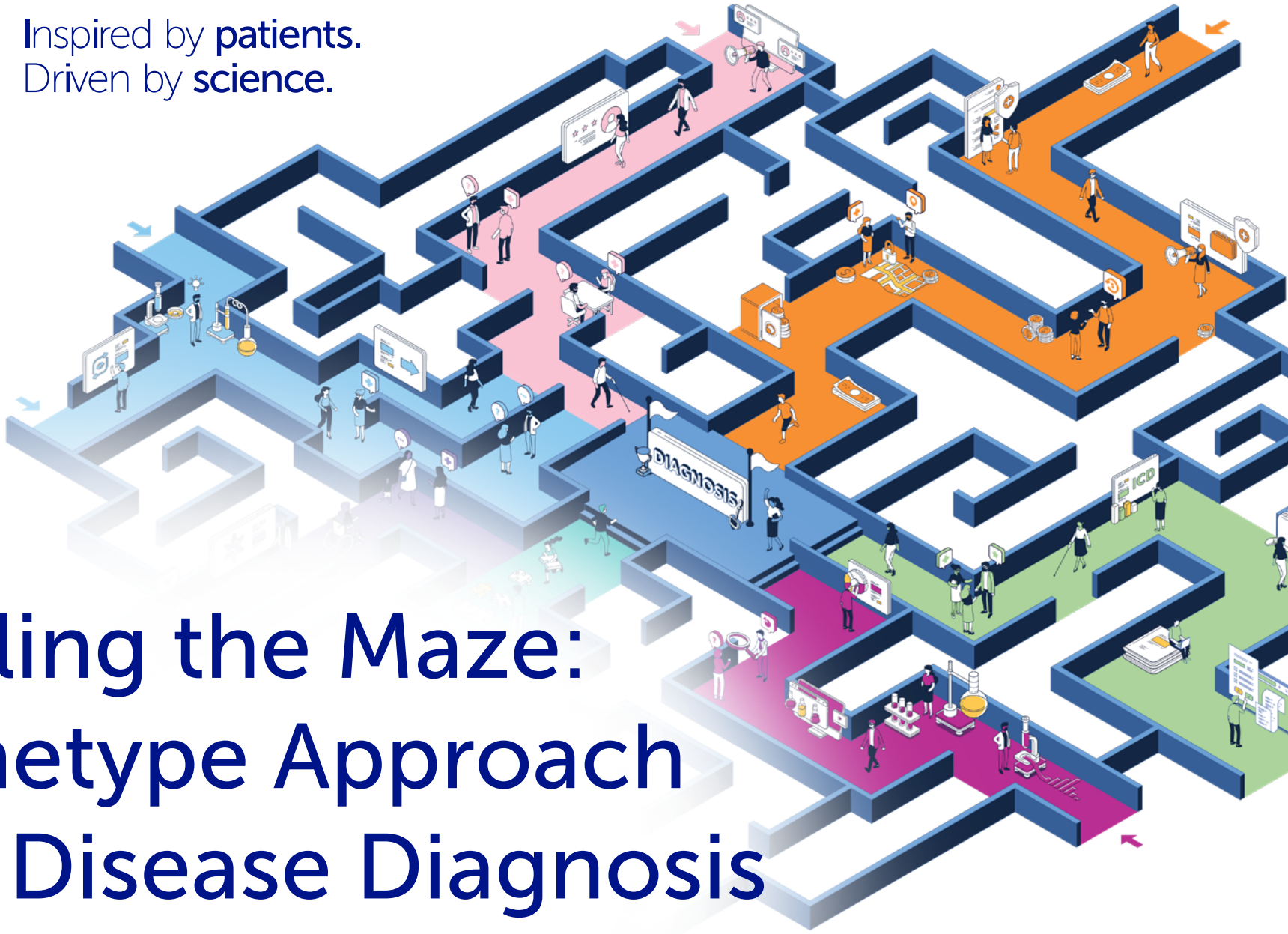
Aspire 4Rare

Inspired by **patients.**
Driven by **science.**



Untangling the Maze: An Archetype Approach to Rare Disease Diagnosis

A multi-stakeholder tool for addressing the diagnostic odyssey

Aspire4Rare is a UCB-funded initiative developed in collaboration with stakeholders across the rare disease community, including policymakers, healthcare professionals, and patient organizations, to support progress in rare disease care and policy.

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Chair's Foreword: Our Archetype Approach to Diagnosis

Diagnosis is a complex concept because of all the different moving parts involved. With the rapid acceleration of technologies that can help diagnose diseases earlier, faster, and with more precision, we can see that, for many people living with rare diseases, a diagnosis does not reliably translate into access, treatment or support. In some contexts, diagnosis can even introduce new risks (financial, social, or psychological) rather than resolve uncertainty.

