

Establishing The Australian Undiagnosed Disease Network (UDN-Aus); Australia's first national rare disease diagnostic network

Ellenore M Martin

elle.martin@mcri.edu.au

Murdoch Children's Research Institute <https://orcid.org/0000-0002-8188-5896>

Madeleine Harris

Murdoch Children's Research Institute

Tegan Stait

Murdoch Children's Research Institute

Sarah Casauria

Murdoch Children's Research Institute

Esther Pierini

Murdoch Children's Research Institute

Susan M White

Victorian Clinical Genetics Services Ltd

Azure Hermes

Australian National University

Julie McGaughan

Royal Brisbane and Women's Hospital

Rocio Rius

Centre for Population Genomics Garvan Institute of Medical Research

Daniel G. MacArthur

Centre for Population Genomics Garvan Institute of Medical Research

Timo Lassmann

The Kid's Research Institute

Christopher Richmond

Royal Brisbane and Women's Hospital

Janine Smith

Sydney Children's Hospitals Network

Mathew Wallis

Royal Hobart Hospital

Suzanne Sallevelt

Women's and Children's Hospital Adelaide

Michael Field

Genetics of Learning Disability Service

Chloe Cunningham

Victorian Clinical Genetics Services Ltd

David A Stroud

The University of Melbourne Bio21 Molecular Science and Biotechnology Institute

Simon Sadedin

Victorian Clinical Genetics Services Ltd

Tracy Dudding-Byth

Genetics of Learning Disability Service

Sandra Cooper

Sydney Children's Hospitals Network

Ilias Goranitis

The University of Melbourne

Ira W Deveson

Garvan Institute of Medical Research

Shannon LeBlanc

Women's and Children's Hospital Adelaide

Maie Walsh

The Royal Melbourne Hospital

Simon Bodek

Austin Hospital

Andrew Paul Fennell

Monash Health

Emma Krzesinski

Monash Health

Sarah Jelenich

Murdoch Children's Research Institute

Evanthia O. Madelli

Murdoch Children's Research Institute

Rachel Austin

Royal Brisbane and Women's Hospital

Ryan Pysar

Sydney Children's Hospitals Network

Hannah Thompson

Genetics of Learning Disability Service

Louise Cilento

Women's and Children's Hospital Adelaide

Lauren Dreyer

Perth Children's Hospital

Ella Jane Wilkins

Victorian Clinical Genetics Services Ltd

Elly Lynch

Victorian Clinical Genetics Services Ltd

Molly Carr

Sydney Children's Hospitals Network

Ella Zurita

Sydney Children's Hospitals Network

Julia Broadbent

Murdoch Children's Research Institute

Daniz Kooshavar

Murdoch Children's Research Institute

Laura Wedd

Centre for Population Genomics Garvan Institute of Medical Research

Elaine Zhang

Murdoch Children's Research Institute

Tian Zhao

Murdoch Children's Research Institute

Cassandra Gray

Centre for Population Genomics Garvan Institute of Medical Research

Edward Formaini

Centre for Population Genomics Garvan Institute of Medical Research

Mohammadreza Hajjari

Centre for Population Genomics Garvan Institute of Medical Research

Christopher Richards

Centre for Population Genomics Garvan Institute of Medical Research

Francisco Santos Gonzalez

The University of Melbourne

Cas Simons

Centre for Population Genomics Garvan Institute of Medical Research

Tiffany Boughtwood

Murdoch Children's Research Institute

Elizabeth E. Palmer

Sydney Children's Hospitals Network

Tiong Yang Tan

Victorian Clinical Genetics Services Ltd

Gareth Baynam

Perth Children's Hospital

Research Article

Keywords: genomics, genetics, rare disease, Australia, genomic sequencing, undiagnosed diseases program, proteomics, RNA sequencing, Long read sequencing

Posted Date: July 16th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-8091344/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background:

An estimated 1 in 12 individuals across the world have a rare disease. The Undiagnosed Diseases Network International (UDNI) recommend Undiagnosed Disease Programs (UDPs) as the best approach to facilitate diagnosis and support for those affected. The Australian Undiagnosed Disease Network (UDN-Aus) is the first National Australian UDP initiative funded by the Medical Research Future Fund's Genomic Health Futures Mission (GNT2007567).

Aims:

UDN-Aus brings together an unprecedented national collaborative network for rare disease, aiming to improve the rate of genomic diagnoses for those with undiagnosed rare genetic conditions, enabling precise, personalised care to individuals throughout Australia.

Methods:

The research program recruited Australians who have been seen through a clinical genetics service and remained undiagnosed following clinically available genomic testing. This paper outlines the approach taken to establish a national research project at 12 clinical recruitment sites. The methods detail the funding, aims, governance, study design, population and participation process, health economic research and preliminary results, and recommendations for future sustainability and implementation.

Results:

The study was approved by the Royal Children's Hospital Human Research Ethics Committee on 19 November 2021 (RCH79712), with relevant site-specific approvals at local recruitment sites. Key benefits and barriers in the establishment of UDN-Aus are outlined.

Conclusion:

The successful establishment of this program required several components, including meaningful and ongoing community and stakeholder engagement, strategic appointment of key operational staff, and a tailored approach to facilitate more equitable enrolment. It also highlighted several imperative areas for consideration to ensure future sustainable implementation of a national UDP. These include continued investment in Australia's national genomic data transfer policy and infrastructure, and research ethics and governance procedures is imperative for the sustainable delivery of genomic research for rare disease.

1. Background

Rare disease affects 1 in 12 individuals worldwide, and therefore these disorders are collectively common (1). For individuals with rare, suspected monogenic conditions, access to genomic sequencing has transformed the approach to diagnosis. However, individuals often endure a lengthy diagnostic odyssey involving numerous costly and invasive diagnostic investigations (2–4). For example, a 2017 survey of 462 Australian children with rare disease found that 38% had consulted with over six different doctors and waited for more than three years for a correct diagnosis (5). This diagnostic odyssey is particularly marked for those from priority populations: such as people from culturally and linguistically diverse, Indigenous, rural and remote communities and those with disabilities and low socioeconomic status. Barriers to achieving a timely genetic diagnosis include recognition of the presentation of rare disease by clinical specialists, access to skilled diagnostic teams and appropriate testing, and socio-cultural factors (6). Moreover, even for those with access to clinically available genomic testing - the diagnostic rate plateaus at around 50%; meaning approximately 1 in 2 of those with a suspected monogenic condition remain undiagnosed (7, 8).

The importance of receiving a definitive genetic answer cannot be overstated: a precise diagnosis guides clinical care, facilitates the prediction and prevention of complications, connects people and their families to support groups and opportunities for clinical research and enables accurate genetic counselling and reproductive options for an individual and their family members (9, 10).

International Joint Recommendations to address the Specific Needs to Undiagnosed Rare Disease Patients, were published in 2016, and endorsed by signatures representing more than 70 million people living with rare disease. These recommendations called for the establishment of national Undiagnosed Disease Programs (UDPs) by each country to enable rapid and equitable access to diagnosis and social support, that the coordination of these occur at a national level to optimise the use of existing resources and promote equity, and that patients should be equally involved in the governance of these programs (11).

Subsequently, UDPs, pioneered in the US (12) have been developed and globalised through the Undiagnosed Diseases Network International (UDNI) (13). By bringing together interdisciplinary clinical and research teams to critically assess phenotypic information, and initiate genomic and multi-omic sequencing, the diagnostic journey has been transformed for thousands of patients in 55 different countries (6). Although generally UDPs require individuals to have a high suspicion of a monogenic condition as a prerequisite to enrolment, there is notably, 'no quantifiable metric' for the extent of previous investigations for enrolment in many UDPs, and enrolment criteria are often not strictly defined, relying on subjective medical record review by experts (6, 14). Furthermore, traditionally UDPs have prioritised access for paediatric patients as they are thought more likely to benefit from rapid diagnosis and treatment

implementation (15). This is despite evidence for utility and comparable diagnostic yield in targetable phenotypes such as syndromic intellectual disability and multi-system disorders (16).

While research has highlighted the utility of genomic sequencing in the discovery of novel disease genes for those with rare conditions, studies reporting on the utility of exome sequencing (ES) and whole genome sequencing (WGS) report significantly varying yields, ranging from 13%–70%. A marginal increase in diagnostic yield is seen when using WGS (17). Previous application of ES and WGS within Australia has yielded diagnostic rates of up to 58% in the paediatric setting (15, 18–21). Of 13 UDPs included in a 2023 systemic review, the diagnostic yield ranged between 3% and 53%. Consequently, those programs who enrolled individuals already having comprehensive genetic work up had lower yields (14).

Currently in the Australian clinical setting, patients with suspected genetic conditions can access clinical genetic testing through their local clinical genetics service, via their paediatrician or, for certain indications, their general practitioner or subspecialist. Singleton (proband-only) and duo/trio (proband and parent/s) genomic sequencing is usually undertaken with analysis focused on genes known to be causative of the proband's phenotype. Typically, this is ES; used routinely in clinical practice since 2018. However, the diagnostic utility of WGS in the rare disease space is increasingly being recognised due to declining cost, and its ability to detect non-coding, structural, and copy number variations (22). WGS could also be considered a 'lifelong investment' allowing for regular polygenic score calculation and reinterpretation of the data as new disease-causing variants and genes emerge in the literature (23). The emerging shift towards WGS is reflected by Australia's clinical test ordering; WGS made up just 0.25% of genomic sequencing ordered in Australia in 2018, with this jumping to 16.5% in 2021 (24). Five publicly funded, and six private laboratories within Australia offer genomic sequencing. Due to the unfederated government model of genomic test funding and jurisdictional boundaries, WGS or ES is most often undertaken in the corresponding laboratory located in a clinic's local state.

Data interpretation is performed by laboratory-employed variant curators, with both the manual process of variant prioritisation and resource limitations acting together to bottleneck results delivery (23). Turnaround times for genomic testing are laboratory-dependent, with reported times ranging from 3 days in cases where ultrarapid results are essential to guide acute clinical management, to 3–4 months (25, 26) (and 6–9 months anecdotally). There is no singular repository for clinically generated genomic data within Australia, with data generation, interpretation and storage siloed within respective states. While sharing of variant specific data between some Australian laboratories has begun following establishment of the Shariant project (27), sharing of raw genomic data between laboratories and research studies is not common practice. Once generated, data is also not routinely reanalysed, with reanalysis only being initiated following a request by a clinical geneticist or in some cases, other clinical subspecialties (24).

The Australian Federal Government has recognised the importance of prioritising rare disease research and the utility of genomic testing for genetic diagnosis, and in 2020 formerly endorsed the *National Strategic Action Plan for Rare Diseases*. This plan aims to coordinate a national effort to address rare disease in Australia by increasing awareness and education, providing care and support, and enabling coordinated and collaborative data collection. To achieve this, several recommendations have been made, including national leadership and coordination to facilitate more equitable access to genetic testing and timely and accurate diagnosis, integrating mental health and social wellbeing into rare disease care and support, and ensuring research into rare diseases is collaborative and person centred; all which should be considered when establishing an Australian UDP (28). Moreover, Australian's first National Recommendations for Rare Disease Health Care, endorsed by 12 colleges and the peak body for rare disease, encouraged clinicians to reach out to access UDP for those patients who remained undiagnosed after clinical diagnostic efforts (29).

