183-1. Epub 2022 Nov 17. PMID: 36415776; PMCID: PMC9669520.

Weber JS, Carlino MS, Khattak A, Meniawy T, Ansstas G, Taylor MH, Kim KB, McKean M, Long GV, Sullivan RJ, Faries M, Tran TT, Cowey CL, Pecora A, Shaheen M, Segar J, Medina T, Atkinson V, Gibney GT, Luke JJ, Thomas S, Buchbinder EI, Healy JA, Huang M, Morrissey M, Feldman I, Sehgal V, Robert-Tissot C, Hou P, Zhu L, Brown M, Aanur P, Meehan RS, Zaks T. Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study. Lancet. 2024 Feb 17;403(10427):632-644. doi: 10.1016/S0140-6736(23)02268-7. Epub 2024 Jan 18. PMID: 38246194.

Wickramasinghe N, Ulapane N, Zelcer J, Saffery R. 'Omics-Based Digital Twins for Personalised Paediatric Healthcare. Stud Health Technol Inform. 2024 Sep 24;318:180-181. doi: 10.3233/SHTI240917. PMID: 39320206.

Williams CG, Lee HJ, Asatsuma T, Vento-Tormo R, Haque A. An introduction to spatial transcriptomics for biomedical research. Genome Med. 2022 Jun 27;14(1):68. doi: 10.1186/s13073-022-01075-1. PMID: 35761361; PMCID: PMC9238181.

Xiao Y, Bi M, Guo H, Li M. Multi-omics approaches for biomarker discovery in early ovarian cancer diagnosis. EBioMedicine. 2022 May;79:104001. doi: 10.1016/j.ebiom.2022.104001. Epub 2022 Apr 16. PMID: 35439677; PMCID: PMC9035645.

Yang S, Hu H, Kung H, Zou R, Dai Y, Hu Y, Wang T, Lv T, Yu J, Li F. Organoids: The current status and biomedical applications. MedComm (2020). 2023 May 17;4(3):e274. doi: 10.1002/mco2.274. PMID: 37215622; PMCID: PMC10192887.

Yépez VA, Gusic M, Kopajtich R, Mertes C, Smith NH, Alston CL, Ban R, Beblo S, Berutti R, Blessing H, Ciara E, Distelmaier F, Freisinger P, Häberle J, Hayflick SJ, Hempel M, Itkis YS, Kishita Y, Klopstock T, Krylova TD, Lamperti C, Lenz D, Makowski C, Mosegaard S, Müller MF, Muñoz-Pujol G, Nadel A, Ohtake A, Okazaki Y, Procopio E, Schwarzmayr T, Smet J, Staufner C, Stenton SL, Strom TM, Terrile C, Tort F, Van Coster R, Vanlander A, Wagner M, Xu M, Fang F, Ghezzi D, Mayr JA, Piekutowska-Abramczuk D, Ribes A, Rötig A, Taylor RW, Wortmann SB, Murayama K, Meitinger T, Gagneur J, Prokisch H. Clinical implementation of RNA sequencing for Mendelian disease diagnostics. Genome Med. 2022 Apr 5;14(1):38. doi: 10.1186/s13073-022-01019-9. PMID: 35379322; PMCID: PMC8981716.

Young C, MacDougall D; Authors. An Overview of Pharmacogenomic Testing for Psychiatric Disorders: CADTH Horizon Scan [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2023 Jun. Available from: https://www.ncbi.nlm.nih.gov/books/NBK595332/.

Yu D, Li Y, Wang M, Gu J, Xu W, Cai H, Fang X, Zhang X. Exosomes as a new frontier of cancer liquid biopsy. Mol Cancer. 2022 Feb 18;21(1):56. doi: 10.1186/s12943-022-01509-9. PMID: 35180868; PMCID: PMC8855550.

Yu Q, Jiang M, Wu L. Spatial transcriptomics technology in cancer research. Front Oncol. 2022 Oct 13;12:1019111. doi: 10.3389/fonc.2022.1019111. PMID: 36313703; PMCID: PMC9606570.

Zhang M, Liu J, Xia Q. Role of gut microbiome in cancer immunotherapy: from predictive biomarker to therapeutic target. Exp Hematol Oncol. 2023 Sep 28;12(1):84. doi: 10.1186/s40164-023-00442-x. PMID: 37770953; PMCID: PMC10537950.

Zhang T, Li H, Jiang M, Hou H, Gao Y, Li Y, Wang F, Wang J, Peng K, Liu YX. Nanopore sequencing: flourishing in its teenage years. J Genet Genomics. 2024 Dec;51(12):1361-1374. doi: 10.1016/j.jgg.2024.09.007. Epub 2024 Sep 16. PMID: 39293510.

Zhao T, Chiang ZD, Morriss JW, LaFave LM, Murray EM, Del Priore I, Meli K, Lareau CA, Nadaf NM, Li J, Earl AS, Macosko EZ, Jacks T, Buenrostro JD, Chen F. Spatial genomics enables multi-modal study of clonal

heterogeneity in tissues. Nature. 2022 Jan;601(7891):85-91. doi: 10.1038/s41586-021-04217-4. Epub 2021 Dec 15. PMID: 34912115; PMCID: PMC9301586.

Zheng G, Xie ZY, Wang P, Wu YF, Shen HY. Recent advances of single-cell RNA sequencing technology in mesenchymal stem cell research. World J Stem Cells. 2020 Jun 26;12(6):438-447. doi: 10.4252/wjsc.v12.i6.438. PMID: 32742561; PMCID: PMC7360991.

Zhou M, Zhang H, Bai Z, Mann-Krzisnik D, Wang F, Li Y. Single-cell multi-omics topic embedding reveals cell-type-specific and COVID-19 severity-related immune signatures. Cell Rep Methods. 2023 Aug 18;3(8):100563. doi: 10.1016/j.crmeth.2023.100563. PMID: 37671028; PMCID: PMC10475851.

Zhu Y, Zhu L, Wang X, Jin H. RNA-based therapeutics: an overview and prospectus. Cell Death Dis. 2022 Jul 23;13(7):644. doi: 10.1038/s41419-022-05075-2. PMID: 35871216; PMCID: PMC9308039.

Zhu, S., Cao, Z., Liu, Z., & He, Y. (2021). CRISPR-based functional genomics for identifying novel therapeutic targets. *Theranostics*, 11(9), 4203-4221. https://doi.org/10.7150/thno.56002

Zushin PH, Mukherjee S, Wu JC. FDA Modernization Act 2.0: transitioning beyond animal models with human cells, organoids, and AI/ML-based approaches. J Clin Invest. 2023 Nov 1;133(21):e175824. doi: 10.1172/JCI175824. PMID: 37909337; PMCID: PMC10617761.