



Health Care and Rare Disorders

Evidence brief

Office of the Chief Science Advisor
2023

This document is an evidence brief and as such, the findings do not reflect government policy. It is intended as background to support health agencies' further work.

Citation: Ministry of Health. 2024. *Health Care and Rare Disorders: Evidence brief*.
Wellington: Ministry of Health.

Published in December 2024 by the Ministry of Health
PO Box 5013, Wellington 6140, New Zealand

ISBN 978-1-991324-15-3 (online)
HP 9109



This document is available at health.govt.nz



This work is licensed under the Creative Commons Attribution 4.0 International licence. In essence, you are free to: share ie, copy and redistribute the material in any medium or format; adapt ie, remix, transform and build upon the material. You must give appropriate credit, provide a link to the licence and indicate if changes were made.

Contents

Executive summary	1
Background and context	1
Scope of the brief	1
Summary of findings	1
Summary of recommendations	2
Background	3
Introduction	4
Scope and methodology	5
Rare disorder definition	5
International context	5
Asia Pacific region	6
Aotearoa New Zealand context	6
Te Tiriti o Waitangi and equity	8
Epidemiology, costs and benefits	10
Costs and economic implications	10
Funding pharmaceuticals	11
Clinical and long-term support pathways	12
Diagnosis	12
Pharmaceutical and medical treatment	12
Non-pharmaceutical treatment	13
Quality of life	14
The role of research	15
Why do we need New Zealand-based research?	15
Data, digital, analytical and epidemiological infrastructure	15
Digital solutions and enabling analytics	16
Limitations	18
Conclusion	19
Recommendations	20
Appendix 1. Key international organisations	24

Appendix 2. Summary of diagnostic practices for rare disorders	26
Appendix 3. Summary of treatment pathways and future strategic considerations	28
Appendix 4. Comparisons of approaches to cost of illness studies for rare disorders	30
Appendix 5. Summary of rare disorder research landscape and future recommendations	34
References	38

Executive summary

The Aotearoa New Zealand Rare Disorders Strategy was published on 25 July 2024. It sets out the direction for the health system to better support people living with rare disorders and their whānau.

This evidence brief underpinned the development of the strategy. Its aim was to provide:

- a summary of current knowledge and scientific literature on the treatment of and care for people who have a rare disorder
- evidence to inform the development of a rare disorder strategy for Aotearoa New Zealand.

Background and context

Rare disorders are a heterogeneous group of conditions that are referred to as a whole due to the low prevalence of each disorder. Rare disorders tend to be chronic multi-system disorders which can have a substantial impact on a person's wellbeing. The World Health Organization has not yet published an agreed definition, guidelines or standards pertaining to rare disorders. In New Zealand, where fewer than 1 person per 50,000 people (approximately 100 people) have a given disorder, that disorder is classified as a rare disorder, and authorities make decisions about funding medicines for it accordingly. This is considerably lower threshold than both the European Union and the United States' definitions. The complex and unique problems faced by people with rare disorders are similar across the globe, and there is substantial international, often community-driven, work occurring to address these problems.

Scope of the brief

The brief is a scoping review of national and international evidence to identify current knowledge, medical and technological advances, and the ways in which other jurisdictions and health care systems meet the needs of people with rare disorders.

Summary of findings

Provision of health care

Delayed and/or incorrect diagnosis can prevent people from accessing the treatment they need. This can result in harmful health outcomes from delayed or inappropriate treatment and can have significant impacts on quality of life. The major reason for a

delay in diagnosis is a lack of access to comprehensive diagnostic testing along with the limited availability of appropriate speciality expertise. Best practice care, screening, earlier diagnosis, treatment and coordinated care help to decrease costs by reducing morbidity and caregiver load.

Costs of health care

Not all people with rare disorders have costly health care needs, but the chronicity of many rare disorders can cause a significant financial burden over time. Costs can be defined as direct or indirect costs to the person with a rare disorder, their carers or their support network. Drugs to treat rare disorders are some of the most expensive, and the financial burden of rare disorders on people and their whānau is consequently considerable. Non-financial costs related to quality of life, such as grief, pain, emotional problems or anxiety, can be equally burdening. Multi-disciplinary teams can support people and whānau living with a rare disorder and can positively influence their economic status through providing symptom mitigation or, in some cases, even a cure.

Quality of life

Quality of life is a predictor of treatment success and for meeting the obligations detailed in the United Nations Convention for the Rights of Persons with Disabilities (2006) and the United Nations Resolution on Persons Living with a Rare Disease and their Families (2021). Disorder-specific community-based organisations throughout the world play a pivotal role in providing social and emotional support to families, providing connection to a community as well as expertise in and knowledge of particular disorders.

The role of research

There is a fundamental need for clinical and epidemiological knowledge about the different rare disorders. Key enabling requirements for this research include disease registers, genomic databases and biobanks. International data-sharing arrangements and research collaborations are necessary for these, due to the small numbers which make up each rare disorder. In Aotearoa New Zealand, equity and Indigenous data sovereignty need to be considered for any such arrangements.

Summary of recommendations

This brief makes the following recommendations.

1. Te Tiriti o Waitangi and equity need to be at the centre of any forthcoming strategy for rare disorders.
2. Specific diagnosis and treatment pathways need to be developed for people with a rare disorder.
3. A nationally coordinated approach to research focused on rare disorders is required.
4. Dedicated infrastructure development is required to meet the specialised needs of people with rare disorders. Such infrastructure may include registries, biobanks and genomic databases.

Background

The development of a rare disorder strategy by the Ministry of Health – Manatū Hauora is a result of the 2022 review of Pharmac¹. The Pharmac review recommended that the Ministry of Health develop a rare disorder strategy due to the increasing science and evidence about effective management of rare disorders, the likely associated costs of diagnosis and treatment and existing and ongoing equity considerations. The review recommended:

- an official New Zealand definition of rare disorders
- a commitment to ensure more equitable access to necessary health care services for people with rare disorders
- funding, particularly for medicines, for rare diseases, taking into account the increasing scale of the problem and the impact it will have on health services more generally (Pharmac Review Panel 2022).

¹ Pharmac was established in 1993 and is the national Crown institute responsible for funding medical supplies.

Introduction

Rare disorders are a heterogenous group; they are grouped together due to the low prevalence² of each disorder. This can result in several issues, including:

- difficulties or delays in diagnosis
- unclear clinical management pathways for diagnosis, referral and treatment
- a lack of up-to-date and reliable information for people, whānau and health care professionals once a diagnosis has been made
- a lack of availability, access to and funding for specialised medications or treatments.

Rare disorders tend to be chronic multi-system disorders which have a substantial impact on a person's wellbeing. While each rare disorder is, by definition, uncommon, research commissioned by Rare Disorders NZ (Reid and Prates 2023) supports international suggestions that these disorders collectively contribute to a significant burden of disease within the community and for health services and systems (World Economic Forum 2020; Rare Diseases International; Adachi et al 2023). An accurate calculation of the burden of disease depends on the how 'rare disorder' is defined. In December 2019, Rare Diseases International signed an agreement with the World Health Organization (WHO) to develop an operational definition (Adachi et al 2023). The proposed definition is as follows.

People living with rare diseases face distinct and significant challenges that arise from the infrequency of their medical conditions, such as a long diagnostic journey, inadequate clinical management, and limited access to effective treatments. The burden of rare diseases on patients, their carers and families, healthcare systems, and society overall, merits greater visibility and recognition. A rare disease is a medical condition with a specific pattern of clinical signs, symptoms, and findings that affects fewer than or equal to 1 in 2000 [5 per 10,000] persons living in any WHO-defined region of the world. Rare diseases include, but are not limited to, rare genetic diseases. They can also be rare cancers, rare infectious diseases, rare poisonings, rare immune-related diseases, rare idiopathic diseases, and rare undetermined conditions. While the frequency of most rare diseases can be described by prevalence, some rare diseases, such as rare cancers and rare infectious diseases, can be more precisely described by incidence (Rare Diseases International 2022 p.2).

People with rare disorders face complex and unique problems in similar ways across the globe, and there is substantial international (often community-driven) work to address these problems. The aim of this evidence brief is to therefore provide:

- a summary of current knowledge and scientific literature on the treatment of and care for people who have a rare disorder

² Rare disorders can be referred to in different ways in accordance to prevalence: Smith et al (2022) categorise rare (<1/2000), ultra-rare (<1/50,000) and hyper-rare (<1/108) disorders.

- evidence to inform decision-making in the development of a rare disorder strategy for Aotearoa New Zealand.

Scope and methodology

We undertook a review of national and international evidence to identify current knowledge, medical and technological advances, and the ways in which other jurisdictions and health care systems meet the needs of people with rare disorders. We purposely sought evidence in this scope to address Aotearoa New Zealand's unique health care environment, and included biomedical and socio-cultural science, economic and operational information to support informed decision-making. In addition, we deliberately sought Māori and international Indigenous research related to rare disorders. Given the rapidly evolving technologies and research, and to ensure we reviewed the most up-to-date evidence, we prioritised publications (including grey literature) from the last three years from global and regional collaborations. We also prioritised publications from WHO, the United Nations and Asia-Pacific economic forums to ensure alignment with over-arching global and Asia-Pacific objectives. We prioritised literature if it was from a peer-reviewed journal article, was a systematic review and incorporated high-level policy or data analyses/synthesis. We reviewed all relevant Aotearoa New Zealand published research from grey and academic literature. We excluded evidence if it was about one disorder or service only.

Rare disorder definition

Defining a rare disorder for the Aotearoa New Zealand population requires agreement on terminology as well as prevalence. The phrases 'rare disease', 'rare disorder' and 'orphan disorder' are used interchangeably in the literature; this evidence brief uses the term 'rare disorder'.

The prevalence of a condition in a population is used to define a disorder as 'rare'; this varies between countries. For example, in the European Union (EU), a rare disorder is defined as a condition affecting <5 per 10,000 people, whereas in the United States (US) a disorder is considered rare if it affects fewer than 200,000 people nationally (Kolkhir et al 2023); this equates to 6 per 10,000 people. In New Zealand, Pharmac, the national medicines funding agency, currently uses a threshold of <1 per 50,000 people to define a rare disorder for the purposes of funding decisions (Pharmac 2023). This is considerably lower than both the EU and US rates and equates to approximately 100 people in New Zealand per disorder.

International context

The international context for rare disorders is fragmented. The WHO does not publish an agreed definition, guidelines or standards, and there is no specific mention of rare disorders in the WHO Western Pacific region 2020–2025 plan (WHO 2020). In December 2021, the United Nations adopted its first-ever Resolution on Addressing the Challenges of Persons Living with a Rare Disease and their Families (United Nations

2021). Within this document, the General Assembly detailed 16 resolutions for the WHO and member states as part of its work toward achievement of universal health coverage and the 2030 Agenda for Sustainable Development (United Nations 2021). Non-government organisations and economic-oriented organisations appear to be driving development in the sector. Appendix 1 lists key international rare disorder organisations and networks referred to throughout this evidence brief.

Asia Pacific region

An estimated 258 million people are affected by rare disorders across Australia, China, Japan, South Korea and Taiwan; 50% are reported to be children. A 2020 report by CSL Behring stated that of these rare disorders, 94% did not have an approved medical treatment and two-thirds of people affected were not receiving evidence-based care (CSL Behring 2020). The Asia Pacific Economic Cooperation (APEC) has produced an action plan for rare disorders as part of its wider regional health working group mandate (APEC 2019) and has established its own rare disease network. Aotearoa New Zealand is not listed as a member in this network (APEC 2021) but is represented in the Asia Pacific Alliance of Rare Disease Organisations through the membership of Rare Disorders NZ and the New Zealand Amyloidosis Patients Association.³ The APEC rare disorders action plan recommends the following.

1. Define rare diseases and orphan products⁴ with policies and processes.
2. Raise public and political awareness of rare disease issues.
3. Promote innovative research and development.
4. Build human resource capacity in medical, nursing, nutrition and other allied health and non-health sectors.
5. Facilitate early, accurate and systematic diagnosis.
6. Coordinate patient-centred care across medical and other health disciplines, life courses and locations.
7. Deliver new and accessible treatments to patients.
8. Support the financial and social needs of patients and their families.
9. Manage pooling and usage of patient data securely and effectively.
10. Prioritise comprehensive domestic rare disease policy (APEC 2019).