While genomic technology and research rapidly expands, another essential consideration in Australia is ensuring access for underrepresented populations, including people from culturally and linguistically diverse, rural and remote communities, those with disabilities and low socio-economic status and Aboriginal and Torres Strait Islander people (28). This mandates the codesign of equitable and culturally appropriate research opportunities for these populations, but also, the recognition for Aboriginal and Torres Strait Islander people, that their own data is a cultural, strategic and economic asset (30). Yet, this has been poorly prioritised and achieved (31). Inclusion of Aboriginal and Torres Strait Islander people throughout the establishment of research along with prioritisation of operationalised data and sample sovereignty principles is now recognised as a priority (32). Both the National Centre for Indigenous Genomics and The Australian Alliance for Indigenous Genomics (ALIGN) have provided genomics research groups within Australia with resources and opportunities to engage and build trust within this landscape. In 2024, the *LINEAGE: Law, Sociology and Ethics in Data Governance for Genomics* study, was established. This group of over 50 experts in law, bioethics and genomics, including those with lived experience of a genetic condition and Aboriginal or Torres Strait Islander people, are acting to build an empirically informed and robust governance framework for the generation and sharing of genomic data (33).

Australian UDPs were originally state or site-based and have been successfully implemented in Victoria (Rare Diseases Now and AHA-UDP), New South Wales (GeneAdd/ Gene2Care), WA (WA Undiagnosed Disease Program) and Tasmania. These state-based UDPs have paved the way to developing a tiered approach to the application of genomic technologies to enhance rare disease diagnosis within Australia (10, 15, 16, 34–36). While successful, the benefits of a national approach have also been recognised, which could enable more equitable and standardised access to a rare disease diagnostic program across the country. Limitations of state-based approaches include differing inclusion and exclusion criteria, reliance on shorter cycles of grant funding, and variable access to public health funding, resulting in some states and territories being unable to implement a rare disease program for individuals, with consequent inequity of access to genomic testing across Australia. Further issues faced by state-based UDPs include challenges around data transfer and sovereignty and lack of infrastructure to support this.

The approaches used by UDP networks globally are powerful and diverse but require tailoring to the national Australian healthcare context. We established the Australian Undiagnosed Diseases Network (UDN-Aus), implementing lessons learnt by pioneering state-based UDPs, and our global colleagues, to map requirements for the implementation of a national approach that could be sustainable and equitable. We also endeavoured to implement this program within a framework of principles, practice and operational standards that best fit with the Australian healthcare and community contexts, ensuring cultural safety and appropriateness.

UDN-Aus has representation from existing and nascent state UDPs, clinical genetics services from all states and territories and other key stakeholders. Embracing guidance from the Aboriginal and Torres Strait Islander and Rare Disease communities, we have developed governance processes to enable responsible sharing of expertise, data and tools to nationally maximize diagnostic rates for individuals with rare diseases and their families, whilst abiding by the preferences and requirements for Indigenous data sovereignty. Furthermore, UDN-Aus recognised the potential utility of leveraging existing clinically generated genomic data, and of upskilling clinicians in the interpretation of these data and continues to build on existing clinical and research networks that were established and led through Australian Genomics (37).

In this paper we outline our approach to the establishment of UDN-Aus outlining the funding, aims, governance, design, genomic data and sample acquisition and storage, health economic research, return of results and research outcomes and results. We also discuss challenges faced, including establishment of multi-institute agreements, ethics and governance approvals and data transfer agreements.

1.2. Aims

The primary aim of UDN-Aus is to develop a national collaborative network and processes to facilitate the recruitment of genetically unsolved families into a robust re-evaluation pipeline and flow through to frontier genomic technologies in selected cases. Objectives include:

- To evaluate the implementation of an Australian national UDP, including equitable and standardised enrolment criteria, and explore barriers and enablers to standardised and sustainable data workflows and infrastructure;
- To assess program outcomes including the number and proportion of eligible families recruited into the study, number of diagnoses made, number of cases where there was a change in management and reproductive outcomes;
- To understand family and clinician experiences, including the health economic implications of access to expanded genomic sequencing and functional analyses;
- To evaluate the benefits, shortfalls and workforce requirements in relation to establishing a national UDP, and the utility of upskilling clinicians in genomic analysis.

1.3. Study design

The study developed a nationally coordinated collaborative network and processes to empower clinical teams in each state with a robust pathway that could be pursued for undiagnosed rare disease individuals. This approach is summarised in Fig. 1.

2. Methods

2.1 Funding, Multi- Institute Agreement, research collaboration agreements and Ethics Committee Approval

This study was funded by the Australian Government's Medical Research Future Fund (MRFF) as part of the Genomics Health Futures Mission (MRFF2007567). The study was overseen by a core research team situated at the Murdoch Children's Research Institute (MCRI, Victoria, Australia). A Multi-Institute Agreement (MIA) was developed initially to include 15 national collaborators (including the MCRI), outlining funding administration across institutes, conduct of the project, and clauses relating to Intellectual Property, Confidentiality, Indemnity and Insurance. This MIA was amended and re-executed an additional time throughout the study to include funding and institute changes. An additional five research collaboration agreements were obtained in cases where recruitment sites were included following MIA execution, or an additional agreement was required by site-specific governance offices (Supplementary File S1). The study obtained Human Research Ethics Committee (HREC; RCH-79712) and site-specific governance approvals to conduct the study in 12 publicly funded clinical genetics services and hospitals, and 4 laboratory and research sites (Supplementary File S2).

2.2 Study Governance

Study governance is summarised in Figure 2. UDN-Aus is administered by a national coordination team within the MCRI, leveraging existing materials and frameworks established by Australian Genomics (a national research network building evidence for the integration of genomic medicine into the healthcare system from 2016 to 2025), and existing state UDPs (10,15,34,36–38).

The National Steering Committee oversees the study's strategic direction and is responsible for overall project oversight. Members include leads from each established state UDP, participating clinical genetics sites, and representatives from Australian Genomics. Community advisory groups (CAG), including an Indigenous Advisory Group (IAG) were established to ensure that the project's goals and activities align with the needs of Australian rare disease and Indigenous communities, and that project materials such as consent forms and policies are socially and culturally appropriate. These groups provided consultation throughout all stages of the project.

Three additional committees have been established for key project areas: Data Acquisition and Sharing Group (DASG), Clinical Review/Multi-Disciplinary Team (MDT), and The Investigator Committee. The DASG is responsible for oversight of data governance, phenotypic data acquisition, data storage and the project's genomic data acquisition policy. The Clinical Review Committee, with representative state clinical leads, defined the inclusion, exclusion and prioritisation criteria for patient recruitment. The Investigator Committee meetings provide updates to all project investigators across the span of the study.

Additional to these committees, the National Coordination Team works alongside the National Steering Committee and is responsible for the day-to-day research activities. The National Coordination Team is responsible for the operational and variant curation teams which both contribute to project activities.

Staffing

Funding allocation for five genetic counsellors (2.0 Full-Time Equivalent [FTE]) and five clinical geneticists (2.0FTE) across initial recruitment sites was provided by the study for a four-year period. Funding was flexibly delivered to services to allow for employment of suitable staff embedded at each site and appropriate FTE allocation (e.g. increased genetic counselling time, and in-kind clinical geneticist support). Funding was provided for two variant curators (totalling 0.6 FTE). Additional in-kind variant curation support was provided by the Centre for Population Genomics (CPG), and MCRI totalling 3.0FTE. Initially, 0.6FTE of national project coordination time was funded, but this was expanded to 1.4FTE in year two of the study due to recognition of the administrative burden of site governance approvals and overall project coordination. In year three of the study this was again expanded to 1.6FTE due to continuing governance and recruitment activities. A national sample coordinator (0.2FTE) based at the MCRI was also employed in years 2-4 of the study.

2.3 Resource development

UDN-Aus adapted and developed a suite of materials to ensure tailored information was delivered to both participants and clinical referrers, and robust data collection occurred. Consent forms were initially adapted from those used by the Victorian RDNOW study (15). These included paper-based consent forms and verbal consent options for adult, paediatric and mature minor participants (Supplementary File S3). Consent forms, following review by the IAG, specifically included wording around data sovereignty and consultation with next of kin regarding data sharing and storage preferences in case of death. Subsequently, e-consent platforms (including the CTRL dynamic consent portal) (39), and a patient facing website (udnaus.org) were developed and deployed by the study, following extensive genetic counsellor, IAG and CAG review.

2.4 Population

State and Territory clinical leads were responsible for identifying cases for potential enrolment in this study in accordance with the inclusion and exclusion (Table 1), and prioritisation criteria (Table 2). Potential participants were proposed from state and territory leads’ local clinical genetics services. In most cases, participants had genomic sequencing completed through their local genetic services. These services committed a portion of staff time and skills for data reanalysis and phenotypic information provision.

2.5 Study participation process

The UDN-Aus clinical review committee developed both recruitment and prioritisation criteria to maximise the potential for equitable recruitment across states and territories. Transparency in how patients were considered for inclusion into the study was paramount, with these criteria iteratively reviewed over the course of the project and made available to all recruiting clinicians and project investigators. Priority for enrolment was given to individuals as a balance of clinical need and scientific likelihood that the UDN-Aus will achieve a diagnosis. Individuals proposed for inclusion in the study were assessed according to the criteria listed below in Table 1.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Patient with a high likelihood of a monogenic cause for their condition but remains without a confirmed genetic diagnosis despite clinically indicated appropriate diagnostic testing*	• Low likelihood monogenic condition
• Any age	• Clinically indicated first-line tests not yet done at state/territory level
• Lives in Australia	• Proband does not live in Australia
• Is referred to their study from a participating clinical genetics service	• Genomic data is stored in a laboratory where it cannot be transferred into the UDN-Aus bioinformatics system readily.
• Genomic data available for transfer into the UDN-Aus bioinformatics system readily	• No availability of samples e.g., no clinically accessible tissue appropriate for study
• Potential for a diagnosis to impact care of the patient and family (i.e., likelihood that a genetic diagnosis would change management, impact reproductive counselling, improve psychosocial/mental health outcomes for family**)	• Low potential for a diagnosis to impact care of the patient and family (i.e., low likelihood that a genetic diagnosis would change management, impact reproductive counselling, improve psychosocial/mental health outcomes for family, etc.)***

* For most phenotypes, appropriate diagnostic testing means a non-diagnostic genomic test (most commonly exome sequencing), but may also mean, depending on phenotype, additional tests such as chromosomal microarray, expansion testing, methylation, etc.