Instead of providing another set of overarching recommendations to address this paradox, we would like to separate out each part of the diagnostic odyssey and analyse how they work in practice, as well as how they interact. This will help to describe the challenges people living with rare diseases face in getting a diagnosis, reflecting their real, lived experiences. It will also draw attention to each of the parts in their own right, reminding rare disease strategy planners to address the entire diagnostic odyssey.

When we began the Aspire4Rare initiative in 2024, one message emerged consistently from stakeholders: progress looks different depending on where you stand. Following the warm reception of the first Aspire4Rare report, we were enthused about taking a similar framework approach to the often non-linear and fragmented topic of diagnosis. To bring structure to the diagnostic odyssey, we propose example categories of rare disease diagnosis-related challenges that we refer to as archetypes.

We have defined "archetypes" as fundamental categories that represent distinct patterns within a particular context – in this case, diagnosis challenges for rare diseases – that are structured in relation to specific inflection points in the diagnostic odyssey. Not every archetype will automatically apply in every setting – and that is intentional.

With this report, our aim is to formulate a high-level overview that can capture these diagnosis challenges, while also speaking to the lived experiences of those who are about to embark on or already navigating the journey.

The archetypes we have proposed have been refined and validated by a distinguished expert panel in an iterative manner, but are also not 'set in stone'. As there is still much to learn about rare disease, we believe these archetypes can serve as a starting point, and evolve over time in line with rare disease community needs and priorities.

A diagnosis alone implies more than identifying a disease or a condition; it connects to social value judgements, including resource allocation and principles for what can be considered 'fair' and 'just' decision-making.

Although this report alone cannot provide answers to these questions, we hope that having a practical document that showcases specific policy actions can contribute to the broader rare disease policy agenda and be used as a door-opener to future conversations that, ultimately, will result in improved diagnosis.

Sheela Upadhyaya



Holm Graeßner



Acknowledgements of expert contributions

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How to Use This Report

Rare disease diagnosis is not a single-policy problem with a single solution. It is a system challenge that requires coordinated action across policy, health services, clinical practice, research, and community support. This report is structured so that readers can enter where it is most relevant to them.

If you are a policymaker, payer, or health authority: start with the 'Call to Action' and the archetype recommendations and indicators. Use the indicators to translate priorities into measurable commitments over the next five years.

If you lead a healthcare system, service network, or centre of expertise: focus on the archetypes as a practical guide to strengthening pathways, referral systems, workforce capability, and data and digital infrastructure.

If you are a clinician or part of a professional or medical society: use the archetypes and case studies to identify where diagnostic delays and misdiagnoses arise in practice and what guidelines, training, decision support, and referral routes can help reduce them.

If you represent a patient organisation or community: use the case studies, targeted messages, and indicators to support advocacy, highlight barriers that matter in real life, and frame priorities in ways decision-makers can act on.

If you are a researcher or research funder: focus on the 'Research Advances' archetype and the report's recommendations on registries, data reuse, reanalysis, and equitable inclusion, to ensure current and future research accelerates real-world diagnosis.



Executive Summary

The Aspire4Rare Diagnosis report aims to address barriers to timely and accurate diagnosis for people living with rare diseases worldwide. Developed together with a multidisciplinary expert group, this report uses an archetype framework to identify challenges throughout the diagnostic odyssey.

This archetype *framework* reflects the patterns repeatedly highlighted by the rare disease community. It consists of seven categories grounded in the real-world experience of obtaining a rare disease diagnosis. These categories reflect the non-linear nature of the diagnostic odyssey. Readers can choose to jump to the actions and indicators they find most relevant, while the framework reminds them to think about the broader connections between archetypes.

These seven categories are, in no particular order, *building awareness to support referrals to centres of expertise, access to technology, diagnosis in social context, dynamic diagnosis throughout the patient journey, economic aspects of diagnosis, standardisation of diagnosis process, and advancing research to provide answers.*

This is not just a policy report. Many of the most decisive levers for diagnosis sit across the health workforce, professional education, service design, data infrastructure, research translation, and community support. For that reason, Aspire4Rare Diagnosis is designed as a multi purpose action framework: it sets out what different actors can do– individually and together– to reduce diagnostic delay, improve accuracy, and widen access to diagnosis in ways that are measurable and feasible in different contexts.

Why archetypes?

Diagnosis is complex to understand and to improve, because of all the different moving parts involved. The archetype approach separates out each of those parts and analyses how they work in practice, as well as how they interact throughout the journey to a diagnosis. This helps to describe the challenges people living with rare diseases face in getting a diagnosis, reflecting their real-world experiences. It also draws attention to each of the parts in their own right, reminding rare disease strategy planners to address the entire diagnostic odyssey.