Aotearoa New Zealand context

Currently, neither Manatū Hauora nor Health New Zealand – Te Whatu Ora collect or hold data specifically on rare disorders. This makes it difficult to estimate the burden of rare disorders within the existing national data collections systems; we do not know

³ See www.apardo.org

⁴ An orphan product is used to treat, prevent or diagnose a rare disorder (also known as an orphan disease).

how many people have a rare disorder in Aotearoa New Zealand. The Pharmac review (Pharmac Review Panel 2022) provided a comparison of the estimated number of people who have a treatable rare disorder depending on different assumptions of rates in the population and how many disorders are treatable (p.85). For example, assuming a 1.5% prevalence of rare disorders in the population, and assuming 2.4% of these disorders are treatable, we can assume that 76,839 people in New Zealand have a rare disorder and that 1,884 have a treatable rare disorder. Conversely, if we assume a 6.2% prevalence, and that 5% are treatable, the numbers are much greater: 317,601 people with a rare disorder and 15,880 with a treatable rare disorder.

The most recent information regarding the prevalence and range of rare disorders in New Zealand comes from the 2021 Rare Disorders NZ national survey. The survey attracted 718 respondents and represented 239 different disorders. While this survey provides a snapshot, it is not an accurate representation of how many people have a rare disease, and which disorders are most prevalent, due to the voluntary and self-reported nature of the survey. Nonetheless, the survey results illustrate the 10 most frequently reported disorders. Of the survey respondents, 85% identified as being of New Zealand European ethnicity. Representation of other ethnic groups was low: 3% identified as Māori, 0.6% as Pacific peoples and 0.6% as Asian. Parents of young people or children made up 28% of respondents. These findings are similar to those in a survey conducted by Rare Disorders NZ in 2019.

The major themes arising from the survey were isolation, lack of timely diagnosis, poor treatment access, lack of coordinated care, significant carer impact and a feeling of being lost in the system (Rare Disorders NZ 2022). Rare Disorders NZ also commissioned an in-depth report from Business and Economic Research Limited (BERL) to provide data and evidence on the prevalence of rare disorders and burden factors that need to be considered in the development of health policies. The analysis concluded that the quantity of publicly available data on rare disorders in Aotearoa New Zealand is 'strikingly low' (Reid and Prates 2023). With this limitation in mind, the BERL report recommended several foci for a strategy:

- increasing awareness among and training for health workers
- addressing research and data gaps
- reviewing diagnostic services such as the National Screening Unit
- removing barriers to treatment from funding gaps in accessing medicine and coordination of services (Reid and Prates 2023).

People with a rare disorder may access services through their local health, disability and social support service providers, generally through a referral from their general practitioner. Organised support for different disorders is largely provided through community-based organisations, many of which are affiliated with the Rare Disorders NZ consortium. While not all rare disorders result in a disability, many do. People with these rare disorders are likely to be included within the wider population cohort of disabled people. The shifting of power to communities through iwi-Māori co-governing boards, the influence of the newly formed Whaikaha – Ministry of Disabled People and the Enabling Good Lives funding model are important emerging contexts for consideration (Whaikaha 2023b).

Te Tiriti o Waitangi and equity

A rare disorders strategy for the Aotearoa New Zealand context must incorporate a te ao Māori worldview of hauora/health and the principles of Te Tiriti o Waitangi, as outlined in *Whakamaaua: Māori Health Action Plan* (Ministry of Health 2020). The management of rare disorders in traditional health services is often highly medicalised and focused on individual body functions and systems. Traditional Western medical approaches are often individualised and deficit based. In colonised countries such as Aotearoa New Zealand, these approaches can often be overlaid with a worldview that sees people having disabilities as being disabled or a burden (Ingham et al 2022). People who do not self-identify with such labels, or who identify with a cultural worldview which does not include such constructs, may be poorly represented in services based on these concepts (Ingham et al 2022; Te Roopu Waiora 2023; Caron et al 2020). Te Roopu Waiora (2023), a kaupapa Māori organisation founded and entirely governed by whānau experiencing a range of impairments, explains this further:

... many of our tīpuna, tohunga and atua with impairments were celebrated, sometimes feared, and always utilised as contributors to Māori development. They were hautipua, extraordinary beings with differences that were embraced ... Considering people as needing to be fixed, normalised or institutionalised as a concept of disability has no place in Te Ao Māori.

In the context of rare disorders, as in the context of other health conditions, Indigenous cultural practices can add complexity to ethical issues surrounding research, data collection and use of genomics at both the individual and population levels. Inability to effectively partner with communities and accommodate local cultural practices into research may negatively influence decisions about participation in a research project. For example, some Indigenous peoples believe that blood specimens and other tissue samples remain part of their ancestors and lands, which can raise issues related to the collection, storage and use of biospecimens (Kowal 2015; Aramoana et al 2020). These issues lead to questions about collective ownership, tribal belonging, repatriation and the use of biospecimens beyond national borders (Aramoana et al 2020). Indigenous concerns around data use and sharing comprise another barrier to research participation that is highly relevant to rare disorder data collections (Nanibaa et al 2019; Hudson et al 2020). As a response, mechanisms of control for Indigenous people over their biological samples and associated data are emerging (eg, tribal review/oversight boards, research codes and policies), and there is a growing global call for Indigenous data sovereignty – the right of Indigenous peoples and tribes to govern the collection, ownership and application of their own data (D'Angelo et al 2020).

Manatū Hauora has workstreams within the Māori Health Directorate to address Māori data sovereignty and the data held in the national health collections. Te Kāhui Raraunga⁵ has recently released its Māori Data Governance Model for Aotearoa New Zealand public services to use as an operational guide for developing data systems which align with Tiriti o Waitangi principles (Kukutai et al 2023). Researchers have

⁵ Te Kāhui Raraunga Charitable Trust is an independent body established in 2019 to lead the action required to realise the advocacy of the Data Iwi Leaders Group. Te Kāhui Raraunga's aim is to enhance the social, cultural, environmental and economic wellbeing of Māori; to enable iwi, hapū and whānau Māori to access, collect and use Māori data. See <https://www.kahuiraraunga.io/>

produced guidance for the express purpose of guiding culturally safe practices for Māori data and specimens in genomic and biobank research and collections, which may be helpful when agencies are operationalising workstreams for rare disorders (Beaton et al 2017; Hudson et al 2016). There is international concern that the development of genomic testing may be accentuating a 'genomic divide' for Indigenous communities, which may be underrepresented in the development of testing or therapeutics based on genomics (Caron et al 2020). In 2017 only 12% of participants in global genome-wide association studies were of non-European ancestry. People of African and Latin American descent and Indigenous people combined represented less than 4% of participants; Indigenous peoples comprised 0.02% (Mills and Rahal 2019). Several Indigenous genomic databases are emerging in Australia, Canada, Aotearoa New Zealand and the US to counter these inequities (D'Angelo et al 2020), and a Global Indigenous Data Alliance⁶ has been formed to guide international Indigenous data governance (Wilkinson et al 2016).

Along with the express responsibilities New Zealand health providers have in terms of Te Tiriti o Waitangi, there are many other equity issues a rare disorders strategy should consider. In a position statement for the United Nations Universal Health Coverage Day in December 2021, Rare Diseases International stated:

If governments really aim to achieve Universal Health Coverage, 'Leave No One Behind' by 2030, and build inclusive societies, then the focus needs to be on equity. Actions to achieve greater equity should be responsive to diverse realities and multiple forms of inequalities, including the inequities experienced by vulnerable populations throughout a lifetime such as people living with rare diseases and their families (Rare Diseases International 2021).

Internationally, there is a growing equity gap between those who endure the greatest health disparities and those most likely to benefit from scientific discoveries and progress in rare disease management such as genomics (Caron et al 2020). These disparities often occur due to the lifetime costs associated with having a rare disorder and the high costs of medications or treatments, which are often unfunded and therefore only available to people with significant wealth or access to financial supports (United Nations 2021; Zozaya et al 2023; Li et al 2022). In 2017, the first European survey (n=3071) on the everyday impact of rare diseases found that the consequences of living with a rare disease reached well beyond the impact on the health of individual people. For example, 7 in 10 people who lived with someone with a rare disease had to reduce or stop their professional activities, and 69% had experienced a decrease in income for this reason (Rare 2030 2019).

In Aotearoa New Zealand, as in many countries, layers of inequities intersect. In terms of rare disorders, there has been low representation of the Māori, Pacific and Asian ethnicities in surveys and research (Rare Disorders NZ 2022; Reid and Prates 2023). Disabled young people who identify as Māori, Pacific or Rainbow have been found to face more socio-cultural barriers accessing services when compared to double majority youth (that is, Pākehā non-Rainbow or Pākehā without a disability or chronic condition) (Roy et al 2020). Barriers to accessing health care are a significant issue in some regions, particularly for rural and poorly served lower socioeconomic communities (Whitehead et al 2020).

⁶ See www.gida-global.org

Epidemiology, costs and benefits

In 2020, the World Economic Forum estimated that rare disorders affect between 350 and 475 million people (3.5% and 5.9% of the global population) globally. However, given the diverse definitions of rare disorders, it is likely that these figures significantly underestimate the true burden of rare disorders. Current evidence to inform epidemiology and cost analyses is limited (Adachi et al 2023). The need for evidence to inform decision-making is driving development of international collaborations of registries, genomic databases and biobanks for rare disorders. This type of information is crucial to decision-making processes relating to prioritisation of limited health resources. In this way, decision-makers can determine the value for money of different interventions and technologies used in the treatment of rare disorders.

Costs and economic implications

There is limited literature about the costs and cost-effectiveness of health interventions or policies for rare disorders. Costs can be defined as direct or indirect costs to the person with a rare disorder, their carers or their support network. Direct costs may include medical or non-medical interventions. Indirect costs represent loss due to disability, morbidity and mortality as a result of a rare disorder. Costs related to quality of life, such as grief, pain, emotional problems or anxiety, are often outside cost analyses, as they are not directly measurable by many health economic methods. The financial burden of rare disorders on individuals and their whānau is considerable. The Rare Disorders NZ survey conducted in 2022 found that 54% of respondents felt that the costs associated with their rare disorder were hard to manage. Participants reported costs relating to special diets (77%), transport (74%), counselling (58%), private health care professionals and therapists (51–53%), devices, equipment and housing (51%), home help or childcare (46%), medications (41%), respite care (33%), specialist assessments (24%) and hospital admissions (10%) (Rare Disorders NZ 2022). These wide-ranging costs are an indication of the multi-disciplinary support and care those with rare disorders require. Multi-disciplinary teams can support people and whānau living with a rare disorder and positively influence their economic status through providing symptom mitigation or, in some cases, even a cure. Best practice care, screening, earlier diagnosis and treatment and coordinated care save costs through both reduced morbidity and reduced caregiver or individual load. For this reason, indirect costs also affect funding and prioritisation goals (World Economic Forum 2020). Appendix 4 provides some examples of cost-effectiveness studies and comparative analysis between costs associated with rare disorders and those associated with other diseases.

Funding pharmaceuticals

Drugs to treat rare disorders and rare cancers are some of the most expensive on the market (Annemans 2023). These 'orphan drugs' may be listed on general reimbursement schedules. However, many publicly funded jurisdictions consider funding for orphan drugs on a per-patient basis, rather than making a specific drug available for all patients with the corresponding disorder. The US Government passed the Orphan Drug Act in 1983 to offer drug companies certain financial benefits for developing orphan drugs that are safe and effective. The EU passed a similar Act in the year 2000: the EU Regulation on Orphan Medicinal Products. Australia's Life Saving Drugs Program does not have a fixed budget, but funds orphan medicines on a case-by-case basis. The program currently covers 18 medicines for 11 different conditions (Pharmac 2019).

In Aotearoa New Zealand, Pharmac assesses and funds medicines for rare disorders through its pharmaceutical schedule and exceptional circumstances framework.⁷ It makes decisions on applications received through its Rare Disorders Advisory Committee⁸ (Pharmac Review Panel 2022). Pharmac does not have a separate budget for orphan medicines. In an analysis the agency conducted in 2020, it established that the unit price of orphan drugs was roughly five times more than that of comparable non-orphan drugs (Chambers et al 2020).