**1) treatment options 2) reproductive decision-making 3) clinical surveillance

*** Avoid unduly raising expectations, alternative avenues explored (e.g., acutely deteriorating participant may be less appropriate)

For those meeting inclusion criteria, the following prioritisation criteria were applied by the clinical leads of the study to determine approval (Table 2). One point was assigned for each of the below criteria if met for a total out of 15

Table 2: Prioritisation Criteria

Category A: High likelihood of finding an answer through UDN-Aus with resources available and timeline of project	Category B: Optional criteria for consideration by Clinical Review Committee if criteria from Category A are equivocal.
1. Multi-systems involved (may need to consider single systems on case-by-case basis)* 2. Severe intellectual disability (ID) OR ID of any level + other features (e.g., dysmorphism, epilepsy, movement disorder) - do not double count with Criterion 1 3. Identifiable specific phenotype with no definitive molecular diagnosis identified after appropriate testing, including two or more individuals with a similar phenotype (cohort)# 4. Single variant in a gene associated with autosomal recessive disease that fits phenotype of patient^	1. In the presence of a family history, phenotype segregates with Mendelian inheritance 2. Consanguineous% parents (don't count if B1 selected) 3. <i>De novo</i> VUS/GUS 4. Phenotype that has high likelihood of discovery of novel gene 5. Phenotype that has high likelihood of discovery of novel mechanism
If a proposed patient is still deemed to be equivocal after application of criteria in Categories A and B, Clinical Review Committee then considered Category C; a score ≥2 in the Equity section below would warrant recruitment	
1. Individuals living in regional and remote centres+ 2. Aboriginal and Torres Strait Islander individuals 3. Individuals of culturally and linguistically diverse backgrounds 4. Individuals with low socioeconomic status~ 5. Individuals who identify as gender diverse 6. Individuals with disability (other than neurodevelopmental disability if counted under criteria A) 7. Individuals undiagnosed for more than 2 years 8. No alternative diagnostic pathways available§	

* Single system phenotypes might be lower priority than multisystem disorders, due to the clinical utility of testing

If you have a cohort of patients you would like to enrol in this study, please discuss this with your state clinical lead

^ Variants of unknown significance (VUS) in a gene with potential to discover a novel mechanism of disease (e.g., non-nonsense mediated decay (NMD)-predicted VUS associated with phenotype that is atypical or different to phenotype associated with loss of function (LOF) variants) should be prioritised to the Australian Functional Genomics Network (AFGN)

% Especially if limited regions of loss of heterozygosity (LOH)

+ Those classified as living in zone 3 and above using the Rural, Remote and Metropolitan Area classification map

~ as per proxy measure e.g. postcode classified in the lowest 25% of the Australian Bureau of Statistics' Socio Economic Indexes for Areas and/or family accessing income support

§e.g., other Australian MRFF funded undiagnosed disease programs such as mitoMDT or KidGen

The patient study participation process is outlined in Figure 3. The three stages are: 1) pre-enrolment, 2) enrolment, and 3) post-enrolment. At pre-enrolment, patients are identified as potentially eligible for recruitment, clinicians then provided patients with a pre-consent form and completed necessary data entry for study proposal. The enrolment stage involves review of the patient data by the project team and acceptance into the study. If accepted, patient informed consent is completed. Post-enrolment involves data and/or sample collection and subsequent investigations undertaken. Once all indicated investigations are undertaken a research report (Supplementary File S4) is generated and the report and result communicated back to the participant via their referring clinician or study genetic counsellor.

2.6 Study set up

The study set up is outlined in Figure 4.

The study set up is as follows:

Step 1: Case review.

Patients were proposed by referring clinicians via a Research Electronic Data Capture (REDCap) survey (40) following verbal consent to participate and reviewed in accordance with the study prioritization criteria. This review was initially conducted for each proposed patient at the national MDT (nMDT) meeting; however, it was rapidly determined that a formal national review was not required for most participants. The study adopted a fast-tracked approval

process – where participants clearly meeting enrolment criteria were reviewed by two designated clinical leads via the REDCap database. Participants were then either approved, referred for eligibility discussion at the national MDT should further information be required, or deemed ineligible.

Pre-enrolment verbal consent

Potentially eligible patients were identified by their genetics clinician during their clinical care, and clinicians provided the potential participant with a pre-enrolment information sheet and obtained verbal consent from the potential participant to forward their deidentified clinical and demographic details and minimal identifying details (name, date of birth, Medical Record Number and contact details) to the study team, via the secure REDCap database for consideration of eligibility. Clinical photographs, to be shared following informed consent via screensharing during the online nMDT, were also requested.

Post-approval study consent

If deemed eligible following review, the referring clinician or local site genetic counsellor accessed the participant's identifying contact details via the REDCap database and was responsible for obtaining the patient's informed consent to participate in the study. The investigator explaining the study and gaining informed consent was either a specialist in the service or a genetic counsellor supported by the study.

If deemed ineligible for enrolment, referring clinicians received an automated email via REDCap either asking for more clarifying information to allow re-review for eligibility, or prompting them to inform the referred family that they were ineligible for the study.

Data capture:

This study utilised the REDCap platform hosted at the MCRI to create and host the national electronic study database (40). Capturing relevant data pertaining to patient's previous testing, demographics, clinical and family history was essential to this project, not only to ascertain the information required to ensure equitable recruitment, but also to allow for phenotypic data linkage to the CPG's *seqr* platform (41). To ensure this database captured useful clinical data, it leveraged questions developed by Victorian, NSW and WA state-based programs, and existing frameworks developed by Australian Genomics to develop a system that was fit for purpose. This database also enabled the use of e-consent and CTRL (42) a dynamic consent portal, for participants in the study.

Step 2: Genomic data and sample acquisition.

UDN-Aus acknowledged that participants in this program were likely to have been through many rounds of clinical investigation and potentially have previously been enrolled in several research studies. As such, the UDN-Aus set out to reduce the burden of additional sample collection for participants by obtaining existing clinically generated genomic data and clinically obtained biological samples where available. Participation in the study firstly required the acquisition of existing clinically generated genomic data (ES or WGS) from recruited families, generated and stored by participating labs within Australia. Once families were approved for recruitment and consented to the study, this existing data was transferred to the CPG's rare disease genomic analysis platform (CaRDinal) to facilitate multi-centre, collaborative research through *seqr* (41) for initial clinician-led genomic reanalysis, and to the Interpretable Modular Platform for the Prediction of Relevant Obscure Variants by Expression (IMPPROVE), a phenotype specific model for variant prioritisation (43). In rare cases where individuals were approved for study enrolment, and clinical ES or WGS data proved subsequently unavailable, new genomic sequencing was undertaken via the study.

The CaRDinal platform, built and maintained by the CPG, supports integrated analysis across all variant types. It incorporates *seqr* which enables comprehensive filtering of genomic variation by inheritance mode, functional impact, population frequency, and other variables. It also allows for rapid visualisation of the raw read data supporting variants, automated reanalysis, and integrates key external resources (e.g. OMIM, ClinVar, GTEX) with variant and clinical data in an intuitive interface that supports variant interpretation and gene discovery.

The current landscape of genomic data sharing in Australia is complicated by siloed data repositories, differing genomic reference sequence utilisation, and variable access to clinical genomic testing across jurisdictions, and is lacking infrastructure for efficient and traceable data transfer (37). Enabling a process for efficient data sharing to occur was essential for UDN-Aus, and as such, significant effort was placed on developing overarching data transfer agreements with four laboratories in Australia (Supplementary File S5), with existing data transfer request processes used for genomic data transfer from Blueprint Genomics. These agreements aimed to maximize the potential for streamlined data transfer, and to ensure strict laboratory data security and intellectual property considerations were met. The study also attempted to obtain existing genomic data from the private provider, Australian Clinical Labs, but this pathway was unable to be negotiated within the study period.

If a clear genetic answer was not identified from reanalysis of participants' clinical data, participants were then generally approved by the clinical review committee for either expanded genomic sequencing or further functional testing if a candidate variant was identified. This required obtaining at least one biological sample, for example fresh blood, saliva, urine, stored DNA where possible, or (in limited cases) a skin biopsy (or tissue samples, e.g. muscle or liver, if the participant was undergoing surgery). These biological samples were obtained from each participant clinically diagnosed with the condition, and in certain circumstances other family members who did not have the condition.

Upskilling of clinicians in variant analysis and use of the bioinformatics platform *seqr*:

As part of upskilling the clinicians involved in the research, two UDN-Aus/CPG *seqr* training workshops were held to educate and support clinicians to analyse their patients' sequencing data. The workshops were held in September 2022, using live-streamed lectures, and April 2023, using pre-recorded lectures. A total of 98 UDN-Aus members attended. Participants were invited to complete pre- and post-workshop surveys, and descriptive statistics, non-parametric testing quantitative data and inductive content data analysis occurred (44).

Step 3: Data generation and sharing

Depending on the initial sequencing reanalysis outcome, some participants had additional testing and data generation. This included expansion to research trio genomic sequencing, RNA-Seq (via Victorian Clinical Genetics Service [VCGS]) or long-read sequencing (via the Garvan Institute of Medical Research), with interpretation by the study team.

Novel candidate genes and candidate Variants of Uncertain Significance (VUS) arising from the above testing were submitted to the Matchmaker Exchange platform (45). In cases of candidate VUS, flow through to functional investigations included referrals to other MRFF funded project collaborators for proteomic testing (RDMassSpec) and functional investigations (e.g., via the Australian Functional Genomics Network). In some cases, functional studies were conducted offshore, following identification of collaborators from Matchmaker Exchange and establishment of tailored material transfer agreements. Following consultation with the project's IAG, it was determined that no samples or genomic testing for those participant's identifying as Aboriginal or Torres Strait Islander would be conducted offshore.

Step 4: Health economic evaluation

As part of the study, health economic research is aiming to understand the cost-benefit of genomic technologies. Two surveys were administered to participants, the first being after consent, and then second being after at least one study investigation has occurred. These results have been published elsewhere (46).

Step 5: Returning results

All participants receive a research report after clinically indicated study investigations are conducted. These detail what testing has occurred and any research findings. Reports indicate either that no cause of the patient's phenotype was identified- 'No Abnormality Detected' (NAD) or describe the reportable variant(s) identified. Incidental findings not associated with the patient's condition were only reported if they were determined to be clinically actionable, following discussion with the referring clinical team. Research reports are communicated back to participants by their referring clinician, treating genetics clinical team or study team genetic counsellor (GC).

Step 6: Publishing and sharing

Results of the UDN-Aus study will be published to allow information and knowledge sharing. This study will aim to deliver on the following outcomes as a means of ensuring that the study aims are met:

- Number and proportion of eligible families recruited from each site
- Number of molecular diagnoses achieved, phenotypic categories of highest diagnostic yield and what combination of approaches was needed to reach the diagnosis
- Number of diagnoses in known disease genes, including novel phenotypes involving known genes
- Number of novel gene and disease mechanism discoveries
- Number of VUS resolved by adjunctive assays
- Number of cases where there was a change in management and documentation of what changes were made, including access to clinical trials
- Reproductive outcomes in those families where a genetic diagnosis was achieved vs those families where a genetic diagnosis remained elusive
- Individual participant and family costs and benefits because of being involved in this project
- Number of clinical staff upskilled in the application of the optimised re-analysis pipeline

3. Results

3.1 Multi-Institute Agreements and Research Collaboration Agreements

The study's initial (V1) MIA included twelve collaborating sites and took an average of 11.5 weeks for sign off from all parties (range: 12–21 weeks). Due to the evolving nature of the study, it was determined two additional collaborators (The Garvan Institute of Medical Research and VCGS) were required to be party to this agreement to ensure standardised governance, and they were added to the second iteration (V2) of the MIA, which took an additional average of 12 weeks to execute (range: 9–17 weeks).

The Royal Melbourne Hospital, Austin Hospital and Monash Hospital were added as sites in year 3 of the study. As such, they required separate Research Collaboration Agreements (RCA) (adapted from MCRI templates) for site specific governance, taking 48, 39 and 13 weeks to execute respectively (Supplementary File S1).