They also reinforce our key system priorities for change: *rare disease training across the health workforce, expanded access to advanced diagnostics and genetic services, interoperable health information systems and registries, stronger primary care referral pathways and telehealth, promotion of collaborative research and secondary use of data, and awareness and inclusion for underserved and marginalised groups.*

These system-wide priorities are supported by the archetype framework. In practice, this brings together a structured approach to diagnosis challenges with six actionable aims. Such action requires input from all stakeholders and involvement of local communities, in order to ensure everyone living with a rare disease can get a timely diagnosis.

Aspire4Rare Diagnosis is designed to complement ongoing global, regional, and national rare disease strategies and action plans. Its archetype framework helps translate high-level commitments into practical reforms that work across different healthcare system realities. The overall goal is to align these recommendations with regional priorities and existing policy momentum, so that diagnosis becomes an actionable pillar within global rare disease commitments.

Archetype Framework Overview

Building Awareness to Support Referrals to Centres of Expertise

This archetype focuses on the critical early stages of the diagnostic odyssey, from first symptoms to reaching specialist care. It emphasises awareness of both healthcare professionals and the public.

Access to Technology

This archetype focuses on technological barriers that prevent early and accurate diagnosis, even when patients reach appropriate care settings. There are two overarching topics within the archetype: infrastructure and training.

Diagnosis in Social Context

This archetype places diagnosis into the wider social, cultural, and systemic context that affects its meaning and its practical repercussions. It addresses the non-medical factors that create and reinforce barriers to seeking a diagnosis and persisting in doing so.

Dynamic Diagnosis throughout the Patient Journey

This archetype focuses on the way diagnosis changes over time and in light of changes in other fields, such as scientific advancement, funding allocations, and the political environment. It reflects the fact that the diagnostic odyssey does not always move forward in a straight line; someone may wish to revisit their diagnosis in the future to secure additional answers.

Economic Aspects of Diagnosis

This archetype focuses on the economic barriers that can make it more difficult for people living with rare diseases to find answers by seeking a diagnosis. Addressing these economic barriers is not only an equity imperative but also a system-efficiency strategy,as delayed diagnosis often results in additional cumulative healthcare costs and avoidable morbidity.

Standardisation of Diagnosis Process

This archetype focuses on consistency and systematic approaches to diagnosis, including clinical guidelines, referral pathways, and data harmonisation.

Advancing Research to Provide Answers

This archetype focuses on translating research into practice and ensuring insights from clinical practice feed back into research. When research teams and clinicians work in silos, opportunities for shared learning are missed. Clinicians also rely heavily on literature and peers' experience for rare disease diagnoses, making the generation and dissemination of clinical research on rare disease diagnosis essential for training the wider workforce.



Aspire4Rare: Our Ambition for Rare Disease Diagnosis

Achieving timely, equitable diagnosis is the foundation of our healthcare systems. Diagnosis determines whether people can access adapted care, receive accurate information, avoid unnecessary or harmful interventions, plan for the future, and participate in research. Yet for too many people living with rare diseases, diagnosis remains delayed, fragmented, or out of reach.

Despite advances in genomics, data sharing, and specialist knowledge, for many the rare disease diagnostic odyssey continues. The challenges associated with this journey are not confined to any country or income level; instead, they reflect how we, as a society, design, resource, and define the value of diagnosis.

The initial Aspire4Rare[1] report in 2024 was designed to drive impactful change in rare disease policy. It includes a policy framework, examples of good practices, and outcome measurement tools to support healthcare systems in assessing their performance on rare disease care and implementing actionable change.

Motivated by calls for a global rare disease action plan and ongoing discussions about rare disease strategies at global, regional, and national levels, we have since then supported action to develop the World Health Assembly's 10-year global action plan[2] on rare disease. We have also provided a blueprint that can support any healthcare system in any country to develop a rare disease strategy.

This significant progress in rare disease policy is a result of long-standing advocacy and commitment from the rare disease community through various instruments, such as (but not limited to) the

- EURORDIS Rare Barometer studies[3],
- Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease[4],
- The International Rare Diseases Research Consortium[5],
- The Rare2030 comprehensive policy recommendations[6],
- The Rare Diseases International-Lancet Commission on Rare Diseases (RDI-LCRD)[7].

Aspire4Rare has always sought to integrate and build on these efforts through practical activities and measurements.

In that vein, Aspire4Rare was the collaborative effort of a multidisciplinary group of rare disease experts – including people living with rare diseases, healthcare professionals, policymakers, and academics. The co-created output serves as a discussion starter with policymakers, a reference for community priorities, and a tool to support the development and implementation of rare disease strategies.

Aspire4Rare's ambition and practical impact inspired the development of this tool. Similarly to its predecessor, it will apply meaningful policy actions and indicators of progress backed up by concrete, validated example. This edition's output will focus on rare disease diagnosis.