⁷ Pharmac considers applications for assessment and funding of medicines for rare disorders in the same way as it does for all other medicines on the pharmaceutical schedule. The exceptional circumstances framework helps people in exceptional clinical circumstances who are seeking medicines not on the pharmaceutical schedule or medicines that are on the schedule but are not listed for a particular condition or clinical circumstances.

⁸ The Rare Disorders Advisory Committee is a specialist advisory committee of the Pharmacology and Therapeutics Advisory Committee.

Clinical and long-term support pathways

Diagnosis

In the Rare Disorders NZ survey, 42% of respondents (n=718) reported they had received a diagnosis within one year, 38% reported that a diagnosis had taken over five years and 23% reported it had taken over 10 years. Furthermore, 64% had to visit three or more doctors to get an accurate diagnosis, and 62% were misdiagnosed at least once before the final diagnosis was confirmed (Rare Disorders NZ 2022). Delayed and/or incorrect diagnosis can prevent people from accessing the treatment they need, can result in harm such as inappropriate surgeries and can significantly affect people's quality of life (Bauskis et al 2022; Kenny et al 2022; Boycott et al 2017). Early diagnosis of a disease or disorder is best undertaken at the population level through newborn screening programmes (Boycott et al 2017). While the method of testing and range of diseases tested for differ globally, newborn screening has been shown to be a highly effective strategy for improving health outcomes, quality of life, health costs and equitable access to rare disorder diagnosis (World Economic Forum 2020; Adachi et al 2023; Castilla-Rodríguez et al 2017). Aside from the lack of newborn screening programmes, the major reason for a delay in diagnosis is the limited availability of appropriate levels of speciality expertise, including knowledge of disorders and diagnostic technologies (Rare 2030 2019). Appendix 2 summarises current and best practices for rare disorders.

Pharmaceutical and medical treatment

In the last two decades, there have been substantial advances in the treatment of rare disorders (Zozaya et al 2023). Not all people with rare disorders have costly health care needs, but the chronicity of many rare disorders can cause a significant financial burden over time (Postma et al 2022). There is a need for innovative payment models to ensure that people with rare disorders have cost-effective access to effective treatments while keeping health systems financially sustainable (Annemans 2023). Medical treatment can be highly effective in achieving long-term outcomes for some rare disorders, but often comes with prohibitive cost barriers. The high cost per health gain of many orphan drugs means that health system decision-makers need to balance the provision of funded access to orphan drugs against the wider health needs of the

general population.⁹ In the Rare Disorders NZ survey, 85% of respondents reported that they were taking medicine for their disorder, but the majority of these medicines were for managing symptoms such as pain or inflammation¹⁰ rather than disease-modifying treatment. Of those respondents, 30% reported that they had to self-fund at least some of their medicines (Rare Disorders NZ 2022).

Non-pharmaceutical treatment

People with rare disorders require a wide range of social support, depending on their level of impairment and the specialised treatments and expertise they require (Groft and Posada de la Paz 2017). The emotional and psychological wellbeing of family members, especially if there is a genetic component to the disease, can be vital for positive long-term outcomes. Counselling and support must be tailored to each individual and family's situation (Groft and Posada de la Paz 2017). This often requires a multi-disciplinary team. A recent project in Ireland mapped essential services within the health system for 29 different rare conditions. Genetic counsellors, nurse specialists, psychologists, medical social workers, database managers and therapeutic health professionals such as physiotherapists, occupational therapists and speech and language therapists were all identified as being important for the management of the majority of these conditions (Ward et al 2022). However, access to these services depends on locality. Living in a rural setting can often exacerbate disparities in access to treatment; some studies found that people with a rare disorder spent extended periods away from whānau support or even had to permanently relocate to an urban centre to access care (Adachi et al 2023; Rare 2030 2019).

Disorder-specific community-based organisations throughout the world play a pivotal role in providing social and emotional support to families, providing connection to a community as well as expertise in and knowledge of particular disorders. For this reason, it is essential to empower community organisations to participate in decision-making processes (Adachi et al 2023; Groft and Posada de la Paz 2017). There is a high likelihood for people with rare disorders who are not engaged with such organisations and/or have limited access to health care services to miss out on services they could be eligible for (Groft and Posada de la Paz 2017). The role of people with lived experience and their advocates is now recognised as integral to decision-making processes; these voices are essential parts of policy-making processes in many countries. Keeping participating families at the centre of everything researchers and rare disorder services increases the likelihood of early identification and resolution of issues (Boycott et al 2022). Appendix 3 summarises current and future direction in the treatment for rare disorders.

⁹ For example, in 2014 a Canadian evaluation of the orphan drug eculizumab, which is used to treat the rare disorder paroxysmal nocturnal hemoglobinuria, calculated the incremental cost per life year and per quality-adjusted life year gained as CAN\$4.62 million and CAN\$2.13 million respectively. Based on established thresholds, funding eculizumab for one year would result in the loss of more than 100 healthy life years elsewhere in the system through forfeited funding of other treatments and interventions (Postma et al 2022).

¹⁰ The most reported medicines were ibuprofen for 220 people (36%), melatonin for 99 (16%), prednisolone for 82 (14%), paracetamol for 63 (10%), gabapentin for 62 (10%), salbutamol for 62 (10%) and hydrocortisone for 61 (10%). People reported taking a broad range of different treatments, including antibiotics, antipsychotics, anti-depressants and vitamins C, D and E.

Quality of life

Quality of life is important for decision-making in the management of rare disorders. It is a predictor of treatment success and for outcomes such as the achievement of equity and meeting the obligations detailed in the United Nations Convention for the Rights of Persons with Disabilities 2006 and the United Nations Resolution on Persons Living with a Rare Disease and their Families (United Nations 2021). It is also an essential component of economic evaluation of interventions in the treatment of rare disorders. People who have a rare disorder often have difficulties with daily activities, affecting their ability to have an active social and/or professional life (von der Lippe et al 2017; Daly 2018). A high percentage of people with a rare disease are affected by motor, sensorineural or intellectual impairments, and can experience these simultaneously (Hedley et al 2019). Living with a rare disorder often decreases people's capacity to work, creating a barrier to employment and education (Daly 2018). These barriers often extend to whānau, because people with rare disorders must often rely on their family network financially and to provide care. Many caregivers have to reduce or limit their employment commitments, putting households under financial strain (Pelentsov et al 2016).

The role of research

Why do we need New Zealand-based research?

Research and knowledge about the course of rare disorders is essential for decision-making on treatment effectiveness, quality of life, care pathways and monitoring of patients over time. Clinical trials, genomic studies and cost-of-illness studies have been identified as important sources of evidence for rare disorder strategies and national plans (Adachi et al 2017). Many of these studies require patient registries to estimate clinical requirements and the likely needs across the life course. This would also assist in improving coordination of research efforts worldwide. The International Rare Diseases Research Consortium¹¹ has provided policies and guidelines for jurisdictions to follow to support research productivity and benefit to people with rare disorders (Lochmüller et al 2017). In a comprehensive review of current evidence policies and challenges for equitable rare disorder diagnosis and treatment, Adachi et al (2023) provide several key recommendations for future directions in rare disorder research; Appendix 5 sets these out. Underpinning many of the recommendations is a fundamental need for clinical and epidemiological knowledge about rare disorders, including surveillance of the use of orphan drugs and treatments off-label, and for the purposes of planning health and social services (Kodra et al 2018). In Aotearoa New Zealand, research involving rare disorders is likely to fall under several research strategies, frameworks and initiatives, including an initiative to develop a new clinical trials ecosystem. Appendix 5 summarises these.

Data, digital, analytical and epidemiological infrastructure

Aotearoa New Zealand does not have a national registry of diagnosed rare disorders; this limits our ability to understand the collective needs of people with rare disorders. A 2020 World Economic Forum analysis suggested that the only way to meet economic and social costs and provide effective care for people with rare disorders is to apply a model of sharing data internationally and across governing structures such as federal systems (World Economic Forum 2020). The European Union Committee of Experts on Rare Diseases has provided comprehensive guidance for rare disorder registration and data collection. This guidance suggests that data collection should be obtained from all sources possible (recommendation 2) and should be delineated in national rare disorder strategies (2.4) (European Union Committee of Experts on Rare Diseases 2013).

¹¹ The International Rare Diseases Research Consortium is a consortium of research funders that focuses on improving diagnosis and therapy for rare disease patients. See <https://irdirc.org/>

There is a need for effective methods to capture data to support national epidemiological analysis and funding and planning for rare disorder service development. The national health data collection system, which uses National Health Index numbers, is a key data source; we discuss this in the following section, dealing with digital solutions and analytics. In the Aotearoa New Zealand context, the international data sharing and research collaborations international agencies are recommending could bring significant equity and Indigenous sovereignty risks. We set out some of these risks below. To achieve more accurate epidemiological and cost-of-illness analyses, several infrastructure elements must align and have interoperable functionality. The three main requirements for rare disorders are registers, genetic databases and biobanks; these have different purposes, functional requirements and technological needs.

Digital solutions and enabling analytics

One of the persistent requests from the rare disease community has been appropriate classification of rare diseases in standard diagnostic coding resources. There are classification codes available through the WHO International Classification of Diseases (ICD-11) (WHO 2021b) which were supported by the WHO Rare Diseases Technical Advisory Group in this latest revision (WHO 2021b). ICD classifications and the associated sub-codes can assist in determining the prevalence of rare diseases. Integrating these codes into medical records systems may increase health systems' ability to obtain useful data from summary information in patient records, particularly where these are electronic (Groft et al 2017). The Orphanet¹² consortium produces a nomenclature and classifications specific to rare disorders; the consortium is part of the WHO ICD-11 technical working group.

There has been a drive to harmonise general health data system architecture to enable data sharing, storage and access on a global scale (Boycott et al 2017). In the wider context of general health data, specific data about rare disorders tends to have limited visibility or priority in health information systems (Choquet et al 2014). Codes used to define disorders can vary between countries, regions and sometimes even hospitals, and many rare diseases have traditionally been missing from coding terminologies. The lack of standardisation has made it difficult to identify rare diseases and complicates the combining of data using traditional health data collection systems.¹³ Standards,

¹² Orphanet was established in France in 1997 at the advent of the internet to gather scarce knowledge on rare diseases so as to improve the diagnosis, care and treatment of patients with rare diseases. This initiative became a European endeavour from 2000, supported by grants from the European Commission. Orphanet has gradually grown to a network of 41 countries, within Europe and across the globe. Over the past 20 years, Orphanet has become the reference source of information on rare diseases. Each rare disorder is given a unique identifier as it is discovered and verified; this is called an ORPHAcode. Most EU member states are using ORPHAcodes in research centres, national registries, hospitals and national coding systems. See <https://www.orpha.net/>

¹³ Some provinces of Canada have integrated diagnostic data specifications into the electronic health record, but this has not been applied through a mandated centralised system due to the country's federal structure of governance (Boycott et al 2022). A rare disorder data lake has been established to centralise and harmonise genomic, clinical investigation, patient and health system outcomes for people with rare disorders. The data lake has three levels of data access: open (eg, public access to lists of

definitions and classifications play a critical role in the interoperability of data on a domestic and international scale. In the research context, the FAIR (findable, accessible, interoperable and reusable) principles articulate guidance for data management and open access to data (Wilkinson et al 2016); The CARE (collective benefit, authority to control, responsibility and ethics) principles apply to collection of Indigenous data (Carroll et al 2020). Enhancing interoperability of data is a key requirement in terms of both the FAIR principles (Hedley et al 2019) and the CARE principles (Caron et al 2020; Hudson et al 2020; McCartney et al 2023). In the context of rare disorders, there needs to be international support for interoperability and analytic capability, to increase our shared understanding of specific disorders. As detailed in 'Te Tiriti o Waitangi and equity' above, handling issues of data sovereignty equitably is a complex undertaking and an important Tiriti o Waitangi responsibility. The recently released Māori data governance model provides guidance on achieving ethical data stewardship (Kukutai et al 2023).

candidate genes), registered (rare disorder researchers outside of Canada for specific use cases) and controlled (researchers with an approved protocol with full access to specific data) (Boycott et al 2022). After two years curating the new system, the architects recommended the inclusion of mandatory information of phenotype and inheritance patterns for all databases feeding into the data lake, to make global matchmaking more efficient (Boycott et al 2022)

Limitations

The main limitation of this brief is the need to inform the wide range of decisions that need to be made in a rare disorder strategy while keeping the Aotearoa New Zealand context front of mind. The breadth of evidence required made a systematic review or similar methodology impossible to implement. Evidence was prioritised for relevance to Aotearoa New Zealand and the current stage of the health reforms. The quality of this evidence has not been formally assessed using a recognised tool. Instead, quality was assessed by a close reading of content and the reputation of the source.