3.2 Ethics and Governance

To encapsulate the evolving requirements of the study throughout a five-year period, 11 amendments were made to the initial ethics application via the Royal Children's Hospital HREC, with subsequent site-specific governance amendments and requirements listed in Supplementary File S2. Collectively, to obtain site specific governance approval, 13 differing requirements in addition to the overarching HREC application, including external research collaboration agreements, hard copy applications, IT security assessments, detailed budget reviews and working with children checks were required (Supplementary File S2). In total, UDN-Aus spent \$5,329 AUD on ethics and governance applications, with a conservative estimate of one FTE staff dedicated to gaining ethics and governance approvals for 2 full years of the study (at an approximate cost of \$250,000 AUD). The average time for approval across the 12 clinical sites

20.2 weeks, which is consistent with previous findings from Australian Genomics (Haas et al., 2019). The longest approval time was King Edward Memorial Hospital with approval taking 102 weeks. Delays were generally attributed to lack of staffing at local sites, the complex nature of the study, COVID-19 departmental shutdowns, additional research collaboration agreement negotiation requiring legal team review, and the installation of new data security measures across institutes. At two sites, delays in governance approvals resulted in reallocation of site-specific staff funding and impacted the ability for patients at these sites to participate in the study.

3.3 Data transfer agreements

Data Transfer Agreements (DTAs) were established with four clinical genomics providers throughout Australia (Supplementary Table S5). UDN-Aus leveraged the existing commercial request pathway through private provider Blueprint Genetics. Agreements were also pursued with Australian Clinical Labs, and PathWest (WA), however these were unable to be established within the timeframes required for this project.

DTA templates were taken from each laboratory (except for SA Pathology) as a starting point for negotiation. It took an average of 22.25 weeks (range 17–33 weeks) to establish and execute a DTA with each laboratory provider to enable data transfer that was fit for the purposes of the project, while remaining within the required parameters of the clinical lab.

3.4 Pathology collection and testing pathway establishment

The requirement to obtain fresh biological samples for participants approved for expanded genomic sequencing or further functional testing, meant that pathology sign-off was required from participating sites. This process involved applying for research agreements at each site by providing information on the sample type, processing, storage and transport requirements. There were multiple sample types requested throughout the study. These included stored DNA aliquots, fresh blood collections, stored fibroblasts vials, and fresh skin biopsies. We developed a Standard Operating Procedure (SOP) document outlining our requirements for the collection, handling, and shipping of biological specimens as part of our study (Supplementary File S6). This document was provided as a guide to pathology sites as well as clinicians and genetic counsellors. Pathology sites provided quotes, based on our sample requirements, for signoff by the study team (Supplementary Table S7).

The next step was to develop a study specific request form template (Supplementary File S8) including the patient and clinical/study team details, sample requested, test requested, billing information, and any specific pathology collection and specimen reception instructions. Some pathology sites developed their own request form for our study samples to meet their own needs, whereas others were satisfied using our template and adapted it to include any specific additional information they required. These request forms were provided by clinicians or genetic counsellors to study participants to take to the appropriate pathology site for sample collection. We requested that study participants notified their clinician or genetic counsellor when they had presented for sample collection. This allowed the UDN-Aus sample coordinator to ensure samples were received at the required location and follow up if necessary.

3.5 *seqr* workshop evaluation

The *seqr* workshop analysis found that the training increased individuals' confidence and understanding in using the *seqr* resource. However, the level of knowledge and competency gained through the course was less than anticipated by course conveners, despite meeting the expectations of participating individuals (44).

In practice, while there was broad clinician interest in engaging in hands-on variant analysis, throughout the study we saw a shift towards variant curator-led analysis comparable to clinician-led analysis. Thirty-five clinicians were recorded in our variant curation tracker. Of these, 10 (29%) regularly or occasionally completed their own primary analysis. The remaining 25 (71%) relied on the UDN-Aus variant curation team (N = 10) for primary analysis at a diagnostic standard.

3.6 Subcommittee establishment, recruitment and stakeholder engagement

To date, UDN-Aus comprises a national network of 50 clinical geneticists, 17 genetic counsellors and 35 researchers. Since year one of the study, it has conducted 64 nMDT meetings, (~ 96 hours), 16 Investigator meetings (~ 16 hours), 8 CAG & IAG meetings (~ 12 hours), 27 DASG meetings (~ 27 hours), 20 operations meetings (~ 10 hours), and 21 Steering Committee meetings (~ 21 hours).

UDN-Aus has enabled standardised review of 250 families for enrolment in this study across all Australian states and territories. Two hundred families have been approved for enrolment with research analysis and testing ongoing.

Discussion

This pioneering initiative in the Australian rare disease research space has approved the enrolment of 200 families across Australia and provided access to cutting edge genomic reanalysis and flow through to frontier genomic technologies. Importantly, this effort has gone beyond individual case outcomes; it has also offered a crucial and timely opportunity to evaluate the current landscape of clinical genomic data infrastructure and identify barriers and facilitators to a national undiagnosed disease network within Australia at the clinical "coalface".

Throughout the program, establishing processes to maximize equity of access to the project was paramount. Establishing IAG and CAG oversight and guidance enabled efficient review of project materials and acted to inform crucial project strategy and policy. Following review with each subcommittee, consent forms, prioritisation criteria, data and sample storage and policy and patient materials were all significantly and prospectively adjusted to ensure that our research values and priorities continued to align with patient needs (e.g., all genomic data and sample storage for Aboriginal and Torres Strait Islander participants remained onshore). We were also mindful of the importance of standardised recruitment and prioritisation criteria to ensure referral sites in each state had transparency in relation to recruitment; a learning from other international UDPs. The establishment of prioritisation criteria also

enabled the project to recognize and quantify those participants identifying as from a CALD, low socio-economic-status or rural and remote background, and thus assisted in the program in ensuring more representative inclusion for these families.

Adaptable approaches were required for implementation throughout many other aspects of the program, including staggering nMDT meeting timing to maximise clinician attendance, allowing each site to have flexible recruitment targets based on demand, and moving to fast-tracked approvals for clearly eligible and high priority participants. If clinicians were unable to attend MDT meetings to present their cases, email communication was often utilised, which while successful in progressing cases through the program, required significant operational staff and program clinician time.

After mapping existing infrastructure and pathways in relation to both genomic data and sample transfer across each participating Australian laboratory, it became evident that the negotiation of bespoke agreements was required to enable data and sample transfer in timelines acceptable for the 4.5-year study. Establishment of these agreements placed a substantial burden on the study coordination staff and introduced various limitations pertaining to data use, and establishment of an agreement with one private sequencing provider was unsuccessful. Furthermore, the practical requirements for genomic data transfer after these agreements were established also varied between each lab and required manual input (such as emails or individual data request form submission) from the study coordination staff, genetic counsellors and clinical geneticists, and the CPG's data management team. These logistical challenges underscore the urgency of a national framework for genomic data governance in keeping with recommendations from the Blueprint for a National Approach to Genomic Information Management (NAGIM) which advocates for streamlined, secure, and standardised approaches to data sharing and management (47). Until these frameworks and infrastructure are established, we would recommend future studies carefully consider the cost-benefit of utilizing clinical data, versus proceeding with generating new genomic data from a single laboratory.

Another critical factor that emerged was the impact of current workforce limitations on establishing routine clinician-led variant curation. While workshops to upskill the clinical genomics workforce in variant interpretation using the *seqr* platform were successful in increasing clinician confidence, it quickly became evident that it was uncommon for a clinical geneticist or genetic counsellor to have sufficient time to independently undertake data analysis and variant interpretation. This reality of limited clinician time acted to curtail broader engagement, and the project quickly shifted to a heavy reliance on dedicated variant curators to prevent a bottleneck in result delivery. Variant analysts within this study not only were required to perform manual variant curation, but to assist with preparation of slide decks for MDTs and generate research reports. With 21.2 FTE bioinformaticians reported as employed in Australian clinical labs from the latest available data in 2017 (26) and approximately 3.0 FTE dedicated to this study collectively throughout the project, this highlights a critical need for both automation of curation processes and report generation, and expansion of this workforce.

The biggest barrier to study implementation was the time-intensive and variable requirements for research governance approvals across sites. This is concordant with findings from similar national genomic research undertaken by Australian Genomics, which in 2019 published a suite of recommendations including standardised Site-Specific Assessment (SSA) approval systems, training programs for research governance offices (RGOs) to ensure competency and consistent policies, reduced duplication of forms, abolishment of hard copy form requirements, and template provision for all requested documents (48). Despite these recommendations, at the time of the UDN-Aus governance application process it was not evident to the study team that these recommendations had been implemented across RGOs. Eleven subsequent amendments to our initial ethics application were required to capture the evolving needs of the study. In hindsight, the considerable operational time required for this was limiting, and we would suggest future studies map program needs thoroughly, or engage with appropriate consultancy prior to submitting an initial ethics application. Negotiation of the project's MIA also required a significant amount of time to execute. All the above factors required substantial operational staff time, in keeping with findings from Australian Genomics which invested \$831,850 AUD of operational staff time (6.5FTE with an annual salary of \$127,000 AUD) solely for obtaining ethics and governance approvals from 28 clinical sites over a period of two years (48). As such, UDN-Aus increased national program management FTE from 0.6 to 1.6FTE.

While facilitating biological sample movement and tracking was challenging, ensuring allocation of funding for a centralised sample coordinator was essential to ensure assay sample requirements were consistently met, pathology request forms were accurately completed, and research samples were robustly documented and processed. Employment of genetic counsellors (GCs) embedded within each clinical recruitment site was also critical for the success of this UDP. The role of the GC continues to expand, and their ability to facilitate equitable and safe access to genomic testing is unparalleled (49, 50). In the UDN-Aus program, GCs facilitated efficient sample send-away, reviewed study consent forms and patient information sheets, conducted timely data entry, facilitated patient enrolment, answered patient enquiries, contributed to MDT meetings, performed variant curation in some cases, and provided tailored pre- and post-test genetic counselling for participants. They also acted as a primary site contact, facilitating engagement with geneticists and patients at each site. A GC was also employed as the national program manager. Due to funding limitations and the extension of the study, GCs were unfunded partially for the final year of the study, which we recognised acted to decrease engagement at sites and the efficiency of site communication and data entry. Considering these observations, we recommend that any future national programs ensure sustained funding for research GCs.

UDN-Aus benefited greatly from a strong governance structure, subcommittee establishment, IAG and CAG oversight and guidance and strong and varied stakeholder engagement throughout the study. This national network continues to expand and has been essential in establishing the study's diagnostic momentum.

Conclusion

UDN-Aus has established vital groundwork for the future of national undiagnosed disease diagnostic pathways in Australia. The program benefited greatly from a standardised governance structure and referral criteria, subcommittee establishment, IAG and CAG oversight and guidance and strong stakeholder engagement throughout the study. This national network continues to expand and has been essential in establishing the study's diagnostic momentum. We hope that our observations work to provide both proof of concept and strategies for future national genomics of rare disease research studies. Furthermore,

we provide a compelling argument for systemic genomic data sharing reform and national genomics infrastructure investment to continue to improve diagnostic genomic outcomes for patients and their families.