Why Diagnosis Warranted a Dedicated Extension

This report applies the Aspire4Rare approach to one of the most complex challenges in rare disease: diagnosis. Often described by the rare disease community as a "diagnostic odyssey," the journey from experiencing first symptoms to confirmed diagnosis can take years and frequently involves repeated misdiagnoses, unnecessary procedures, and psychological distress, as well as economic burden.

About
70%
of rare diseases are genetic,

72%
begin in childhood[8]

Most rare diseases are genetic, and most begin in childhood but a substantial share do not. Adults with late onset or undiagnosed conditions face different barriers to recognition and referral; systems must plan for them explicitly.

While these figures underscore the importance of early and paediatric diagnosis, they have also shaped assumptions about who people living with rare diseases are and where diagnostic effort should be directed. This has contributed to a lack of understanding and attention to the differing challenges faced by the remaining **30% of people living with rare diseases.**[9]

The remaining 30% include adults with late onset conditions and those whose childhood symptoms were never recognised.

Many systems still link screening for disease to the availability of an 'accepted treatment'[10]. However, this precondition no longer reflects how people navigate rare disease diagnosis.

In many cases, diagnosis delivers value even in the absence of a disease-specific treatment – through validation, reduced risk of unnecessary interventions, informed decision-making, access to adapted care, and future research participation.

This report covers the entire diagnostic process, rom first symptoms to confirmed diagnosis and beyond, recognising that timely, accurate diagnosis is fundamental for everything that follows.

> "When common things fail to explain the clinical picture, systematically consider the uncommon. Rare diseases are rare individually, but collectively affect 1 in 17 people[11] worldwide."
>
> **Maurizio Scarpa**







Framing Diagnosis through Cross-Cutting Challenges

To ensure that diagnosis is examined in its full context, this report identifies four cross cutting themes that shape experiences across countries, life stages, and healthcare systems:

- **The Treatment Independent Value of Diagnosis,** encompassing psychological, social, safety, and research benefits
- **Healthcare system Disparities,** driven by geography, resourcing, infrastructure, and reimbursement
- **Beyond the Medical Model,** including gender bias, ageism, cultural factors, and social determinants of health
- **The Undiagnosed Adult Population,** including adult onset conditions and gaps during life course transitions

These themes expose the systemic pressures that delay diagnosis and deepen inequities, providing the lens through which the diagnostic odyssey must be understood.

The Treatment-Independent Value of Diagnosis

The value of diagnosis is closely tied to the availability of a treatment for the condition in question. Diagnosis is often understood primarily as a gateway to a defined care pathway, such as access to specialist clinics or reimbursed services. This is essential for people living with rare diseases, as it provides them with access to care and support. Facilitating access to treatment will remain a core function of diagnosis, although there are other benefits of diagnosis that matter to the rare disease community.

Evidence from people living with rare diseases illustrates this broader impact. Following diagnosis, 45% noted[12] improved access to the most appropriate care, 56% reported a better understanding of disease progression, and 24% reported improved access to clinical trials[13]. In cases where the most appropriate care does not (yet) include treatments targeted at the specific disease, a diagnosis can also provide access to interventions that address some of the symptoms or to wider supportive care. Improved understanding of disease progression can help anticipate future needs, while access to clinical trials may result in improved standards of care for the individual patient and the affected community.

However, such benefits are not always fully considered by healthcare systems, which have an understandable focus on diagnosis as a path to available treatments. Nonetheless, there are advantages in receiving a diagnosis, particularly for the vast majority of rare diseases that do not have a specific treatment.

Beyond care pathways, diagnosis carries significant personal, social, and preventive value. It can provide validation and psychological relief by confirming that symptoms are real and recognised. For individuals and families affected by genetic conditions, diagnosis enables informed decision-making around family planning and access to genetic counselling.
It can also reduce harm by preventing unnecessary, ineffective, or potentially dangerous interventions intended for other conditions.

Importantly, the absence of a disease-specific treatment at the time of diagnosis does not preclude future benefit. Identifying individuals with a rare disease enables participation in registries, supports research into natural history, and creates opportunities for inclusion in future clinical trials as new therapies emerge. Diagnosis processes should involve ongoing discussion between clinicians and patients. In this way, the person living with a rare disease can be supported to develop a clear sense of potential outcomes and benefit from scientific developments, while the clinician can learn from and take into account the priorities and needs of the person living with a rare disease.

Taken together, these factors highlight that the value of diagnosis extends well beyond immediate treatment decisions and should be recognised as a foundational element of patient-centred care, system learning, and long-term innovation in rare disease.