Conclusion

There is a large body of international research and evidence dedicated to rare disorders but a paucity that is Aotearoa New Zealand-specific. At present, it is difficult to understand and plan for the unique needs of people and whānau living in Aotearoa New Zealand who have a rare disorder, due to the current methods of health data management. Technological solutions and international data sharing are emerging fields but need to be considered in the context of Te Tiriti o Waitangi. The health reforms present an opportunity to develop a rare disorders strategy that incorporates community-generated advice and leadership, including for hauora Māori, and guidance on how to support the community effectively.

Recommendations

1. Te Tiriti o Waitangi and equity need to be at the centre of a strategy
 - Decisions about collaboration with international research, registries, genomic databases and biobanks for rare disorders may improve data collection and epidemiological knowledge about different rare disorders, but these need to be made in partnership with Māori.
 - The shifting of health decision-making power from central government to communities presents an opportunity to bring in expertise from organisations such as those within the Rare Disorders NZ consortium; this could result in a national strategy that is both locally delivered and equity-focused.
 - Māori, Pacific and ethnic communities are not well represented in Aotearoa New Zealand research or community surveys. It will require dedicated time and engagement to ensure that a rare disorders strategy effectively represents these communities.
2. Specific diagnosis and treatment pathways need to be developed for people with a rare disorder
 - To ensure timely diagnosis and nation-wide equitable treatment for rare disorders, we need a dedicated clinical pathway that takes into account quality of life, life course needs and direct and indirect medical costs.
 - Community organisations are a primary resource for non-medical treatment and social support. We need to fully fund these organisations as key stakeholders in strategic planning.
 - We need to ensure multi-disciplinary expertise and care coordination for the treatment of most rare disorders.
3. A nationally coordinated approach to research focused on rare disorders is required
 - A rare disorders research strategy should be developed that establishes a pathway that can address multiple research and infrastructure needs to develop epidemiological knowledge, enable cost-effectiveness analyses and provide evidence for life course and quality of life treatment.
 - Integrating key stakeholders such as the Aotearoa New Zealand Health Research Council, Genomics Aotearoa and Te Whatu Ora in such a strategy will be key for operational decision-making and aligning infrastructure requirements.
4. Dedicated infrastructure development is required to meet the specialised needs of rare disorders
 - The National Health Index and the current reform of the national digital system bring advantages; we can use these elements to develop technical solutions to advance services, research and knowledge about rare disorders.

- A national rare disorder registry, biobank and genomic database should be established (further details are provided below). This needs to be sustainable and interoperable with the current digital transformation, and needs to adhere to the FAIR and CARE data-sharing principles.

Registries

Registries can collect multiple forms of data, including quality of life and qualitative and clinical observations, in a uniform way, to help researchers evaluate specified outcomes for a population defined by a particular disease or condition (Hageman et al 2023). Registries can be used for:

- describing the natural history and phenotypic diversity of rare diseases
- improving case definition and indication to treat
- identifying strategies for risk stratification and early prediction of disease severity
- evaluating the impact of preventive, diagnostic and therapeutic strategies on individual health, health economics and society
- informing guideline development and policy-making (Kölker et al 2022).

High-quality rare disease registries can facilitate clinical and epidemiological research, clinical trials and post-marketing surveillance of orphan drugs and treatments used off-label. Our recommendations for the development of patient registries are:

- clear definitions of the objective
- methods to protect sustainability over time
- ethical governance (Boulanger et al 2020)
- adaption to capture the most relevant data, such as through patient-reported outcomes, data aggregation from electronic medical records, smartphone apps or mobile data-logging devices
- deployment of artificial intelligence systems to aid data aggregation and analysis by making data more searchable, accessible and extractable
- development of methods to enable increased person-centred control, security, privacy and interoperability of health data; for example, through block chain technologies (Beck et al 2022)
- incorporation of phenotypic (clinical manifestation) data, including imaging data, such as (3D) facial analysis (D'Angelo et al 2020).

Aotearoa New Zealand examples of registries

An Aotearoa New Zealand-specific example of a registry is that originally named the New Zealand Neuromuscular Disease Registry, which is fully funded by the research trust of the Muscular Dystrophy Association of New Zealand, Neuromuscular Research New Zealand. The registry was established in 2012. It is led by a small team led by a neurologist and genetic counsellor based at Te Whatu Ora in Auckland. After five years, it had enrolled 1,019 people with 70 different diagnoses and has acted as a conduit for many global prevalence, treatment and genomic sequencing projects for rare neurological disorders (Rodrigues et al 2017). The registry has since

been renamed Pūnaha Io Neuro-Genetic Registry and BioBank. It continues to provide access to subjects primarily for research and clinical trial purposes (Muscular Dystrophy New Zealand nd).

The New Zealand Congenital Anomalies Registry, Te Tari Manaaki Haua, is curated by Environmental Health Intelligence New Zealand, Massey University. The registry is funded under a contract with the Ministry of Health. One of its main purposes is to provide reliable and valid data on the prevalence of birth defects in New Zealand. These are not necessarily rare. The latest publication of this registry covers the time period 2012–2019 and reports on 42 different birth anomalies with the rates per 1,000 births for each reporting year (Massey University nd).

Biobanks

Biobanks collect, process and store tissues and cells (including blood, muscle, nerve and cerebrospinal fluid) for ethically approved research studies (Hudson et al 2016). Effective use, governance and operation of a biobank is challenging. An ISO quality control standard for biobanks, ISO 20387:2018. Biotechnology – Biobanking – General requirements for biobanking, has been created through international consensus.

Regulations and ethical requirements for the establishment of a biobank vary from country to country (Chandrashekar et al 2022). There are a range of biobanks in Aotearoa New Zealand (Hudson et al 2016) but no formal central organising structure (Hudson et al 2016). At the international level, the rare disorder consortium Orphanet includes and lists biobanks as a research-related resource. Biobanks can be registered with Orphanet and included in the global Orphanet database (Orphanet 2023).

Te Ira Kāwai – the Auckland Regional Biobank

Te Ira Kāwai – the Auckland Regional Biobank was opened in 2016. This large biobank is held by the University of Auckland Faculty of Medical and Health Sciences. Its Academic Scientific Advisory Board leads the development of future biobanking practices, including in terms of tikanga and emerging ethical protocols. This leadership includes collaboration with biobanks in other centres to facilitate medical research across New Zealand. Te Ira Kāwai uses OpenSpecimen, a specialist biobank database, which enables it to track storage locations of individual samples efficiently to ensure stored tissue can be monitored at all times to minimise the risk of sample loss.¹⁴

Genomic databases

The rapid acceleration of genomic and precision medicine are important for the diagnosis of rare disorders, identification of familial genetic risks and targeted therapies (Boycott et al 2017). Even though an estimated 40%–72% of rare disorders are classified as genetic, many disorders remain undiagnosed or receive an incorrect

¹⁴ See www.biobank.ac.nz

diagnosis (Tesi et al 2023). Large-scale genomic databases are producing projects that include worldwide populations (Caron et al 2022; Boycott et al 2022). Organisations such as the Global Alliance for Genomics and Health¹⁵ are working to enable responsible genomic data-sharing by building tools to address common barriers to data-sharing across the globe. The availability of whole exome and whole genome sequencing has drastically affected genetic diagnostics, and the clinical genetics specialty is undergoing rapid expansion (Stranneheim et al 2021).

Although whole genome sequencing has the ability to increase the detection rate of underlying genetic abnormalities, the significance of many of these genetic alterations is not yet known, and for this reason we have not yet seen a significant alteration to the wellbeing of individuals (Maron et al 2023).

Genomics in Aotearoa New Zealand

In Aotearoa New Zealand, Genomics Aotearoa has led a 'collaborative platform, established to ensure that Aotearoa New Zealand is internationally participating and leading in the rapidly developing fields of genomics and bioinformatics'.¹⁶ The platform is currently funded through the Ministry of Business, Innovation and Employment and is an alliance of universities (Auckland, Massey, Otago, Waikato and Te Herenga Waka – Victoria) and Crown research institutes (AgResearch, ESR, Plant & Food Research, Manaaki Whenua – Landcare Research and Scion). There are three genomic work programmes (Health, Primary Production and Environment) and several te ao Māori genomic projects that cross over all these three programmes.

Within the Health work programme, there are several workstreams relevant to rare disorders. These include the Aotearoa New Zealand genomic variome project, clinical genomics and Rakeiora, a pathfinder project which comprises two research projects in primary and tertiary health: one to collect real-time data and one to develop a plan to use health and whakapapa data to test computational systems to create a pilot precision medicine research platform. Genomics Aotearoa also hosts a data repository: a secure place where the Aotearoa research community can store and share genomic data within a Māori values context, following the principles of Māori data sovereignty.

The Genomics Aotearoa future strategy is currently being reviewed and updated.

¹⁵ See www.ga4gh.org/

¹⁶ See www.genomics-aotearoa.org.nz/

Appendix 1. Key international organisations

Name	Location	Purpose	Membership
Orphanet	Europe	A portal for high-quality information on rare diseases and orphan drugs and directories of experts, registries, biobanks, research activities and technical infrastructure	40 countries in Europe
Orphadata	Europe	A repository for aggregated data to provide the scientific community with comprehensive, massive, reusable and computable quality data sets related to rare diseases from the Orphanet knowledge base	40 countries
Rare Diseases International	Virtual	A global alliance of patient-driven organisations that brings together rare disease patients with international federations for specific diseases and multi-stakeholder groups	Membership from most developed countries in most global regions, including Australia and New Zealand
Rare 2030	Europe	A foresight study that gathers the input of a large group of patients, practitioners and key opinion leaders to propose policy recommendations that will lead to improved policy and a better future for people living with a rare disease in Europe	Non-profit non-governmental organisations, universities, Orphanet and the United Kingdom
International Rare Diseases Research Consortium	France	An organisation that aims to contribute to the development of new therapies and the means to diagnose most rare diseases	Funding organisations (ie, public and private funding bodies and groups of funders) investing more than US\$10 million over five years in rare disease research Biotech, pharma and medtech companies investing more than US\$10 million over five years in rare disease research

Name	Location	Purpose	Membership
			Umbrella patient advocacy organisations representing broad patients' interests for all rare diseases in at least one country or larger area
Global Indigenous Data Alliance	Virtual	An alliance that promotes Indigenous control of Indigenous data	Maia Māori Collective (Australia) Te Mana Raraunga Māori Data Sovereignty Network (Aotearoa New Zealand) United States Indigenous Data Sovereignty Network
Asia Pacific Alliance of Rare Disease Organisations	Singapore	An alliance of patient groups representing rare diseases and rare cancers to work together on common goals, facilitating research in the region, sharing resources and best practices, and collaborating on joint initiatives	Ordinary members: non-profit organisations based in the Asia Pacific that directly serve the rare disease community. These members can vote and can raise matters for discussion in meetings. Affiliate members: partner organisations that do not meet all the criteria for ordinary membership. These members have all the rights of ordinary members but cannot vote or raise matters for discussion in meetings.
APEC Rare Disease Network	Virtual	A network that aims to facilitate greater alignment of domestic policies and best practices for addressing rare diseases	Multi-national membership representing academia, industry and government organisations