Abbreviations

Australian Alliance for Indigenous Genomics (ALIGN)

Australian Undiagnosed Diseases Network (UDN-Aus)

Centre for Population Genomics (CPG)

Community advisory group (CAG)

Data Acquisition and Sharing Group (DASG)

Data Transfer Agreement (DTA)

Deoxyribonucleic Acid (DNA)

Full-Time Equivalent (FTE)

Genetic Counsellor (GC)

Human Research Ethics Committee (HREC)

Indigenous Advisory Group (IAG)

Interpretable Modular Platform for the Prediction of Relevant Obscure Variants by Expression (IMPPROVE)

Law, Sociology and Ethics in Data Governance for Genomics (LINEAGE)

Medical Research Future Fund (MRFF)

Medical Record Number (MRN)

Multi-Disciplinary Team (MDT)

Multi-Institute Agreement (MIA)

Murdoch Children's Research Institute (MCRI)

National Approach to Genomic Information Management (NAGIM)

No Abnormality Detected (NAD)

Research Collaboration Agreement (RCA)

Research Electronic Data Capture (REDCap)

RDNOW (Rare Disease Now)

Standard Operating Procedure (SOP)

Site-Specific Assessment (SSA)

Undiagnosed Diseases Network International (UDNI)

Undiagnosed Disease Program (UDP)

Victorian Clinical Genetics Service (VCGS)

Variant of Uncertain Significance (VUS)

Whole Exome Sequencing (WES)

Whole Genome Sequencing (WGS)

Declarations

- **Ethics approval and consent to participate**

The study received ethics approval from the Royal Children's Hospital Human Research Ethics Committee on the 19th of November 2021 (RCH79712). Each participant provided consent to participate in this study

- **Consent for publication**

Not applicable.

- **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- **Competing interests**

The authors declare that they have no competing interests.

- **Funding**

The research conducted at the Murdoch Children's Research Institute (MCRI) was supported by the Victorian Government's Operational Infrastructure Support Program. The Chair in Genomic Medicine awarded to JC is generously supported by The Royal Children's Hospital Foundation.

The Australian Undiagnosed Diseases Network (UDN-Aus) acknowledges financial support from the Australian Government's Medical Research Future Fund (2007567), Australian Genomics and The Centre for Population Genomics (Garvan Institute of Medical Research and Murdoch Children's Research Institute); funded in part by a Medical Research Future Fund (MRFF) Genomics Health Futures Mission grant (2008820).

- **Authors' contributions**

EM, MH and JC conceptualised and planned the manuscript

EP and MH performed the literature review

EM, MH, TS, SC obtained and analysed data to write the original draft

All listed authors contributed to review and editing of the manuscript

JC supervised manuscript writing activities

- **Acknowledgements**

Thank you to Australian Genomics, The Centre for Population Genomics, Victorian Clinical Genetics Service, New South Wales Health Pathology, Pathology Queensland, South Australia Pathology, The Garvan Institute of Medical Research, Blueprint Genetics, Australian Functional Genomics Network, Garvan Institute Long-Read Sequencing project, RDMassSpec, Meg Bourne, Lauren McKnight, Yetong Chen, Emma Tudini, all UDN-Aus Investigators, Rare Disease and Indigenous Advisory Committee Members: Chris Pratt, Rebekah McWhirter, Sean Taylor, Rare Disease Advisory Committee Members: Nicole Millis, Emma Bonser, Heather Renton, Monic Ferrie, Sam Campbell, Jan Mumford, and finally but most importantly, all patients and their families.

The Undiagnosed Disease Network Australia collaborative group is

Alison Yeung. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Andrew Paul Fennell. Monash Health, Melbourne, VIC, Australia; Department of Paediatrics, Monash University, Melbourne, VIC, Australia. Anna Hackett. Genetics of Learning Disability Service, Newcastle, NSW, Australia. Anne Baxter. Hunter Genetics, Newcastle, NSW, Australia. Ansley Morrish. Sydney Children's Hospital Network, Sydney, NSW, Australia. Ashil Davawala. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Azure Hermes. Australian National University, Canberra, ACT, Australia; National Centre for Indigenous Genomics, Canberra, ACT, Australia. Ben Kamien. Genetic Health WA, Perth Children's Hospital, WA, Australia. Ben Lundie. Pathology Queensland, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia. Carolyn Ellaway. Sydney Children's Hospital Network, Sydney, NSW, Australia. Carolyn Shalhoub. Sydney Children's Hospital Network, Sydney, NSW, Australia. Cas Simons. Centre for Population Genomics, Garvan Institute of Medical Research and UNSW Sydney, Sydney, NSW, Australia; Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia. Cassandra Gray. Centre for Population Genomics, Garvan Institute of Medical Research and UNSW Sydney, Sydney, NSW, Australia; Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia. Cathryn Poulton. Undiagnosed Diseases Program, Genetic Health WA and Rare Care Centre, Perth Children's Hospital. Chloe Cunningham. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Chris Barnett. Women's and Children's Hospital, Adelaide, SA, Australia. Christopher Richards. Centre for Population Genomics, Garvan Institute of Medical Research and UNSW Sydney, Sydney, NSW, Australia; Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia. Christopher Richmond. Genetic Health Queensland, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia; School of Medicine, Griffith University, Gold Coast, QLD, Australia. Clara Chung. Sydney Children's Hospital Network, Sydney, NSW, Australia. Daniel G. MacArthur. Centre for Population Genomics, Garvan Institute of Medical Research and UNSW Sydney, Sydney, NSW, Australia; Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia. Daniel Pavlic. Centre for Population Genomics, Garvan Institute of Medical Research and UNSW Sydney, Sydney, NSW, Australia; Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia. Daniella Hock. The University of Melbourne, Melbourne, VIC, Australia. Daniz Kooshavar. Murdoch Children's Research Institute, Melbourne, VIC, Australia. David A. Stroud. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Victorian Clinical Genetics Services,

Melbourne, VIC, Australia; The University of Melbourne, Melbourne, VIC, Australia. David Amor. Victorian Clinical Genetics Services, Melbourne, VIC, Australia; The University of Melbourne, Melbourne, VIC, Australia. David Mowat. Sydney Children's Hospital Network, Sydney, NSW, Australia. Edward Formaini. Centre for Population Genomics, Garvan Institute of Medical Research and UNSW Sydney, Sydney, NSW, Australia; Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia. Elaine Zhang. Murdoch Children's Research Institute, Melbourne, VIC, Australia; The University of Melbourne, Melbourne, VIC, Australia. Elizabeth E. Palmer. Sydney Children's Hospital Network, Sydney, NSW, Australia; The University of Sydney, Sydney, NSW, Australia. Ella Jane Wilkins. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Victorian Clinical Genetics Services, Melbourne, VIC, Australia; The University of Melbourne, Melbourne, VIC, Australia. Ella Zurita. Sydney Children's Hospital Network, Sydney, NSW, Australia. Ellenore M. Martin. Murdoch Children's Research Institute, Melbourne, VIC, Australia. Elly Lynch. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Emma Krzesinski. Monash Health, Melbourne, VIC, Australia; Department of Paediatrics, Monash University, Melbourne, VIC, Australia. Esther Pierini. Murdoch Children's Research Institute, Melbourne, VIC, Australia. Evanthia O. Madelli. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Australian Genomics, Melbourne, VIC, Australia. Francisco Santos Gonzalez. The University of Melbourne, Melbourne, VIC, Australia. Gareth Baynam. Undiagnosed Diseases Program, Genetic Health WA and Rare Care Centre, Perth Children's Hospital. Gunjan Garg. Genetics of Learning Disability Service, Newcastle, NSW, Australia. Hamish Scott. SA Pathology, Adelaide, SA, Australia; The University of Adelaide, Adelaide, SA, Australia. Hannah Thomson. Genetics of Learning Disability Service, Newcastle, NSW, Australia. Himanshu Goel. Genetics of Learning Disability Service, Newcastle, NSW, Australia. Ilias Goranitis. Murdoch Children's Research Institute, Melbourne, VIC, Australia; The University of Melbourne, Melbourne, VIC, Australia. Ira W. Deveson. Genomics and Inherited Disease Program, Garvan Institute of Medical Research, Sydney, NSW, Australia; Faculty of Medicine and Health, St Vincent's Healthcare Clinical Campus, University of New South Wales, Darlinghurst, NSW, Australia. Isabella Pfundt. Monash Health, Melbourne, VIC, Australia. Jacqui Russell. Sydney Children's Hospital Network, Sydney, NSW, Australia. Janine Smith. Sydney Children's Hospital Network, Sydney, NSW, Australia; The University of Sydney, Sydney, NSW, Australia. Jason Pinner. Sydney Children's Hospital Network, Sydney, NSW, Australia. John Christodoulou. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Victorian Clinical Genetics Services, Melbourne, VIC, Australia; The University of Melbourne, Melbourne, VIC, Australia. Julia Broadbent. Murdoch Children's Research Institute, Melbourne, VIC, Australia; The University of Melbourne, Melbourne, VIC, Australia. Julie McGaughan. Genetic Health Queensland, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia; The University of Queensland School of Medicine, St Lucia, Brisbane, QLD, Australia. Karin Kassahn. SA Pathology, Adelaide, SA, Australia. Katherine Lewis. Sydney Children's Hospital Network, Sydney, NSW, Australia. Katrina Bell. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Kaustuv Bhattacharya. Sydney Children's Hospital Network, Sydney, NSW, Australia. Kirsten Boggs. Sydney Children's Hospital Network, Sydney, NSW, Australia. Kirsty West. Genomic Medicine, Royal Melbourne Hospital, Melbourne, VIC, Australia. Kristi Jones. Sydney Children's Hospital Network, Sydney, NSW, Australia. Laura Wedd. Centre for Population Genomics, Garvan Institute of Medical Research and UNSW Sydney, Sydney, NSW, Australia; Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia. Lauren Dreyer. Undiagnosed Diseases Program, Genetic Health WA and Rare Care Centre, Perth Children's Hospital. Leah Frajman. Murdoch Children's Research Institute, Melbourne, VIC, Australia. Leanne Baxter. Pathology Queensland, Royal Brisbane and Women's Hospital, Herston, QLD 4029, Australia. Lilian Downie. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Lily Loughman. Undiagnosed Diseases Program, Genetic Health WA and Rare Care Centre, Perth Children's Hospital. Lisa Bristowe. Sydney Children's Hospital Network, Sydney, NSW, Australia. Lisa Ewans. Sydney Children's Hospital Network, Sydney, NSW, Australia. Louise Cilento. Women's and Children's Hospital, Adelaide, SA, Australia. Lucy Kevin. Sydney Children's Hospital Network, Sydney, NSW, Australia. Lyndal Douglas. Sydney Children's Hospital Network, Sydney, NSW, Australia. Madeleine Harris. Murdoch Children's Research Institute, Melbourne, VIC, Australia. Maie Walsh. Genomic Medicine, Royal Melbourne Hospital, Melbourne, VIC, Australia. Manisha Chauhan. Sydney Children's Hospital Network, Sydney, NSW, Australia. Margit Shah. Sydney Children's Hospital Network, Sydney, NSW, Australia. Martin Delatycki. Victorian Clinical Genetics Services, Melbourne, VIC, Australia; Austin Hospital, Melbourne, VIC, Australia. Mathew Wallis. Tasmanian Clinical Genetics Service, Hobart, TAS, Australia. Matthew Hunter. Monash Health, Melbourne, VIC, Australia. Megan Ball. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Megan Higgins. Genetic Health Queensland, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia. Meutia Kumari. The Garvan Institute of Medical Research, Sydney, NSW, Australia. Michael Fahey. Monash Health, Melbourne, VIC, Australia. Michael Field. Genetics of Learning Disability Service, Newcastle, NSW, Australia. Michelle DaSilva. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Mohammadreza Hajjari. Centre for Population Genomics, Garvan Institute of Medical Research and UNSW Sydney, Sydney, NSW, Australia; Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia. Molly Carr. Sydney Children's Hospital Network, Sydney, NSW, Australia. Monique Dunstan. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Natalie Stewart. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Natalie Tan. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Natasha Brown. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Nicole Van Bergen. Murdoch Children's Research Institute, Melbourne, VIC, Australia. Noelia Nunez-Martinez. Sydney Children's Hospital Network, Sydney, NSW, Australia. Oliver Heath. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Rachel Austin. Genetic Health Queensland, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia. Rani Sachdev. Sydney Children's Hospital Network, Sydney, NSW, Australia. Rebecca Macintosh. Sydney Children's Hospital Network, Sydney, NSW, Australia. Rebecca Vink. Sydney Children's Hospital Network, Sydney, NSW, Australia. Rocio Rius. Centre for Population Genomics, Garvan Institute of Medical Research and UNSW Sydney, Sydney, NSW, Australia; Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia. Ruvi Samarasekera. Sydney Children's Hospital Network, Sydney, NSW, Australia. Ryan Pysar. Genetics of Learning Disability Service, Newcastle, NSW, Australia. Sandra Cooper. Sydney Children's Hospital Network, Sydney, NSW, Australia; The University of Sydney, Sydney, NSW, Australia; The Children's Medical Research Institute, Westmead, NSW, Australia. Sarah Casauria. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Australian Genomics, Melbourne, VIC, Australia. Sarah Collinson. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Sarah Jelenich. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Australian Genomics, Melbourne, VIC, Australia. Sarah Josephi-Taylor. Sydney Children's Hospital Network, Sydney, NSW, Australia. Sarah Sandaradura. Sydney Children's Hospital Network, Sydney, NSW, Australia. Sean Massey. Sydney Children's Hospital Network, Sydney, NSW, Australia. Shannon LeBlanc. Women's and Children's Hospital, Adelaide, SA, Australia. Shuxiang Goh. Hunter Genetics, Newcastle, NSW, Australia. Simon Bodek. Austin Hospital, Melbourne, VIC, Australia. Simon Sadedin. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Victorian Clinical Genetics Services, Melbourne, VIC, Australia; The University of Melbourne, Melbourne, VIC, Australia. Simran Kaur. Murdoch Children's Research Institute, Melbourne, VIC, Australia. Smitha Kumble. Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Susan M. White. Victorian Clinical Genetics