"The cost of a wrong or late diagnosis isn't just financial – I have cared for patients who suffered permanent damage because they were not treated early and appropriately during the onset of the disease.
Separately, many patients describe the experience itself as deeply distressing. This can stem from the severity of the initial episode, as well as the feeling that their symptoms were not taken seriously."

Jacqueline Palace



Healthcare system Disparities

Systemic disparities persist across all aspects of healthcare delivery, and rare disease diagnosis is no exception. Screening programmes and subsequent diagnosis pathways are unevenly implemented across countries and regions, and where they do exist, they may lack the funding and coordination needed to consistently connect people to specialist centres. These gaps have a measurable impact on time to diagnosis; individuals who are referred to a centre of expertise receive a confirmed diagnosis after an average of 4.3 years, compared to 5.4 years for those who are not.[14]

> "Healthcare system leaders need to integrate networks of multidisciplinary care from the specialist centre all the way through to social care, education, and the local physician. Without that integration, patients fall through the gaps."
>
> **Sameer Zuberi**



Healthcare system resourcing further shapes access to diagnosis. Availability and reimbursement of essential procedures – such as MRI scans and genetic testing – vary widely, as does the number and capacity of centres of expertise. In many cases, people living with rare diseases must travel long distances, sometimes across borders, to access multidisciplinary diagnostic services and care, with the associated financial and logistical burden falling on individuals and families.

Disparities do not end with diagnosis. A 2017 EURORDIS study[15] found that 24% of people living with rare diseases were unable to access the treatment they needed because it was not available in their country, while 15% reported being unable to afford it. Even when a diagnosis is obtained through an expert centre, returning to the local healthcare system does not guarantee timely follow up. Care plans may encounter bureaucratic, reimbursement, or technological barriers, including delays in coverage approvals and difficulties integrating specialist reports into local health data systems. These breakdowns can significantly delay the positive effect of diagnosis – access to appropriate care and support.

Fragmentation and under-resourcing also affect patient organisations, which play a critical role in supporting people living with rare diseases. While some individuals are connected to well established organisations, others may lack access entirely – either because no local group exists or because referrals are not routinely made by healthcare professionals. In some cases, patient organisations are run by a single family, often alongside caregiving responsibilities. Regardless of size or structure, many organisations lack the stable funding and resources needed to meet growing demand.

Together, these disparities reveal that inequities in rare disease diagnosis are not limited to clinical capacity alone, but reflect broader gaps in healthcare system coordination, resourcing, and follow through that must be addressed to ensure diagnosis translates into equitable care.



Beyond the Medical Model

Diagnosis is not solely a medical process – it is also shaped by social, cultural, and structural factors that influence how symptoms are perceived, reported, and acted upon. Barriers linked to healthcare system resourcing are often more pronounced for traditionally underserved populations and for people living in remote or rural communities, where access to information, specialist care, and follow up services may be limited.

Patient organisations report that women's health concerns – particularly among younger women – are more likely to be dismissed, normalised, or attributed to mental health causes in primary care. As a result, some women do not receive a rare disease diagnosis until after significant deterioration and hospital admission.

Evidence from France illustrates this disparity: while 75% of men and boys were referred to hospital within three years of symptom onset, it took more than five years for 75% of women and girls to receive a referral, even after controlling for gender related disease prevalence[16]. In a Latin American survey of people living with rare diseases, the negative impacts of diagnosis delay had a greater effect on women than men.[17] Additionally, a Rare Barometer survey found that women have a longer diagnostic odyssey than men – 5.4 years, compared to 3.7 years.[18] Therefore, the journey to diagnosis is also gendered.

Age similarly shapes diagnostic experiences across the life course. Children, adolescents, and young adults are more likely to experience prolonged diagnostic odysseys, while older adults may face a different form of diagnostic bias, with new symptoms of a rare disease being incorrectly attributed to the natural ageing process.[19] In a recent summit on adult onset rare diseases, 96% of participants identified ageism and paternalism as at least a somewhat significant challenge for older people living with rare diseases.[20] Clinicians may also perceive rare diseases as conditions that primarily affect children, reducing the likelihood that they are considered in adult patients.

Social and cultural reference points also influence whether and how people seek diagnosis. Individuals who have never encountered information about rare diseases – or who do not know where to look for reliable guidance – may be less likely to engage with healthcare services or to persist in seeking answers for unexplained symptoms.

Taken together, these factors demonstrate that rare disease diagnosis is shaped not only by clinical expertise and technology, but also by social norms, biases, and life course transitions, underscoring the need for diagnostic approaches that are inclusive, equitable, and responsive to the realities of people's lives.