Appendix 2. Summary of diagnostic practices for rare disorders

Diagnostic technology	International	Aotearoa New Zealand	Best practice considerations
Metabolic newborn screening	<p>Screening is usually performed through a heel-prick blood test; high-income countries around the world have adopted newborn screening programmes (Dima 2021).</p> <p>In the EU, the number of disorders screened for varies between countries, but is generally between 1 and 26; certain regions of Italy offer screening for at least 58 disorders (Rare 2030 2019).</p> <p>In Latin America, Asia Pacific, the Middle East and North Africa, there is no consensus or uniform newborn screening programmes (Adachi et al 2023).</p>	<p>Newborn screening tests for over 20 rare but potentially serious conditions. The screening test is via heel prick within 48 hours of birth. 99% of babies are tested.</p> <p>The current conditions screened for are:</p> <ul style="list-style-type: none"> • amino acid diseases (eg, phenylketonuria and maple syrup urine disease) • fatty acid oxidation diseases (eg, MCAD) • congenital hypothyroidism, cystic fibrosis • congenital adrenal hyperplasia, galactosaemia, biotinidase deficiency • severe combined immunodeficiency (74)(National Screening Unit 2014). 	<p>Potentially treatable diseases with high morbidity and mortality could be candidates for inclusion in an extensive new-born screening panel, even if their prevalence is low (Dima 2021).</p> <p>New-born genomic screening is an emerging practice. Many authors argue that newborn screening is based on genetic testing; some form of informed consent will be necessary due to the potential familial and health status it may reveal (Remec et al 2021).</p> <p>The conditions included in newborn genomic screening should have clear actionability early in life, strong genotype–phenotype correlation, sufficient population-specific variant data, well-defined criteria for reporting and adequate specificity and sensitivity (Remec et al 2021).</p>
Genomic testing	<p>Many international genome centres have been established and several large-scale international and national sequencing projects have been launched.</p> <p>Clinical integration of genomic knowledge is not occurring at fast</p>	<p>The Genetic Health Service New Zealand’s services are publicly funded for New Zealand residents as part of New Zealand’s public health system.</p> <p>Northern Central and South Island Hubs provide:</p> <ul style="list-style-type: none"> • diagnostic assessment of genetic diseases and information about genetic diagnoses 	<p>There is evidence to suggest that genetic screening of newborns could not provide a unified platform for newborn screening, as some of the diseases currently being examined have a very weak genetic background or highly variable penetration (Dima 2021).</p> <p>There are two main limitations associated with the evidence produced through human genomic</p>

Diagnostic technology	International	Aotearoa New Zealand	Best practice considerations
	<p>enough rates to realise its potential (Stranneheim et al 2021).</p> <p>Orphanet provides information on every gene related to a rare disease. This information includes the relationship between genes and their related rare diseases, the genetic international nomenclature, gene typology (gene with protein product, locus, non-coding RNA), chromosomal location and cross-mappings with international genetic databases (Orphanet 2023).</p> <p>The International Indigenous Genomics Advisory Committee is a panel of international Indigenous experts including Indigenous scholars from Canada, the US, Hawaii, Australia and Aotearoa New Zealand. The committee provides the Silent Genomes research team with external guidance, insight and advice on the projects' strategic goals and deliverables and insight into international best practices.¹⁷</p>	<ul style="list-style-type: none"> • diagnostic, pre-conception, prenatal or pre-symptomatic tests for genetic conditions • assistance in the clinical management of genetic diseases and identification of preventable complications by early and accurate diagnosis and surveillance • genetic counselling and management advice for the extended family of affected individuals • a telephone enquiry service for doctors, midwives and other health professionals concerning genetic diseases • genetics education for professional and lay/community groups. <p>The National Travel Scheme can help patients access clinics.¹⁸</p> <p>Genomics Aotearoa is a collaborative research platform for genomics and bioinformatics. It is developing procedures to support good research practices and streamline access to data within the its data repository, including building on established Māori research guidelines.</p> <p>The Genomics Aotearoa Data Repository aims to provide a managed data storage facility that supports Māori interests in genomics research. Data storage and access is managed within a Māori values context that recognises the importance of Māori data sovereignty (Genomics Aotearoa nd).</p>	<p>studies. The first has to do with the under-representation of ethnically diverse populations in these studies. This has important implications for the interpretability of genomic variants and diagnostic assessments. Genome sequencing is often used in the diagnosis of rare disorders; thus, reference genomes from more ethnically diverse populations are needed for reliable interpretation of results of minority populations (Adachi et al 2023).</p> <p>The second limitation is that the consent and counselling of parents seem requisite to genomic screening. Currently, all genetic testing requires informed consent to be obtained from the patient, the patient's parents or the patient's legal guardian during a genetic counselling session performed by a medical geneticist or similar before the testing (Remec et al 2021).</p>

¹⁷ www.bcchr.ca/silent-genomes-project/our-team/iigac

¹⁸ See www.healthpoint.co.nz/public/genetics/genetic-health-service-new-zealand

Appendix 3. Summary of treatment pathways and future strategic considerations

International	Aotearoa New Zealand	Best practice considerations
<p>Dedicated and comprehensive centres for rare disorders have been set up across the EU after the these were mandated to be in national plans over a decade ago.</p> <p>In the United Kingdom, the United Kingdom Strategy for Rare Diseases has also recommended the creation of specialist centres (Choukair et al 2021).</p>	<p>People with a rare disorder are identified and access treatment through routine primary health care delivery services. Best Start Kōwae is a pregnancy and newborn programme established in 2019 intended to:</p> <ul style="list-style-type: none"> • pick up on any health risks or issues in newborns through early screening and referral • connect mothers with support they might need early on in pregnancy • provide information early on in pregnancy to the midwife so that information is available for other health care professionals to access • facilitate better connection and communication between the doctor and midwife over the course of a pregnancy (National Hauora Coalition 2020). <p>Pharmac’s Rare Disorders Advisory Committee is a specialist advisory committee of the Pharmacology and Therapeutics Advisory Committee, established to assess funding applications that require specialist clinical assessment. Committee members have expertise working with people receiving pharmaceuticals for which there is less evidence compared to non-rare diseases and are, therefore, more</p>	<p>Significant improvements can be achieved in the following circumstances.</p> <ul style="list-style-type: none"> • Care and support are organised within a holistic, person-centred, multidisciplinary, continuous and participative approach that considers both the person living with a rare disease and the family carers. • Care providers across sectors are equipped with knowledge, good practice and care coordination strategies allowing them to take into account the specificities of rare diseases. • Integrated care is effectively and timely delivered, in coordination within and between health, social and community services and organisations representing people living with a rare disease. • Mechanisms to meaningfully engage people living with a rare disease and their representative organisations in the design, implementation and monitoring of policies and services are established. • Social and disability policies effectively take into account the specificities of complex conditions and disabilities, such as rare diseases. • People living with a rare disease and their families are informed and empowered to know and to manage their condition (EURORDIS Rare Diseases Europe 2019).

International	Aotearoa New Zealand	Best practice considerations
	<p>readily able to provide advice for decision-making (Pharmac 2023).</p> <p>If a person or child has special needs because of a long-term disability or serious condition, a doctor, midwife or nurse may refer them to a needs assessment and service coordination service, which will examine the available support. This might include funded disability support services and community support (Ministry of Health 2018).</p> <p>Child Development Services are teams of allied health professionals with expertise in:</p> <ul style="list-style-type: none"> • physiotherapy • speech language therapy • occupational therapy • psychology. <p>They provide community-based support and work with families and children to support their achievement of development goals.</p> <p>Services they provide include:</p> <ul style="list-style-type: none"> • specialist assessments • delivery of therapy-based support • working with other agencies to ensure children get the right support at the right time (Whaikaha 2023a). 	

Appendix 4. Comparisons of approaches to cost of illness studies for rare disorders

Bottom-up approach	Findings	Conclusions																																																																																																			
<p>'Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe' (BURQOL-RD Project), funded by the European Commission between 2010 and 2013 (López-Bastida et al 2016).</p> <p>The study involved 3,232 participants living in eight different countries.</p> <p>Ten rare disorders were prioritised for the study (Linertová et al 2012): cystic fibrosis, Prader-Willi syndrome, haemophilia, Duchenne muscular dystrophy, epidermolysis bullosa, fragile X syndrome, scleroderma, mucopolysaccharidosis, juvenile idiopathic arthritis and histiocytosis.</p>	<p>Average total annual costs per patient (€2012)</p> <table border="1"> <thead> <tr> <th></th> <th>Bulgaria</th> <th>France</th> <th>Germany</th> <th>Hungary</th> <th>Italy</th> <th>Spain</th> <th>Sweden</th> <th>UK</th> </tr> </thead> <tbody> <tr> <td>CF</td> <td>22,295</td> <td>28,433</td> <td>53,256</td> <td>21,144</td> <td>29,870</td> <td>32,911</td> <td>46,694</td> <td>48,603</td> </tr> <tr> <td>PWS</td> <td>3,937</td> <td>38,960</td> <td>67,484</td> <td>11,979</td> <td>29,586</td> <td>41,877</td> <td>59,007</td> <td>49,200</td> </tr> <tr> <td>HEMO</td> <td>6,660</td> <td>21,046</td> <td>194,491</td> <td>15,248</td> <td>99,877</td> <td>62,955</td> <td>8,228</td> <td>-</td> </tr> <tr> <td>DMD</td> <td>9,166</td> <td>-</td> <td>55,270</td> <td>7,657</td> <td>41,547</td> <td>34,603</td> <td>43,860</td> <td>34,658</td> </tr> <tr> <td>EB</td> <td>17,671</td> <td>14,931</td> <td>46,116</td> <td>9,809</td> <td>49,233</td> <td>43,137</td> <td>9,509</td> <td>19,758</td> </tr> <tr> <td>FXS</td> <td>-</td> <td>35,737</td> <td>-</td> <td>4,951</td> <td>21,586</td> <td>31,008</td> <td>58,862</td> <td>-</td> </tr> <tr> <td>MPS</td> <td>79,323</td> <td>25,993</td> <td>209,420</td> <td>24,520</td> <td>84,921</td> <td>94,385</td> <td>165,945</td> <td>-</td> </tr> <tr> <td>JIA</td> <td>-</td> <td>-</td> <td>27,634</td> <td>-</td> <td>28,645</td> <td>-</td> <td>36,396</td> <td>31,546</td> </tr> <tr> <td>HISTIO</td> <td>6,832</td> <td>33,283</td> <td>26,442</td> <td>-</td> <td>11,883</td> <td>31,622</td> <td>-</td> <td>-</td> </tr> <tr> <td>SCL</td> <td>-</td> <td>21,557</td> <td>30,797</td> <td>4,607</td> <td>12,560</td> <td>21,640</td> <td>12,728</td> <td>26,542</td> </tr> </tbody> </table> <p>CF = cystic fibrosis, PWS = Prader-Willi syndrome, HEMO = haemophilia, DMD = Duchenne muscular dystrophy, EB = epidermolysis, FXS = fragile X syndrome, MPS = mucopolysaccharidosis, JIA = juvenile idiopathic arthritis, HISTIO = histiocytosis, SCL = scleroderma</p> <p>Mean annual costs were calculated with direct health care costs (eg, drugs, medical visits, exams, material), direct non-health care formal costs (eg, professional carers, social services), direct non-health care informal costs (eg, unpaid carers) and indirect costs (eg, patient's and carer's productivity loss) calculated.</p> <p>In all countries in the study, and for most of the rare disorders, the largest part of the total cost was informal non-paid care, usually provided by family members (Linertová et al 2012).</p>		Bulgaria	France	Germany	Hungary	Italy	Spain	Sweden	UK	CF	22,295	28,433	53,256	21,144	29,870	32,911	46,694	48,603	PWS	3,937	38,960	67,484	11,979	29,586	41,877	59,007	49,200	HEMO	6,660	21,046	194,491	15,248	99,877	62,955	8,228	-	DMD	9,166	-	55,270	7,657	41,547	34,603	43,860	34,658	EB	17,671	14,931	46,116	9,809	49,233	43,137	9,509	19,758	FXS	-	35,737	-	4,951	21,586	31,008	58,862	-	MPS	79,323	25,993	209,420	24,520	84,921	94,385	165,945	-	JIA	-	-	27,634	-	28,645	-	36,396	31,546	HISTIO	6,832	33,283	26,442	-	11,883	31,622	-	-	SCL	-	21,557	30,797	4,607	12,560	21,640	12,728	26,542	<p>There were large direct health care costs related to medication and indirect costs from productivity loss due to early retirements.</p> <p>The amount of informal care provided from unpaid caregivers varied between diseases (eg, Prader-Willi syndrome and Duchenne muscular dystrophy are associated with much higher dependency needs).</p>
	Bulgaria	France	Germany	Hungary	Italy	Spain	Sweden	UK																																																																																													
CF	22,295	28,433	53,256	21,144	29,870	32,911	46,694	48,603																																																																																													
PWS	3,937	38,960	67,484	11,979	29,586	41,877	59,007	49,200																																																																																													
HEMO	6,660	21,046	194,491	15,248	99,877	62,955	8,228	-																																																																																													
DMD	9,166	-	55,270	7,657	41,547	34,603	43,860	34,658																																																																																													
EB	17,671	14,931	46,116	9,809	49,233	43,137	9,509	19,758																																																																																													
FXS	-	35,737	-	4,951	21,586	31,008	58,862	-																																																																																													
MPS	79,323	25,993	209,420	24,520	84,921	94,385	165,945	-																																																																																													
JIA	-	-	27,634	-	28,645	-	36,396	31,546																																																																																													
HISTIO	6,832	33,283	26,442	-	11,883	31,622	-	-																																																																																													
SCL	-	21,557	30,797	4,607	12,560	21,640	12,728	26,542																																																																																													

Top-down approach

Findings

Conclusions

A study across seven cities within the Sichuan Province in China evaluated the costs of curative care (outpatient care, inpatient care, rehabilitative care and long-term health care).