Services, Melbourne, VIC, Australia. Suzanne Sallevelt. Women's and Children's Hospital, Adelaide, SA, Australia. Tegan Stait. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Victorian Clinical Genetics Services, Melbourne, VIC, Australia. Tian Zhao. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Victorian Clinical Genetics Services, Melbourne, VIC, Australia; The University of Melbourne, Melbourne, VIC, Australia. Tiffany Boughtwood. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Australian Genomics, Melbourne, VIC, Australia. Tim Sikora. Murdoch Children's Research Institute, Melbourne, VIC, Australia. Timo Lassmann. The Kid's Research Institute, Perth, WA, Australia; University of Western Australia, Perth, WA, Australia. Tiong Yang Tan. Murdoch Children's Research Institute, Melbourne, VIC, Australia; Victorian Clinical Genetics Services, Melbourne, VIC, Australia; The University of Melbourne, Melbourne, VIC, Australia. Tracy Dudding-Byth. Genetics of Learning Disability Service, Newcastle, NSW, Australia.

References

1. Hartley T, Lemire G, Kernohan KD, Howley HE, Adams DR, Boycott KM. New Diagnostic Approaches for Undiagnosed Rare Genetic Diseases. *Annu Rev Genom Hum Genet* [Internet]. 2020 Aug 31 [cited 2025 June 4];21(1):351–72. Available from: <https://www.annualreviews.org/doi/10.1146/annurev-genom-083118-015345>
2. Sawyer SL, Hartley T, Dymont DA, Beaulieu CL, Schwartzentruber J, Smith A et al. Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care. *Clinical Genetics* [Internet]. 2016 Mar [cited 2025 June 4];89(3):275–84. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/cge.12654>
3. Splinter K, Adams DR, Bacino CA, Bellen HJ, Bernstein JA, Cheattle-Jarvela AM et al. Effect of Genetic Diagnosis on Patients with Previously Undiagnosed Disease. *N Engl J Med* [Internet]. 2018 Nov 29 [cited 2025 June 4];379(22):2131–9. Available from: <http://www.nejm.org/doi/10.1056/NEJMoa1714458>
4. Stavropoulos DJ, Merico D, Jobling R, Bowdin S, Monfared N, Thiruvahindrapuram B et al. Whole-genome sequencing expands diagnostic utility and improves clinical management in paediatric medicine. *npj Genomic Med* [Internet]. 2016 Jan 13 [cited 2025 June 4];1(1):15012. Available from: <https://www.nature.com/articles/npjgenmed201512>
5. APSU Rare Diseases Impacts on Families Study group, Zurynski Y, Deverell M, Dalkeith T, Johnson S, Christodoulou J et al. Australian children living with rare diseases: experiences of diagnosis and perceived consequences of diagnostic delays. *Orphanet J Rare Dis* [Internet]. 2017 Dec [cited 2025 June 4];12(1):68. Available from: <https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0622-4>
6. Palmer EE, Cederroth H, Cederroth M, Delgado-Vega AM, Roberts N, Taylan F et al. Equity in action: The Diagnostic Working Group of The Undiagnosed Diseases Network International. *npj Genom Med* [Internet]. 2024 July 5 [cited 2025 June 4];9(1):37. Available from: <https://www.nature.com/articles/s41525-024-00422-y>
7. Clark MM, Stark Z, Farnaes L, Tan TY, White SM, Dimmock D et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. *npj Genomic Med* [Internet]. 2018 Dec [cited 2021 Feb 20];3(1):16. Available from: <http://www.nature.com/articles/s41525-018-0053-8>
8. Smith HS, Swint JM, Lalani SR, Yamal JM, De Oliveira Otto MC, Castellanos S et al. Clinical Application of Genome and Exome Sequencing as a Diagnostic Tool for Pediatric Patients: a Scoping Review of the Literature. *Genetics in Medicine* [Internet]. 2019 Jan [cited 2025 June 4];21(1):3–16. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1098360021000915>
9. Wright CF, FitzPatrick DR, Firth HV. Paediatric genomics: diagnosing rare disease in children. *Nat Rev Genet* [Internet]. 2018 May [cited 2025 June 4];19(5):253–68. Available from: <https://www.nature.com/articles/nrg.2017.116>
10. Baynam G, Pachter N, McKenzie F, Townshend S, Slee J, Kiraly-Borri C et al. The rare and undiagnosed diseases diagnostic service – application of massively parallel sequencing in a state-wide clinical service. *Orphanet Journal of Rare Diseases* [Internet]. 2016 June 11;11(1):77. Available from: <https://doi.org/10.1186/s13023-016-0462-7>
11. on behalf of the IRDiRC Consortium Assembly, Lochmüller H, Torrent I, Farnell J, Le Cam Y, Jonker AH, Lau LP, The International Rare Diseases Research Consortium. : Policies and Guidelines to maximize impact. *Eur J Hum Genet* [Internet]. 2017 Dec [cited 2025 June 18];25(12):1293–302. Available from: <https://www.nature.com/articles/s41431-017-0008-z>
12. Gahl WA, Mulvihill JJ, Toro C, Markello TC, Wise AL, Ramoni RB et al. The NIH Undiagnosed Diseases Program and Network: Applications to modern medicine. *Molecular Genetics and Metabolism* [Internet]. 2016 Apr [cited 2025 June 4];117(4):393–400. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1096719216300063>
13. Taruscio D, Baynam G, Cederroth H, Groft SC, Klee EW, Kosaki K et al. The Undiagnosed Diseases Network International: Five years and more! *Molecular Genetics and Metabolism* [Internet]. 2020 Apr [cited 2025 June 4];129(4):243–54. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1096719219307681>
14. Curic E, Ewans L, Pysar R, Taylan F, Botto LD, Nordgren A et al. International Undiagnosed Diseases Programs (UDPs): components and outcomes. *Orphanet J Rare Dis* [Internet]. 2023 Nov 9 [cited 2025 June 18];18(1):348. Available from: <https://ojrd.biomedcentral.com/articles/10.1186/s13023-023-02966-1>
15. Cloney T, Gallacher L, Pais LS, Tan NB, Yeung A, Stark Z et al. Lessons learnt from multifaceted diagnostic approaches to the first 150 families in Victoria's Undiagnosed Diseases Program. *Journal of Medical Genetics* [Internet]. 2022;59(8):748–58. Available from: <https://jmg.bmj.com/content/59/8/748>
16. Wallis M, Bodek SD, Munro J, Rafehi H, Bennett MF, Ye Z et al. Experience of the first adult-focussed undiagnosed disease program in Australia (AHA-UDP): solving rare and puzzling genetic disorders is ageless. *Orphanet J Rare Dis* [Internet]. 2024 Aug 2 [cited 2025 June 4];19(1):288. Available from: <https://ojrd.biomedcentral.com/articles/10.1186/s13023-024-03297-5>
17. Shickh S, Mighton C, Uleryk E, Pechlivanoglou P, Bombard Y. The clinical utility of exome and genome sequencing across clinical indications: a systematic review. *Hum Genet* [Internet]. 2021 Oct [cited 2025 June 18];140(10):1403–16. Available from: <https://link.springer.com/10.1007/s00439->