The Undiagnosed Adult Population

Millions of adults are estimated to be living with undiagnosed rare diseases. This reflects a systemic gap in how rare diseases are recognised and investigated: adult onset conditions are frequently overlooked, and rare disease research, training, and diagnostic pathways remain heavily oriented toward paediatric populations. In a survey of patient advocates and healthcare professionals on adult-onset rare diseases, 73%[21] felt that a lack of joined-up rare disease diagnosis infrastructure and inconsistencies between provision for childhood rare diseases and adult-onset rare diseases was a significant or highly significant challenge for adults living with rare diseases in their country.

These gaps have far reaching consequences. Undiagnosed adults may struggle to access appropriate healthcare, employment accommodations, social support, and disability benefits, exacerbating inequities across healthcare systems. In many settings, there are limited or no dedicated pathways for adult onset rare diseases, leaving individuals to navigate fragmented services without clear referral routes.

While the majority of rare diseases begin in childhood, and timely paediatric diagnosis remains a critical priority, this focus can obscure an important reality: children with rare diseases grow into adults, and they may still be undiagnosed as they transition out of paediatric care, losing access to specialised services, coordinated support, and tailored clinical expertise.

In addition, diseases that begin in childhood are not always diagnosed during childhood. Diagnostic delays, evolving scientific knowledge, and historical limitations in testing, mean that some individuals only receive a diagnosis years later, if at all. Adult onset rare diseases further compound this challenge, as clinicians may be less likely to consider a rare disease diagnosis in adults due to persistent perceptions that rare diseases predominantly affect children.

Changing population dynamics also play a role. Conditions such as sickle cell disease[22,23] which have become more prevalent in Europe over time, may remain underdiagnosed in adult populations due to limited screening, low awareness, and outdated assumptions about disease prevalence.

Together, these factors point to a structural under-recognition of rare diseases in adults, underscoring the need for diagnostic pathways, professional awareness, and healthcare system designs that explicitly account for the full life course.

Solutions and Stakeholder Responsibilities: Our Calls to Action

Shortening the Diagnostic Odyssey Together

This report calls on all actors – at global, regional, national, and local levels – to commit to measurable improvements in the diagnostic odyssey over the next five years.



An understanding of the current diagnosis landscape in the target area is a key prerequisite for this commitment. Measuring improvement is only possible if the starting point has also been measured and recorded. Stakeholders will get the most out of this report if they come with an understanding of the context they operate within, their key challenges and opportunities, and their priorities for reform.

Only by considering all seven archetypes, and the way they affect your areas of responsibility, can you determine what your most pressing priorities for reform are. This report is not a checklist of required actions; it may not be feasible or desirable to implement every suggestion in your local context. The decision on how to apply its contents should be informed by an assessment of the current situation, priority areas for improvement, and the system's capacity to make those improvements.

That assessment will serve as your starting point – providing an inventory of the tools you already have – and help you determine where to go next across the seven archetypes. Some of these address fundamental underlying issues, while others have more of a service or policy focus. Each archetype can be used differently, but must be taken as a whole to support improvement throughout the diagnostic odyssey, because timely and equitable diagnosis requires action across multiple levers.

No single stakeholder can address the full set of barriers; collective responsibility is essential.

> Some sit with policymakers and payers: e.g. funding, reimbursement, standards, data governance.
>
> Others sit with health system leaders e.g. pathways, networks, workforce models, interoperability.
>
> Professional bodies and educators also have specific responsibilities e.g. curricula, continuing education, guideline dissemination.
>
> The contributions of communities and patient organisations also help to address many of these challenges: e.g. navigation support, trust, awareness, and culturally competent outreach.

Rare disease strategies can serve as a basis to address some of these challenges, although additional mechanisms will be needed to turn these strategies into action. This section sets out a menu of practical actions and responsibilities. Readers can choose a starting point aligned to their context – while keeping sight of the interdependencies that shape the diagnostic odyssey.

From the beginning, the motivation behind the Aspire4Rare initiative has been to capture measurable aspects of people living with rare diseases' experiences across different healthcare system contexts with different resources, infrastructure, and policy directions. Throughout this report, we emphasise scalable options – from foundational steps that strengthen referral, training, and care coordination, to more advanced reforms involving specialised diagnostics, interoperability, and systematic re-analysis. The shared goal is progress that can be tracked, sustained, and adapted locally.

Measuring progress is complex, and some of the most important issues for people seeking a rare disease diagnosis do not (yet) have commonly used measurements. As such, we have divided the measurements in this report between established metrics, and ideal indicators that do not currently exist but should be implemented to improve understanding of progress in rare disease diagnosis. The ideal indicators also help highlight some key information that is still missing, and what we could do to measure it in the future.