The study involved 9,714 participants who had one of the top 10 (from 83 identified) rare disorders (Li et al 2022).

Disease	Outpatients			Inpatients			Total
	CCE \$million (%)	Average expenditure per visit (\$)	Average drug cost per visit (%)	CCE \$million (%)	Average expenditure per visit (\$)	Average drug cost per visit (%)	CCE \$million (%)
Haemophilia	154.73 (35.34)	221.54	86.76	283.13 (64.66)	2112.22	45.35	437.86 (23.04)
Young onset Parkinson's disease (<50 years)	102.07 (34.35)	74.50	87.12	194.2 (65.55)	5141.82	6.57	296.27 (15.59)
Systemic sclerosis	144.35 (59.02)	88.78	70.03	100.22 (40.98)	1180.98	35.54	244.57 (12.87)
Neuromyelitis optica	80.65 (34.92)	120.04	89.11	150.29 (65.08)	2104.93	30.65	230.94 (12.15)
Autoimmune encephalitis	25.63 (14.47)	308.36	51.78	151.49 (85.53)	3766.57	33.14	177.12 (9.32)
Idiopathic pulmonary fibrosis	6.67 (5.42)	82.97	77.38	116.28 (94.58)	2781.55	33.86	122.95 (6.47)
Multiple sclerosis	16.75 (15.82)	52.02	64.76	89.15 (84.18)	1481.66	31.32	105.91 (5.57)
Congenital scoliosis	4.06 (4.14)	82.96	0.01	93.99 (95.86)	10,491.82	5.15	98.05 (5.16)
Multiple system atrophy	27.86 (28.45)	110.31	86.82	70.06 (71.55)	1515.47	19.78	97.93 (5.15)
Amyotrophic lateral sclerosis	5.89 (6.65)	49.30	75.91	82.64 (93.35)	1601.52	16.21	88.53 (4.66)
Total	568.66 (29.93)	109.33	79.50	1331.45 (70.07)	2411.64	26.65	1900.11 (100.00)

Note: 'CCE' in the table stands for 'curative cost expenditure'.

The cost of these 10 diseases totalled \$19.001 million, 0.06% of the curative cost expenditure of the province in 2018.

The average inpatient cost per visit was \$2,411.64, accounting for 70.99% of per capita disposable income and 30.93% of GDP per capita, placing a heavy cost burden on individuals and families living with a rare disorder.

Medical reimbursement for costs incurred (largely medical insurance in China) was primarily for drug costs rather than non-drug treatments, despite these costing more.

There were gender- and age-specific findings which indicate these factors also need to be considered for the Aotearoa New Zealand population profile. Some of the top 10 diseases mainly affected one gender (eg, haemophilia is mainly a biologically male disease and neuromyelitis optica and multiple sclerosis affect more biological females) and were more common in some age groups (eg, young onset Parkinson's

Top-down approach	Findings	Conclusions
	<p>The three diseases with the highest curative cost expenditure were haemophilia, young onset Parkinson's disease and systemic sclerosis.</p> <p>The average outpatient expenditure per visit (except for congenital scoliosis) was spent mainly on drugs.</p> <p>The average expenditure per visit for nine rare diseases, including haemophilia, was much higher than the average expenditure per visit for diabetes in China in the same year (+\$1,210) and for young onset Parkinson's disease, autoimmune encephalitis and congenital scoliosis were higher than the average expenditure per visit for cancer.</p>	<p>disease in youth and idiopathic pulmonary fibrosis and multiple system atrophy in middle and older ages).</p>

A comparative cost analysis in Canada compared the difference in costs for genetic disorders (n=25) compared to people with asthma (n=1275), people with diabetes (n=255) and the general population (n=1275) (Marshall et al 2019).

Diseases	Estimated prevalence	Frequency	Percent	Disease type
Down syndrome	1:1000b	72	28.2	Static
22q11 deletion syndrome	1:3000b	24	9.4	Static
Turner syndrome	1:18,000b	20	7.8	Static
Noonan syndrome	1:1000–2500b	14	5.5	Static
Williams syndrome	1:9000b	7	2.8	Static
Beckwith-Wiedemann syndrome	1:29,000b	6	2.4	Static
Angelman syndrome	1:13,000	6	2.4	Static
Tuberous sclerosis	1:8500	6	2.4	Static
CHARGE syndrome	1:15,000b	<6	<3	Static
Fragile X syndrome	1:3000	<6	<3	Static
Achondroplasia	1:25,000	<6	<3	Static
Rett syndrome	1:10,000	20	7.8	Progressive
Duchenne muscular dystrophy	1:20,000	19	7.5	Progressive
Cystic fibrosis	1:14,000	19	7.5	Progressive
Dravet syndrome	1: 40,000b	8	3.1	Progressive
Charcot-Marie-Tooth disease type 1A	1:5000-10,000	6	2.4	Progressive
Spinal muscular atrophy	1:4000-16,000	<6	<3	Progressive
Diagnosed ultrarare diseasesd	<1:100,000	11	4.3	Static and progressive
Total		255		

Hospitalisations and physician billing accounted for the majority of costs.

The genetic disease cohort received more care from specialists, whereas the chronic disease cohorts received more care from general practitioners.

^aAll prevalence data from Orphanet, except Noonan syndrome

^bBirth prevalence

^cPatient cohorts of <6 in size were suppressed as per provincial privacy legislation

^dThis group of ultrarare diseases included patients with fibrodysplasia ossificans progressiva, Perrault syndrome, Floating-Harbor syndrome, mandibulofacial dysostosis with microcephaly, cardiac dysfunction, epileptic encephalopathy, spastic paraplegia and dystonia

Top-down approach	Findings	Conclusions
	<p>Direct health-care costs and resource use were estimated five years after diagnosis using five categories: physician billing, same-day surgery, emergency, inpatient hospitalisations and home care.</p> <p>Annual mean total costs for the genetic disease cohort were significantly higher than all other cohorts and were highest in the year after diagnosis.</p> <p>Costs for the genetic disease cohort ranged between 4.54 and 19.76 times higher during the five years.</p>	

Appendix 5. Summary of rare disorder research landscape and future recommendations

International	Aotearoa New Zealand	Key recommendations
<p>International Rare Disease International Research Consortium</p> <p>The consortium provides an important venue through which groups of international stakeholders can convene and discuss essential topics to advance the diagnosis and treatment of rare diseases. The consortium has developed recommendations on metrics that are necessary for the development of new tools that will allow for faster and more accurate diagnosis, and to assess the overall impact of diagnosis and therapies on rare disease patients (Zanello et al 2022).</p> <p>For patients and families, the most important factors to consider are quality-of-life or health outcomes and the socioeconomic burden of rare disorders.</p> <p>Health care systems must consider both the economic cost and the medical efficiency of providing care to rare disorder patients (Zanello et al 2022).</p> <p>Clinical trials</p> <p>Orphanet curates a central repository of global clinical trials and maintains a repository of global registries,</p>	<p>National research, science and innovation strategies</p> <p>As at September 2024 the national Research Science and Innovation strategies are currently being reviewed by an independent Science System Advisory Group (Ministry of Business Innovation and Employment. 2024).</p> <p>New Zealand Health Research Strategy 2017–2027</p> <p>The four strategic priorities for the health research and innovation system (under the leadership variously of the Health Research Council, the Ministry of Health and the Ministry of Business, Innovation and Employment) are to:</p> <ul style="list-style-type: none"> invest in excellent health research that addresses the health needs of all New Zealanders create a vibrant research environment in the health sector build and strengthen pathways for translating research findings into policy and practice advance innovative ideas and commercial opportunities (Health Research Council 2017). 	<p>APEC Action Plan Research Pillar 2025 targets</p> <p>APEC member economies each have streamlined their respective processes for research and clinical trial design, method and ethics approvals in consultation with industry and patient organisations, introducing policy on clinical trials that:</p> <ol style="list-style-type: none"> provides an incentive to reach at most a 60-calendar day timeline for both ethics and governance review for which sponsors would pay a defined additional amount to support increased efficiency supports at most a 120-calendar day maximum timeline for governance review supports at most a 120-calendar day maximum timeline for ethics review, the compliance with which would be a condition of certification of ethical review processes allows concurrent review of the ethics and governance components of a clinical trials allows a ‘stop clock’ during efficient ethics and research governance review when additional

International	Aotearoa New Zealand	Key recommendations
<p>variant databases and biobanks for clinical research, and a repository of 70 global research platforms.¹⁹</p> <p>The US ClinicalTrials.gov provides access to publicly and privately supported clinical studies conducted around the world (National Library of Medicine 2024).</p> <p>The EU's Clinical Trials Register is a database of all interventional clinical trials of medicinal products commencing in the EU from 1 May 2004 onwards (European Medicines Agency 2024).</p> <p>The WHO's International Clinical Trials Registry Platform includes a procedural document on data collection and registration of clinical trials (WHO 2024).</p> <p>Human rights and research</p> <p>The Office of the United Nations High Commissioner for Human Rights is conducting research on the protection of the human rights of persons living with rare diseases and their families and carers as part of work since the adoption of the United Nations Resolution on Persons Living with a Rare Disease and their Families in 2021 (United Nations Human Rights Office of the High Commissioner 2022).</p>	<p>Health Research Council grants for research related to rare disorders in the year ending 30 June 2022</p> <p>The Health Research Council supported 796 research contracts, spending \$124 million on these during the year. Of this, \$2.2 million was spent on research on human genetics and inherited/congenital conditions, including:</p> <ul style="list-style-type: none"> • extending the window of opportunity for saving babies' brains: \$500,000 (Joanne Davidson, University of Auckland) • caffeine for the prevention of intermittent hypoxaemia in late preterm neonates: \$319,995 (Elizabeth Oliphant, University of Auckland) • coaching caregivers of children with developmental disability: a cluster randomised controlled trial: \$233,618 (Fiona Graham, University of Otago) • genetic discoveries for unsolved developmental and epileptic encephalopathies: \$1,199,870 (Lynette Sadleir, University of Otago) • achieving equitable outcomes from critical congenital heart disease in Aotearoa: \$376,978 (Frank Bloomfield, University of Auckland) • identifying biomarkers of aneuploidy in embryos: \$385,232 (Zaramasina Clark, Research Trust of Victoria University of Wellington) • why outcomes of critical congenital heart disease in New Zealand differ by ethnicity: \$260,000 (Simone Watkins, University of Auckland) • utilisation and safety of ondansetron during pregnancy: a national cohort study: \$1,199,994 (Lianne Parkin, University of Otago) 	<p>input is required before consideration can continue (APEC 2019).</p> <p>Adachi, El-Hattab (33) (2023)</p> <ol style="list-style-type: none"> a) Improve national surveillance mechanisms and registries to gather sufficient information to support research, health and social services planning, and policy-shaping. b) Improve monitoring and evaluation of data. c) Improve data standardisation, centralising and sharing to develop mechanisms to support the identification of rare disorders. d) Collectively develop new ways of defining and measuring value, reaching an international agreement on a consistent multidimensional socioeconomic measurement to assess the impact that captures the full scope of benefits for patients, their families and the health system. e) Reach a consensus on clinical outcome measures and defined endpoints of rare disorders treatments. f) Implement/strengthen mechanisms to broaden the research sample by including global data and resource-limited countries in early research. g) Engage patients in the entire product development lifecycle, including priority-setting, design and execution of clinical trials, value-assessing and assessment of decision-making. h) Globally coordinate the diagnosis of patients through innovative technologies. i) Provide incentives for manufacturers and researchers to invest in the development of orphan