18. Palmer EE, Schofield D, Shrestha R, Kandula T, Macintosh R, Lawson JA et al. Integrating exome sequencing into a diagnostic pathway for epileptic encephalopathy: Evidence of clinical utility and cost effectiveness. *Mol Genet Genomic Med* [Internet]. 2018 Mar [cited 2021 Mar 7];6(2):186–99. Available from: <http://doi.wiley.com/10.1002/mgg3.355>
19. Tan TY, Dillon OJ, Stark Z, Schofield D, Alam K, Shrestha R et al. Diagnostic Impact and Cost-effectiveness of Whole-Exome Sequencing for Ambulant Children With Suspected Monogenic Conditions. *JAMA Pediatr* [Internet]. 2017 Sept 1 [cited 2025 June 4];171(9):855. Available from: <http://archpedi.jamanetwork.com/article.aspx?doi=10.1001/jamapediatrics.2017.1755>.
20. Stark Z, Tan TY, Chong B, Brett GR, Yap P, Walsh M et al. A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. *Genetics in Medicine* [Internet]. 2016 Nov [cited 2025 June 4];18(11):1090–6. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1098360021013903>
21. Ewans LJ, Schofield D, Shrestha R, Zhu Y, Gayevskiy V, Ying K et al. Whole-exome sequencing reanalysis at 12 months boosts diagnosis and is cost-effective when applied early in Mendelian disorders. *Genetics in Medicine* [Internet]. 2018 Dec [cited 2025 June 4];20(12):1564–74. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1098360021000150>
22. Ibañez K, Polke J, Hagelstrom RT, Dolzhenko E, Pasko D, Thomas ERA et al. Whole genome sequencing for the diagnosis of neurological repeat expansion disorders in the UK: a retrospective diagnostic accuracy and prospective clinical validation study. *The Lancet Neurology* [Internet]. 2022 Mar [cited 2025 Nov 12];21(3):234–45. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1474442221004622>
23. Bagger FO, Borgwardt L, Jespersen AS, Hansen AR, Bertelsen B, Kodama M et al. Whole genome sequencing in clinical practice. *BMC Med Genomics* [Internet]. 2024 Jan 29 [cited 2025 June 4];17(1):39. Available from: <https://bmcmedgenomics.biomedcentral.com/articles/10.1186/s12920-024-01795-w>
24. Fehlberg Z, Stark Z, Best S. Reanalysis of genomic data, how do we do it now and what if we automate it? A qualitative study. *Eur J Hum Genet* [Internet]. 2024 May [cited 2025 June 4];32(5):521–8. Available from: <https://www.nature.com/articles/s41431-023-01532-4>
25. Australian Genomics Health Alliance Acute Care Flagship, Lunke S, Eggers S, Wilson M, Patel C, Barnett CP et al. Feasibility of Ultra-Rapid Exome Sequencing in Critically Ill Infants and Children With Suspected Monogenic Conditions in the Australian Public Health Care System. *JAMA* [Internet]. 2020 June 23 [cited 2025 June 18];323(24):2503. Available from: <https://jamanetwork.com/journals/jama/fullarticle/2767327>
26. Australian Government Department of Health. Australian Health Genetics/Genomics Survey 2017 Report of Key Findings [Internet]. 2019. Available from: [https://www.rcpa.edu.au/getattachment/c44ac2b4-b9db-437f-9b2c-c05eefc4408e/Australian-Health-Genetics-Genomics-Survey-201-\(1\).aspx](https://www.rcpa.edu.au/getattachment/c44ac2b4-b9db-437f-9b2c-c05eefc4408e/Australian-Health-Genetics-Genomics-Survey-201-(1).aspx)
27. Tadini E, Andrews J, Lawrence DM, King-Smith SL, Baker N, Baxter L et al. Shariant platform: Enabling evidence sharing across Australian clinical genetic-testing laboratories to support variant interpretation. *The American Journal of Human Genetics* [Internet]. 2022 Nov [cited 2025 June 4];109(11):1960–73. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0002929722004542>
28. Australian Government D of H Disability and Ageing. National Strategic Action Plan for Rare Diseases [Internet]. 2020. Available from: <https://www.health.gov.au/resources/publications/national-strategic-action-plan-for-rare-diseases?language=en>
29. Palmer EE, Recsei K, McKnight L, Roberts N, Baynam G, Zurynski Y et al. You get left behind and lost in a complex world of rare care: equity in access to rare disease care—learnings from the Australian Rare Disease Awareness, Education, Support, and Training (RArEST) project. *eBioMedicine* [Internet]. 2025 May [cited 2025 June 18];115:105710. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2352396425001549>
30. Australian Indigenous Governance Institute in Collaboration with the Maïam nayri Wingara Indigenous Data Sovereignty Collective. Indigenous Data Sovereignty Communique [Internet]. 2018. Available from: <https://aigi.org.au/news/indigenous-data-sovereignty-communique>
31. Hudson M, Garrison NA, Sterling R, Caron NR, Fox K, Yracheta J et al. Rights, interests and expectations: Indigenous perspectives on unrestricted access to genomic data. *Nat Rev Genet* [Internet]. 2020 June [cited 2025 June 4];21(6):377–84. Available from: <https://www.nature.com/articles/s41576-020-0228-x>
32. Kraft SA, Cho MK, Gillespie K, Halley M, Varsava N, Ormond KE et al. Beyond Consent: Building Trusting Relationships With Diverse Populations in Precision Medicine Research. *The American Journal of Bioethics* [Internet]. 2018 Apr 3 [cited 2025 June 4];18(4):3–20. Available from: <https://www.tandfonline.com/doi/full/10.1080/15265161.2018.1431322>
33. Lysaght T, Ankeny R, Brown A, McWhirter R, Nicol D, Otlowski M et al. The Australian LINEAGE Study: advancing and implementing international guidance on genomic data within local governance frameworks. *npj Genom Med* [Internet]. 2025 Apr 30 [cited 2025 June 4];10(1):34. Available from: <https://www.nature.com/articles/s41525-025-00492-6>
34. Gene2Care [Internet]. [cited 2025 June 18]. Available from: <https://kr.schn.health.nsw.gov.au/our-research/projects-and-initiatives/gene2care>
35. Baynam G, Broley S, Bauskis A, Pachter N, McKenzie F, Townshend S et al. Initiating an undiagnosed diseases program in the Western Australian public health system. *Orphanet Journal of Rare Diseases* [Internet]. 2017;12(1). Available from: <https://doi.org/10.1186/s13023-017-0619-z>
36. Australian Genomics. Tasmanian Rare Disease Diagnostic Pathways [Internet]. Tasmanian Clinical Genetics Service. 2024 June pp. 1–119. Available from: https://www.australiangenomics.org.au/wp-content/uploads/2022/08/TRDDP-Project-Report-for-Australian-Genomics_FINAL.pdf
37. Stark Z, Boughtwood T, Haas M, Braithwaite J, Gaff CL, Goranitis I et al. Australian Genomics: Outcomes of a 5-year national program to accelerate the integration of genomics in healthcare. *The American Journal of Human Genetics* [Internet]. 2023 Mar [cited 2025 June 4];110(3):419–26. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0002929723000435>
38. Stark Z, Boughtwood T, Phillips P, Christodoulou J, Hansen DP, Braithwaite J et al. Australian Genomics: A Federated Model for Integrating Genomics into Healthcare. *The American Journal of Human Genetics* [Internet]. 2019 July [cited 2021 Jan 25];105(1):7–14. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0002929719302289>

39. Haas MA, Teare H, Prictor M, Ceregra G, Vidgen ME, Bunker D et al. 'CTRL': an online, Dynamic Consent and participant engagement platform working towards solving the complexities of consent in genomic research. *Eur J Hum Genet* [Internet]. 2021 Apr [cited 2025 Nov 5];29(4):687–98. Available from: <https://www.nature.com/articles/s41431-020-00782-w>
40. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L et al. The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics* [Internet]. 2019 July [cited 2025 June 4];95:103208. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1532046419301261>
41. Pais LS, Snow H, Weisburd B, Zhang S, Baxter SM, DiTroia S et al. *seqr*: A web-based analysis and collaboration tool for rare disease genomics. *Human Mutation* [Internet]. 2022 Mar 21 [cited 2025 June 4];humu.24366. Available from: <https://onlinelibrary.wiley.com/doi/10.1002/humu.24366>
42. Haas MA, Teare H, Prictor M, Ceregra G, Vidgen ME, Bunker D et al. 'CTRL': an online, Dynamic Consent and participant engagement platform working towards solving the complexities of consent in genomic research. *Eur J Hum Genet* [Internet]. 2021 Apr [cited 2025 June 4];29(4):687–98. Available from: <https://www.nature.com/articles/s41431-020-00782-w>
43. Lassmann T, Francis RW, Weeks A, Tang D, Jamieson SE, Broley S et al. A flexible computational pipeline for research analyses of unsolved clinical exome cases. *npj Genom Med* [Internet]. 2020 Dec 10 [cited 2025 June 4];5(1):54. Available from: <https://www.nature.com/articles/s41525-020-00161-w>
44. Yetong C. Evaluation of knowledge and attitudes of participants involved in research-based genomic interpretation training [Internet]. University of Melbourne; Available from: <https://murdochchildrens.sharepoint.com/sites/UDN-Aus/Shared%20Documents/Forms/AllItems.aspx?id=%2Fsites%2FUDN%2DAus%2FShared%20Documents%2FGeneral%2FPublications%2FMonograph%5FYetong%20Chen%20%281%29%29%2Epdf&viewid=c1>
45. Philippakis AA, Azzariti DR, Beltran S, Brookes AJ, Brownstein CA, Brudno M et al. The Matchmaker Exchange: A Platform for Rare Disease Gene Discovery. *Human Mutation* [Internet]. 2015 Oct [cited 2025 Oct 29];36(10):915–21. Available from: <https://onlinelibrary.wiley.com/doi/10.1002/humu.22858>
46. Santos Gonzalez F, Mordaunt D, Stark Z, Dalziel K, Christodoulou J, Goranitis I. Microcosting diagnostic genomic sequencing: A systematic review. *Genetics in Medicine* [Internet]. 2023 June [cited 2025 June 4];25(6):100829. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1098360023008420>
47. Australian Genomics. National Approach to Genomic Information Management (NAGIM) Implementation Recommendations [Internet]. 2023. Available from: https://www.australiangenomics.org.au/wp-content/uploads/2021/06/NAGIM-Implementation-Recommendations_January-2023.pdf
48. Haas MA, Boughtwood TF, Quinn MC, Australian Genomics. The ethics approval process for multisite research studies in Australia: changes sought by the Australian Genomics initiative. *Medical Journal of Australia* [Internet]. 2019 Nov [cited 2025 June 4];211(10):440. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.5694/mja2.50397>
49. Ormond KE, Abad PJ, MacLeod R, Nishigaki M, Wessels TM. The global status of genetic counselors in 2023: What has changed in the past 5 years? *Genetics in Medicine Open* [Internet]. 2024 [cited 2025 June 18];2:101887. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2949774424010331>
50. Yanes T, Courtney E, Young M, Pearn A, McLnerney-Leo A, Ingles J. Genetic counsellors: facilitating the integration of genomics into health care. *Medical Journal of Australia* [Internet]. 2025 Feb 17 [cited 2025 June 18];222(3):114–7. Available from: <https://onlinelibrary.wiley.com/doi/10.5694/mja2.52568>

Figures

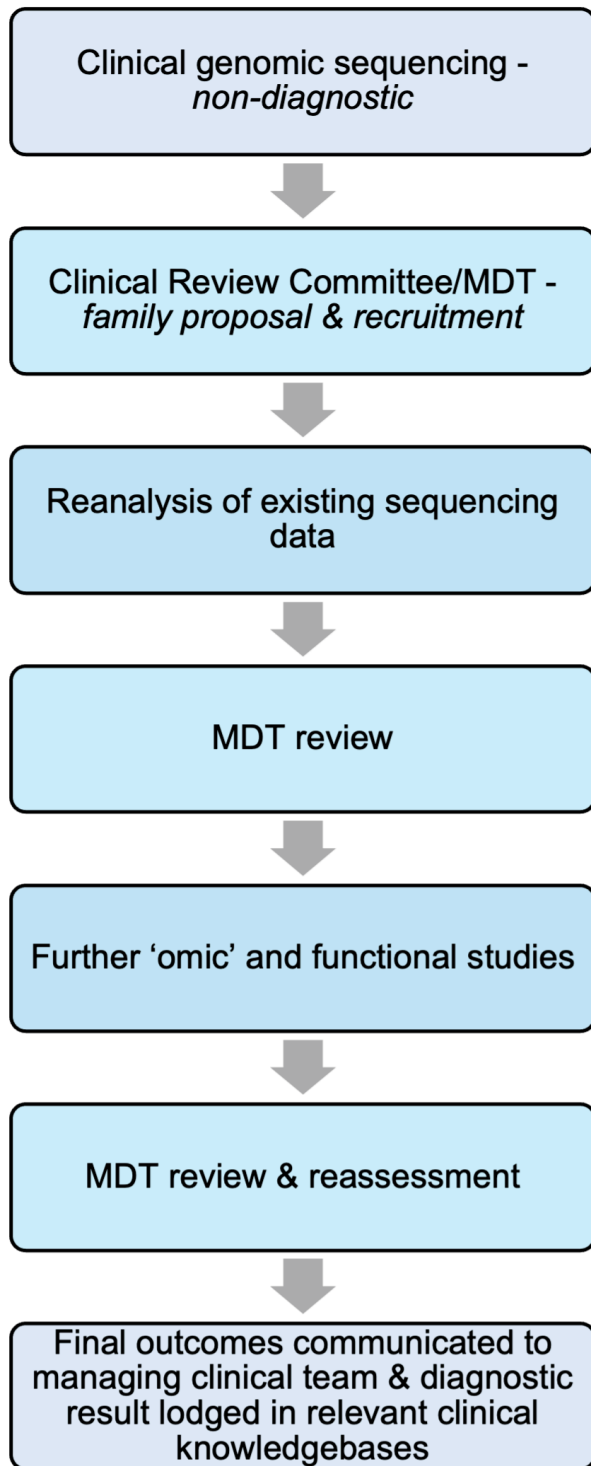


Figure 1

Study Design.