> "You need to raise awareness of the issue before you can present a solution. Policymakers cannot change problems they are not aware of. The problem needs to be contextualised, quantified, and its impact clearly highlighted – only then can they know what needs to be addressed."
>
> **Kelly du Plessis**



Key system wide priorities:

01 Embed rare disease training across the health workforce

02 Expand access to advanced diagnostics and genetic services

03 Invest in interoperable health information systems and registries

04 Strengthen primary-care referral pathways and telehealth access

05 Promote collaborative research and secondary use of data

06 Support awareness and inclusion for underserved and marginalised groups



Key system wide priorities:

- Embed rare disease training across the health workforce
  - Building Awareness to Support Referrals to Centres of Expertise
  - Access to Technology
  - Standardisation of Diagnosis Process
- Expand access to advanced diagnostics and genetic services
  - Access to Technology
  - Diagnosis in Context
  - Economic Aspects of Diagnosis
  - Dynamic Diagnosis Throughout the Patient Journey
  - Standardisation of Diagnosis Process
  - Advancing Research to Provide Answers
- Invest in interoperable health information systems and registries
  - Access to Technology
  - Economic Aspects of Diagnosis
  - Standardisation of Diagnosis Process

Key system wide priorities:

- Strengthen primary care referral pathways and telehealth access
  - Building Awareness to Support Referrals to Centres of Expertise
  - Access to Technology
  - Diagnosis in Context
  - Economic Aspects of Diagnosis
  - Standardisation of Diagnosis Process
- Promote collaborative research and secondary use of data
  - Access to Technology
  - Dynamic Diagnosis Throughout the Patient Journey
  - Advancing Research to Provide Answers
- Support awareness and inclusion for underserved and marginalised groups
  - Diagnosis in Context
  - Dynamic Diagnosis Throughout the Patient Journey
  - Economic Aspects of Diagnosis
  - Standardisation of Diagnosis Process

Each archetype provides a clear set of levers that policymakers, healthcare leaders, patient organisations, and industry can act upon. The following section outlines what each group can do to advance meaningful and measurable progress.

Targeted Messages for People Living With Rare Diseases, Clinicians, Policymakers, and Healthcare system Leaders

For People Living With Rare Diseases & Their Families

Your lived experience is essential. The archetypes in this report can help you structure your input and connect this lived experience to the themes policymakers are focusing on. Engage with patient organisations, share your diagnostic odyssey where you can, and participate in registries, surveys, and awareness efforts. Your voice shapes policy, research priorities, and service design.

For Clinicians

Recognising rare diseases is not about memorising thousands of conditions – it is about maintaining curiosity, using available tools, and seeking specialist input early. Education, digital decision support, and clear referral pathways enable timely diagnosis and reduce harm. Addressing diagnosis as a whole might look insurmountable, but even changing just one thing can make all the difference for people living with rare diseases. Each archetype contains actions that healthcare professionals can take, and you can choose what makes the most sense for you to work on locally.

For Policymakers

Diagnosis is not only a clinical challenge; it is a system design issue. Invest in national strategies, ensure funding for implementation, mandate data interoperability, and integrate rare diseases into broader health policies. The return on investment – medically, economically, socially – is substantial. This report offers you a menu of options to tackle what matters most in your local context, breaking down the wider issue of diagnosing rare diseases into specific reforms you can champion alongside your constituents in the rare disease community.

For Healthcare system Leaders

Systems must enable frontline staff to act. Prioritise sustainable workforce development, support multidisciplinary models, embed genomic services, and ensure that digital and data infrastructures allow seamless sharing of information across care settings. Amid conflicting priorities and pressures, Aspire4Rare Diagnosis recognises that different systems have different resource levels. Its archetypes take this into account, proposing flexible solutions that can work across the board.