¹⁹ See www.orpha.net/

International	Aotearoa New Zealand	Key recommendations
	<ul style="list-style-type: none"> environmental and genetic risk factors for cleft lip and palate: \$1,198,687 (John Thompson, University of Auckland) a clinical: research alliance for diagnosing genetic disorders in New Zealand: \$599,939 (Louise Bicknell, University of Otago) improving genetic diagnosis for tamariki in Aotearoa: \$1,199,920 (Stephen Robertson, University of Otago) (Health Research Council 2023). 	<p>drugs and innovations for more effective rare disorder treatment.</p> <p>j) Ensure governments understand that investment in research and development for rare disorders is an investment of high return for patients' health, quality of life and wellbeing.</p> <p>k) Ensure that governments, manufacturers, researchers, venture capitalists and patient advocate groups promote and invest in rare disorders research and development.</p>
	<p>Genomics Aotearoa</p> <p>Genomics Aotearoa's current health research projects are:</p> <ul style="list-style-type: none"> Extending whole genome analysis into health care: developing whole genome datasets from whānau with an undiagnosed potentially genetic condition to extend capability in laboratory researchers and clinicians Aotearoa New Zealand Genomic Variome: developing a genomic catalogue for Aotearoa by sequencing the genomes of New Zealanders and identifying the genetic variation to better understand variations within our population Identifying genetic drivers of Streptococcus pyogenes: developing a method to predict bacterial characteristics for group A streptococcus infections by understanding the genetic drivers of invasive bacterial strains Rakeiora: A pathfinder for genomic medicine in Aotearoa New Zealand: collecting real-time data from primary and tertiary research projects, testing computational systems and creating a pilot precision medicine research platform that can help to incorporate new genomic-based medicine into New Zealand's health care system. 	<p>l) Prompt the international community to develop and disseminate a global overarching strategy or plan for rare disorders.</p> <p>m) Develop policies and procedures to lower the cost of approvals of new rare disorders drugs and treatments.</p>

Bioinformatics

Bioinformatics' current bioinformatics projects are:

- Bioinformatics Capability (Pharmac Review Panel 2022): providing the tools and strategies needed to analyse information critical to genomics research, including a data archive and bioinformatics infrastructure, a computational platform for national access to bioinformatics tools and a programme to upskill New Zealand's biologists
 - Genome Graphs: constructing pangenomes (the entire gene set of all strains of a species) to better detect gene variation. Pangenome graphs are data structure used to represent and compare that genetic variation within a species or a population (Genomics Aotearoa nd).
-

References

- Adachi T, El-Hattab AW, Jain R, et al. 2023. Enhancing equitable access to rare disease diagnosis and treatment around the world: a review of evidence, policies, and challenges. *International Journal of Environmental Research and Public Health* 20(6): 4732.
- Annemans LJP. 2023. Innovative public price mechanisms for market access of innovative medicines: a marriage between cost-effectiveness, medical need, and budget impact. *Value in Health* 26(3): 400–1.
- Aramoana J, Koea J, CommNETS Collaboration. 2020. An integrative review of the barriers to Indigenous peoples participation in biobanking and genomic research. *JCO Global Oncology* (6): 83–91.
- APEC. 2019. *Action Plan on Rare Diseases*. URL: www.apec.org/docs/default-source/Satellite/Rare-Diseases/APEC_ActionPlan.pdf (accessed 27 November 2024).
- APEC. 2021. Rare Disease Network Members. URL: www.apec.org/rarediseases/members (accessed 27 November 2024).
- Bauskis A, Strange C, Molster C, et al. 2022. The diagnostic odyssey: insights from parents of children living with an undiagnosed condition. *Orphanet Journal of Rare Diseases* 17(1): 233. URL: <https://doi.org/10.1186/s13023-022-02358-x> (accessed 27 November 2024).
- Beaton A, Hudson M, Milne M, et al. 2017. Engaging Māori in biobanking and genomic research: a model for biobanks to guide culturally informed governance, operational, and community engagement activities. *Genetics in Medicine* 19(3): 345–51.
- Beck M, Ramaswami U, Hernberg-Ståhl E, et al. 2022. Twenty years of the Fabry Outcome Survey (FOS): insights, achievements, and lessons learned from a global patient registry. *Orphanet Journal of Rare Diseases* 17(1): 238.
- Boulanger V, Schlemmer M, Rossov S, et al. 2020. Establishing patient registries for rare diseases: rationale and challenges. *Pharmaceutical Medicine* 34(3): 185–90.
- Boycott KM, Hartley T, Kernohan KD, et al. 2022. Care4Rare Canada: Outcomes from a decade of network science for rare disease gene discovery. *American Journal of Human Genetics* 109(11): 1947–59.
- Boycott KM, Rath A, Chong JX, et al. 2017. International cooperation to enable the diagnosis of all rare genetic diseases. *American Journal of Human Genetics* 100(5): 695–705. URL: [https://www.cell.com/ajhg/fulltext/S0002-9297\(17\)30147-7](https://www.cell.com/ajhg/fulltext/S0002-9297(17)30147-7) (accessed 27 November 2024).
- Caron NR, Chongo M, Hudson M, et al. 2020. Indigenous genomic databases: pragmatic considerations and cultural contexts. *Frontiers in Public Health* 8: 111.

- Carroll SR, Garba I, Figueroa-Rodríguez OL, et al. 2020. The CARE Principles for Indigenous Data Governance. *Data Science Journal* 19: 43. URL: <https://datascience.codata.org/articles/10.5334/dsj-2020-043> (accessed 27 November 2024).
- Castilla-Rodríguez I, Vallejo-Torres L, Couce M, et al. 2017. Cost-effectiveness methods and newborn screening assessment. *Rare Diseases Epidemiology: Update and Overview* 267–81.
- Chambers JD, Silver MC, Berklein FC, et al. 2020. Orphan drugs offer larger health gains but less favorable cost-effectiveness than non-orphan drugs. *Journal of General Internal Medicine* 35(9): 2629–36.
- Chandrashekar C, Shetty SS, Radhakrishnan R. 2022. Evolution of biobanks and ethical governance for the emerging applications in biomedical research. *Journal of Oral and Maxillofacial Pathology* 26(4): 433–9.
- Choquet R, Maaroufi M, de Carrara A, et al. 2014. A methodology for a minimum data set for rare diseases to support national centers of excellence for healthcare and research. *Journal of the American Medical Informatics Association* 22(1): 76–85.
- Choukair D, Hauck F, Bettendorf M, et al. 2021. An integrated clinical pathway for diagnosis, treatment and care of rare diseases: model, operating procedures, and results of the project TRANSLATE-NAMSE funded by the German Federal Joint Committee. *Orphanet Journal of Rare Diseases* 16(1): 474. URL: <https://doi.org/10.1186/s13023-021-02092-w> (accessed 27 November 2024).
- CSL Behring. 2020. Suffering in Silence: Rare Disease Patients in Asia-Pacific. URL: www.csl.com/we-are-csl/vita-original-stories/2020/suffering-in-silence-rare-disease-patients-in-asiapacific (accessed November 2023).
- Daly A. 2018. Impact of rare disease quality of life: what it means in real terms for people living with a rare disease. URL: http://download2.eurordis.org.s3.amazonaws.com/ecrd/ECRD_2018/Speaker_Presentations/0401-Daly.pdf (accessed 27 November 2024).
- D'Angelo CS, Hermes A, McMaster CR, et al. 2020. Barriers and considerations for diagnosing rare diseases in Indigenous populations. *Frontiers in Pediatrics* 8. URL: www.frontiersin.org/articles/10.3389/fped.2020.579924 (accessed 27 November 2024).
- Dima V. 2021. Actualities in neonatal endocrine and metabolic screening. *Acta Endocrinologica* 17(3): 416–21. URL: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8919488/> (accessed 27 November 2024).
- European Medicines Agency. 2024. EU Clinical Trials Register. URL: www.clinicaltrialsregister.eu/ctr-search/search (accessed 27 November 2024).
- European Union Committee of Experts on Rare Diseases. 2013. *EUCERD Core Recommendations on Rare Disease patient Registration and Data Collection*. URL: www.rd-action.eu/eucerd/EUCERD_Recommendations/EUCERD_Recommendations_RDRRegistryDataCollection_adopted.pdf (accessed 27 November 2024).

EURORDIS Rare Diseases Europe. 2019. *Achieving Holistic Person-Centred Care to Leave No One Behind*. URL: www.eurordis.org/publications/position-paper-achieving-holistic-person-centred-care/ (accessed 27 November 2024).

Genomics Aotearoa. (nd). Aotearoa Genomic Data Repository. URL: <https://data.agdr.org.nz/> (accessed 27 November 2024).

Groft SC, Posada de la Paz M. 2017. Rare diseases: joining mainstream research and treatment based on reliable epidemiological data. *Rare Diseases Epidemiology: Update and Overview* 3–21.

Hageman IC, van Rooij IALM, de Blaauw I, et al. 2023. A systematic overview of rare disease patient registries: challenges in design, quality management, and maintenance. *Orphanet Journal of Rare Diseases* 18(1): 106. URL: <https://doi.org/10.1186/s13023-023-02719-0> (accessed 27 November 2024).

Health Research Council. 2017. *New Zealand Health Research Strategy*. Wellington: Ministry of Health and Ministry of Business, Innovation and Employment. URL: www.hrc.govt.nz/sites/default/files/2019-05/Resource%20Library%20PDF%20-%20NZ%20Health%20Research%20Strategy%202017-2027.pdf (accessed 27 November 2024).

Health Research Council. 2023. *Annual Report Pūrongo ā-Tau 2022*. URL: www.hrc.govt.nz/sites/default/files/2023-05/HRC%20Annual%20Report%202022%20digital.pdf (accessed 27 November 2024).

Hedley V, Castro R, Rodwell C, et al. 2019. *A Knowledge Base Summary: Integrated, Social and Holistic Care for Rare Diseases*. URL: www.rare2030.eu/knowledgebase/ (accessed 27 November 2024).

Hudson M, Beaton A, Milne M, et al. 2016. *He Tangata Kei Tua: Guidelines for biobanking with Māori*. Hamilton: Te Mata Hautū Taketake – Māori & Indigenous Governance Centre, University of Waikato. URL: www.otago.ac.nz/research/forms/7_Matauranga%20Maori%20Guidelines%20for%20Research/He-Tangata-Kei-Tua-Biobanking-Guidelines.pdf (accessed 27 November 2024).

Hudson M, Garrison NA, Sterling R, et al. 2020. Rights, interests and expectations: Indigenous perspectives on unrestricted access to genomic data. *Nature Reviews Genetics* 21(6): 377–84.

Ingham TR, Jones B, Perry M, et al. 2022. The multidimensional impacts of inequities for tāngata whaikaha Māori (Indigenous Māori with lived experience of disability) in Aotearoa, New Zealand. *International Journal of Environmental Research and Public Health* 19(20): 13558.

Kenny T, Bogart K, Freedman A, et al. 2022. The importance of psychological support for parents and caregivers of children with a rare disease at diagnosis. *Rare Disease and Orphan Drugs* 1: 7. URL: www.oaepublish.com/articles/rdodj.2022.04 (accessed 27 November 2024).