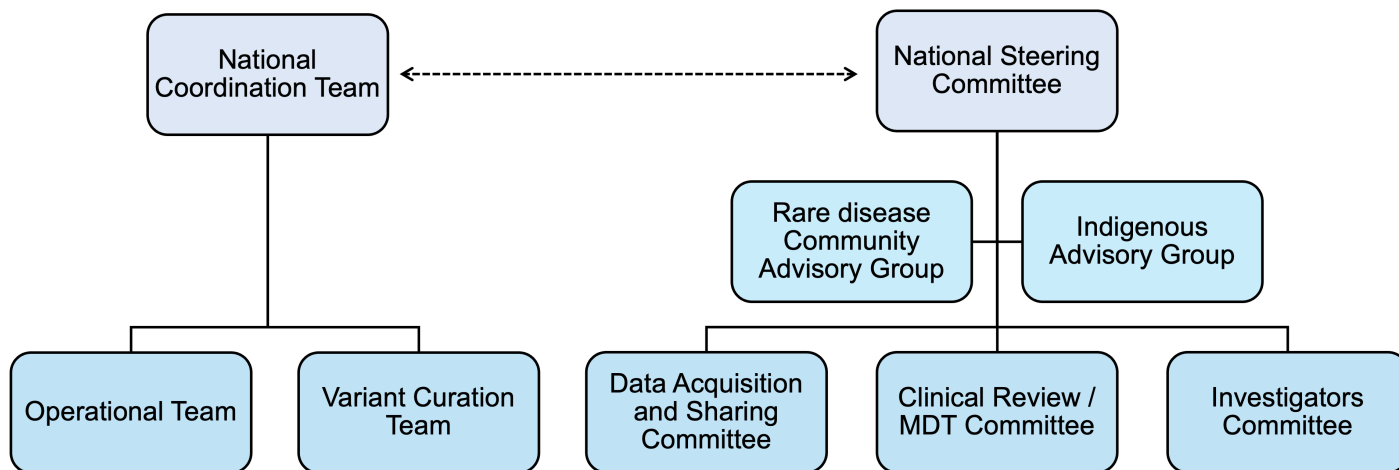


Figure 2

Study Governance chart showing the relationship of UDN-Aus teams and committees

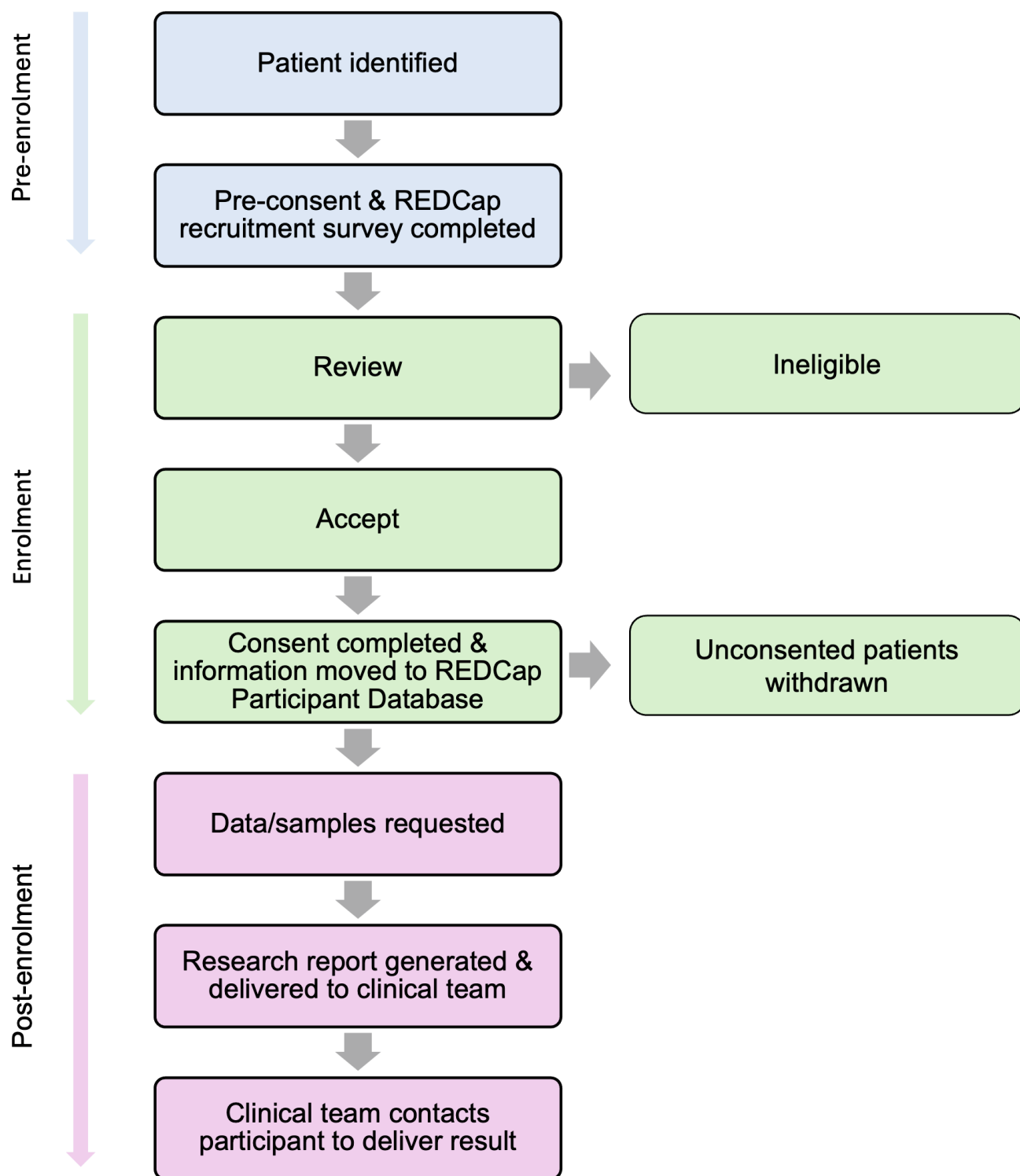


Figure 3

Patient Study Participation

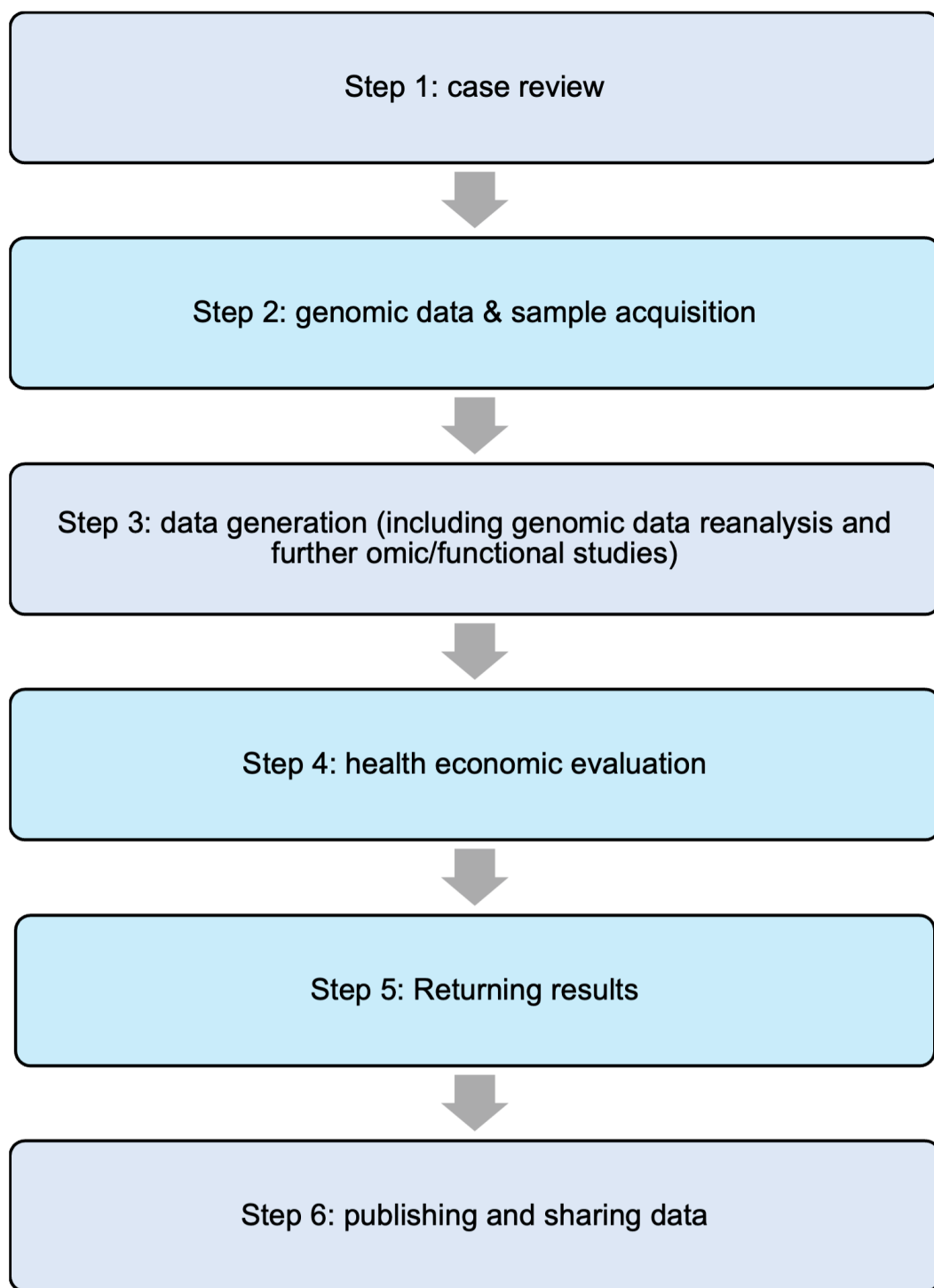


Figure 4

Study Set Up

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryfilesLEGENDS.docx](#)
- [SupplementaryFileS1RCAandMIAtimeframes.docx](#)
- [SupplementaryFileS2HREandRGOApprovals.docx](#)

- [SupplementaryFileS3PICF.docx](#)
- [SupplementaryFileS4ATemplateResearchReportPositive.docx](#)
- [SupplementaryFileS4BTemplateResearchReportNegative.docx](#)
- [SupplementaryFileS5DataTransferAgreementTimelines.docx](#)
- [SupplementaryFileS6SampleHandlingSOP.docx](#)
- [SupplementaryFileS7PathologyAgreementTimelines.docx](#)
- [SupplementaryFileS8TemplateStudyRequestForm.docx](#)