Kodra Y, Weinbach J, Posada-de-la-Paz M, et al. 2018. Recommendations for improving the quality of rare disease registries. *International Journal of Environmental Research and Public Health* 15(8): 1644.

- Kölker S, Gleich F, Mütze U, et al. 2022. Rare disease registries are key to evidence-based personalized medicine: highlighting the European experience. *Front Endocrinology* 13: 832063. URL: www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2022.832063/full (accessed 27 November 2024).
- Kolkhir P, Grad DA, Charalampous P, et al. 2023. An EU task force to assess the burden of rare diseases. *Nature Medicine* 29(3): 516–17. URL: <https://doi.org/10.1038/s41591-023-02207-9> (accessed 27 November 2024).
- Kowal EE. 2015. Genetics and indigenous communities: ethical issues. In: Wright JD (ed). *International Encyclopedia of the Social & Behavioral Sciences* (Second Edition). Oxford: Elsevier. p. 962–8.
- Kukutai T, Campbell-Kamariera K, Mead A, et al. 2023. *Māori Data Governance Model*. Rotorua: Te Kāhui Raraunga.
- Li J, Yang L, Zhang Y, et al. 2022. Rare disease curative care expenditure-financing scheme-health provider-beneficiary group analysis: an empirical study in Sichuan Province, China. *Orphanet Journal of Rare Diseases* 17(1): 373.
- Linertová R, Serrano-Aguilar P, Posada-de-la-Paz M, et al. 2012. Delphi approach to select rare diseases for a European representative survey. The BURQOL-RD study. *Health Policy* 108(1): 19–26.
- Lochmüller H, Torrent IFJ, Le Cam Y, et al. 2017. The International Rare Diseases Research Consortium: policies and guidelines to maximize impact. *European Journal Human Genetics* 25(12): 1293–302.
- López-Bastida J, Oliva-Moreno J, Linertová R, et al. 2016. Social/economic costs and health-related quality of life in patients with rare diseases in Europe. *European Journal of Health Economics* 17(1): 1–5.
- Maron JL, Kingsmore S, Gelb BD, et al. 2023. Rapid whole-genomic sequencing and a targeted neonatal gene panel in infants with a suspected genetic disorder. *JAMA* 330(2): 161–9.
- Marshall DA, Benchimol EI, MacKenzie A, et al. 2019. Direct health-care costs for children diagnosed with genetic diseases are significantly higher than for children with other chronic diseases. *Genetics in Medicine* 21(5): 1049–57.
- Massey University. (n.d). NZ Congenital Anomalies Registry. Te Tari Manaaki Haua. URL: <http://www.ehinz.ac.nz/projects/new-zealand-congenital-anomalies-registry/> (accessed 2 December 2024).
- McCartney AM, Head MA, Tsosie KS, et al. 2023. Indigenous peoples and local communities as partners in the sequencing of global eukaryotic biodiversity. *Biodiversity* 2(1): 8. URL: <https://doi.org/10.1038/s44185-023-00013-7> (accessed 27 November 2024).
- Mills MC, Rahal C. 2019. A scientometric review of genome-wide association studies. *Communications Biology* 2(1): 9.

Ministry of Business, Innovation and Employment. 2024. Science and innovation. URL: www.mbie.govt.nz/science-and-technology/science-and-innovation (accessed 27 November 2024).

Ministry of Health. 2018. Children with serious conditions and special needs 2018. URL: health.govt.nz/your-health/pregnancy-and-kids/services-and-support-you-and-your-child/children-serious-conditions-and-special-needs (accessed November 2023).

Ministry of Health. 2020. *Whakamaua: Māori Health Action Plan 2020–2025*. Wellington: Ministry of Health. URL: health.govt.nz/maori-health/whakamaua-maori-health-action-plan-2020-2025 (accessed 27 November 2024).

Muscular Dystrophy New Zealand. (nd). Pūnaha Io - the New Zealand Neuro-Genetic Registry & BioBank. Retrieved from <https://www.mda.org.nz/Our-Research/Registry--Biobank> (accessed 27 November 2024).

Nanibaa'A G, Barton KS, Porter KM, et al. 2019. Access and management: Indigenous perspectives on genomic data sharing. *Ethnicity & Disease* 29(Suppl 3): 659.

National Hauora Coalition. 2020. Best Start Kōwae. URL: www.gen2040.co.nz/best-start-kowae (accessed 27 November 2024).

National Library of Medicine. 2024. About ClinicalTrials.gov. URL: <https://clinicaltrials.gov/about-site/about-ctg> (accessed 27 November 2024).

National Screening Unit. 2014. Newborn Metabolic Screening Programme. URL: www.nsu.govt.nz/about-us-national-screening-unit/nsu-screening-programmes (accessed 27 November 2024).

Pelentsov LJ, Fielder AL, Esterman AJ. 2016. The supportive care needs of parents with a child with a rare disease: a qualitative descriptive study. *Journal of Pediatric Nursing* 31(3): e207–18.

Orphanet. 2023. Rare disease registries, cohorts and databases. URL: www.orpha.net/consor/cgi-bin/Education.php?lng=EN (accessed 27 November 2024).

Pharmac. 2019. *Funding Medicines for Rare Disorders*. URL: <https://pharmac.govt.nz/assets/2019-Report-Funding-Medicines-for-Rare-Disorders-PDF-version.pdf> (accessed 27 November 2024).

Pharmac. 2023. Funding for rare disorders. URL: <https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/from-application-to-funded-medicine-how-we-fund-a-medicine/medicines-for-rare-disorders/> (accessed 27 November 2024).

Pharmac Review Panel. 2022. *Pharmac Review: Final Report*. Wellington: Ministry of Health. URL: www.health.govt.nz/system/files/documents/publications/pharmac-review-final-report.pdf (accessed 27 November 2024).

Postma MJ, Noone D, Rozenbaum MH, et al. 2022. Assessing the value of orphan drugs using conventional cost-effectiveness analysis: Is it fit for purpose? *Orphanet Journal of Rare Diseases* 17(1): 157.

Rare 2030. 2019a. A knowledge-base summary: Integrated, social and holistic care for rare diseases. URL: www.rare2030.eu/knowledgebase/ (accessed 27 November 2024).

Rare 2030. 2019b. A knowledge-base summary: Rare disease diagnostics. URL: <http://www.rare2030.eu/knowledgebase/> (accessed 27 November 2024).

Rare Diseases International. 2021. *Health Equity: The perspective of Persons Living with a Rare Disease*. URL: www.rarediseasesinternational.org/wp-content/uploads/2021/12/FINAL-EQUITY-STATEMENT-FOR-UHC-DAY.pdf (accessed 27 November 2024).

Rare Diseases International. 2022. *Operational Description of Rare Diseases*. URL: www.rarediseasesinternational.org/wp-content/uploads/2022/08/INFOGRAPHIC-OPERATIONAL-DESCRIPTION-OF-RARE-DISEASES.pdf (accessed 27 November 2024).

Rare Disorders NZ. (2022). Impact of Living with a Rare Disorder in Aotearoa New Zealand. URL: <https://raredisorders.org.nz/about-rare-disorders/resources-reports/> (accessed 2 December 2024).

Reid A, Prates M. 2023. *Rare Disorders Insights Report: Pathways towards better health outcomes*. 2023. Wellington: BERL. URL: <https://berl.co.nz/sites/default/files/2023-05/Rare%20Disorders%20Insights%20Report%202023%20-%20Final.pdf> (accessed 27 November 2024)

Remec ZI, Trebusak Podkrajsek K, Repic Lampret B, et al. 2021. Next-generation sequencing in newborn screening: a review of current state. *Frontiers in Genetics* 12. URL: www.frontiersin.org/articles/10.3389/fgene.2021.662254 (accessed 27 November 2024).

Rodrigues, M. J, O'Grady, G. L, Hammond-Tooke, G, et al. (2017). The New Zealand Neuromuscular Disease Patient Registry; Five Years and a Thousand Patients. *Journal of Neuromuscular Diseases*, 4, 183-188. doi:10.3233/JND-170240

Roy R, Greaves LM, Peiris-John R, et al. 2020. *Negotiating Multiple Identities: Intersecting identities among Māori, Pacific, rainbow and disabled young people*. Auckland and Wellington: Youth19 Research Group. URL: www.myd.govt.nz/documents/resources-and-reports/publications/negotiating-multiple-identities/youth19-intersectionality-report-final.pdf.

Smith CIE, Bergman P, Hagey DW. 2022. Estimating the number of diseases – the concept of rare, ultra-rare, and hyper-rare. *iScience* 25(8): 104698.

Stranneheim H, Lagerstedt-Robinson K, Magnusson M, et al. 2021. Integration of whole genome sequencing into a healthcare setting: high diagnostic rates across multiple clinical entities in 3219 rare disease patients. *Genome Medicine* 13(1): 40. URL: <https://doi.org/10.1186/s13073-021-00855-5> (accessed 28 November 2024).

Te Roopu Wairoa. *Experiences from the Māori disability community in Tamaki Makaurau*. 2023.

Tesi B, Boileau C, Boycott KM, et al. 2023. Precision medicine in rare diseases: What is next? *Journal of Internal Medicine* 294(4): 397–412.

United Nations. 2021. Addressing the challenges of persons living with a rare disease and their families. A/RES/76/132. URL: <https://digitallibrary.un.org/record/3953832?ln=en> (accessed 27 November 2024).

United Nations Human Rights Office of the High Commissioner. 2022. Call for inputs on the protection of the human rights of persons living with rare diseases and their families and carers. URL: www.ohchr.org/en/calls-for-input/2022/call-inputs-protection-human-rights-persons-living-rare-diseases-and-their (accessed 28 November 2024).

von der Lippe C, Diesen PS, Feragen KB. 2017. Living with a rare disorder: a systematic review of the qualitative literature. *Molecular Genetics & Genomic Medicine* 5(6): 758–73.

Ward AJ, Murphy D, Marron R, et al. 2022. Designing rare disease care pathways in the Republic of Ireland: a co-operative model. *Orphanet Journal of Rare Diseases* 17(1): 162. URL: <https://doi.org/10.1186/s13023-022-02309-6> (accessed 28 November 2024).

Whaikaha. 2023a. Child Development Services. URL: www.whaikaha.govt.nz/support-and-services/specific-disability-services/child-development-services (accessed November 2023).

Whaikaha. 2023b. System Transformation and Enabling Good Lives. URL: www.whaikaha.govt.nz/about-us/enabling-good-lives/#Where-to-from-here (accessed 27 November 2024).

Whitehead J, Pearson AL, Lawrenson R, et al. 2020. Selecting health need indicators for spatial equity analysis in the New Zealand primary care context. *Journal of Rural Health* 38(1): 194–206.

WHO. 2020. For the Future. Towards the Healthiest and Safest Region A vision for WHO work with Member States and partners in the Western Pacific. URL: www.who.int/publications/i/item/WPR-2020-RDO-001 (accessed 27 November 2024).

WHO. 2021. International Classification of Functioning, Disability and Health. URL: www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health (accessed 28 November 2024).

WHO. 2022. Evidence, policy, impact. WHO guide for evidence-informed decision-making 2021a. URL: www.who.int/publications/i/item/9789240039872 (accessed 28 November 2024).

WHO. 2024. International Clinical Trials Registry Platform. URL: <https://trialsearch.who.int/Default.aspx> (accessed 28 November 2024).

Wilkinson MD, Dumontier M, Aalbersberg IJ, et al. 2016. The FAIR Guiding Principles for scientific data management and stewardship. *Scientific Data* 3(1): 160018.

World Economic Forum. 2020. *Global Data Access for Solving Rare Disease. A Health Economics Value Framework*. URL: www3.weforum.org/docs/WEF_Global_Data_Access_for_Solving_Rare_Disease_Report_2020.pdf (accessed 27 November 2024).

Zanello G, Chan C-H, Pearce DA, et al. 2022. Recommendations from the IRDiRC Working Group on methodologies to assess the impact of diagnoses and therapies on rare disease patients. *Orphanet Journal of Rare Diseases* 17(1): 181.

Zozaya N, Villaseca J, Abdalla F, et al. 2023. Strategic discussion on funding and access to therapies targeting rare diseases in Spain: an expert consensus paper. *Orphanet Journal of Rare Diseases* 18(1): 41.