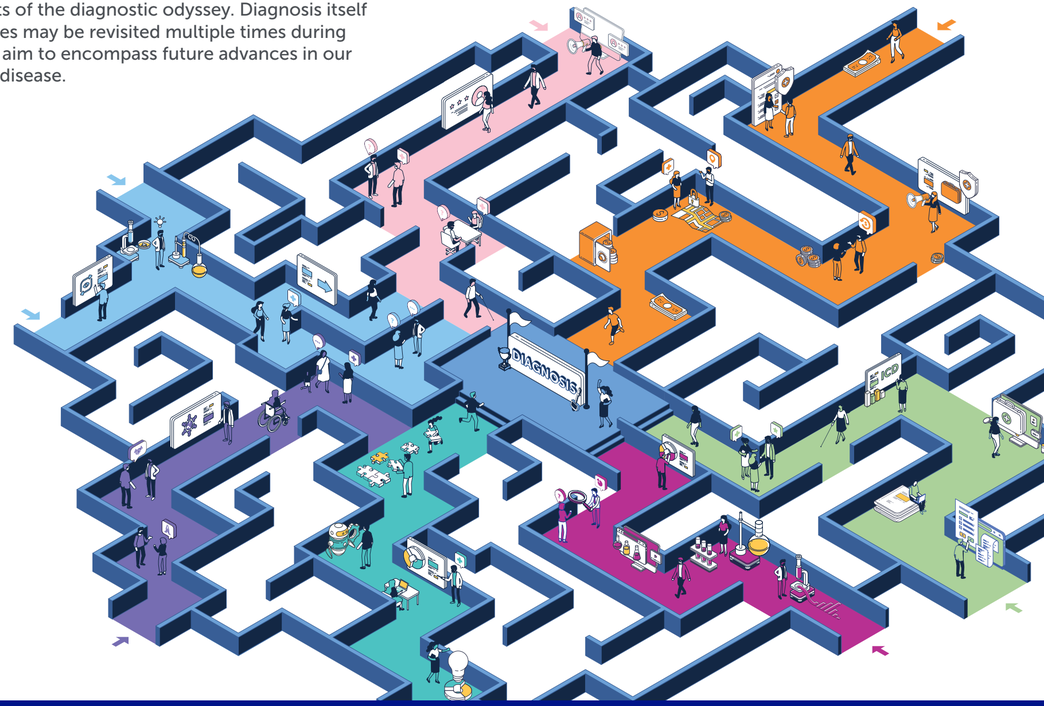
"As someone living with a rare neuromuscular condition, I have experienced first-hand what it means to fight for recognition in systems that are rarely designed for complexity. As a psychiatrist, researcher, and former Member of the European Parliament, I have also seen how fragmented systems and diagnostic inertia can steal years from people's lives. This dual perspective – patient and professional – is what drives everything I do."

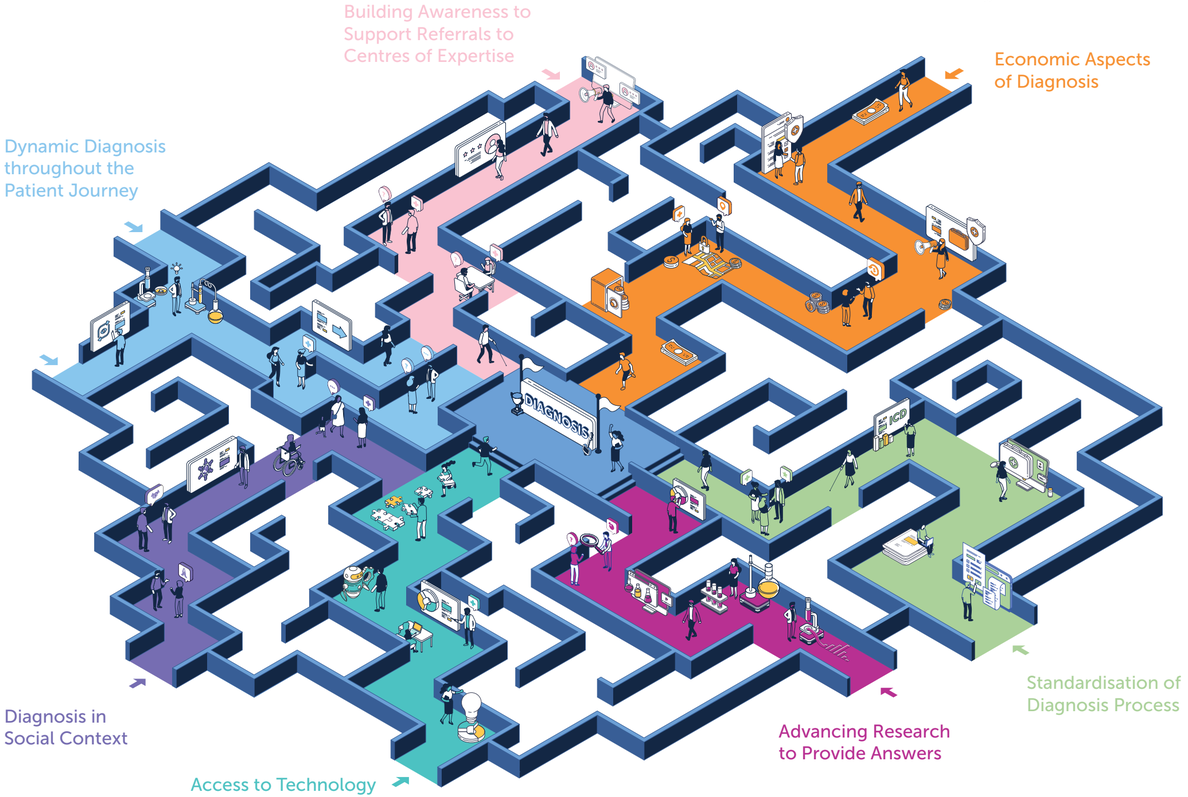
Stelios Kympouropoulous



Diagnosis Challenges for Rare Disease:
An Archetype Approach

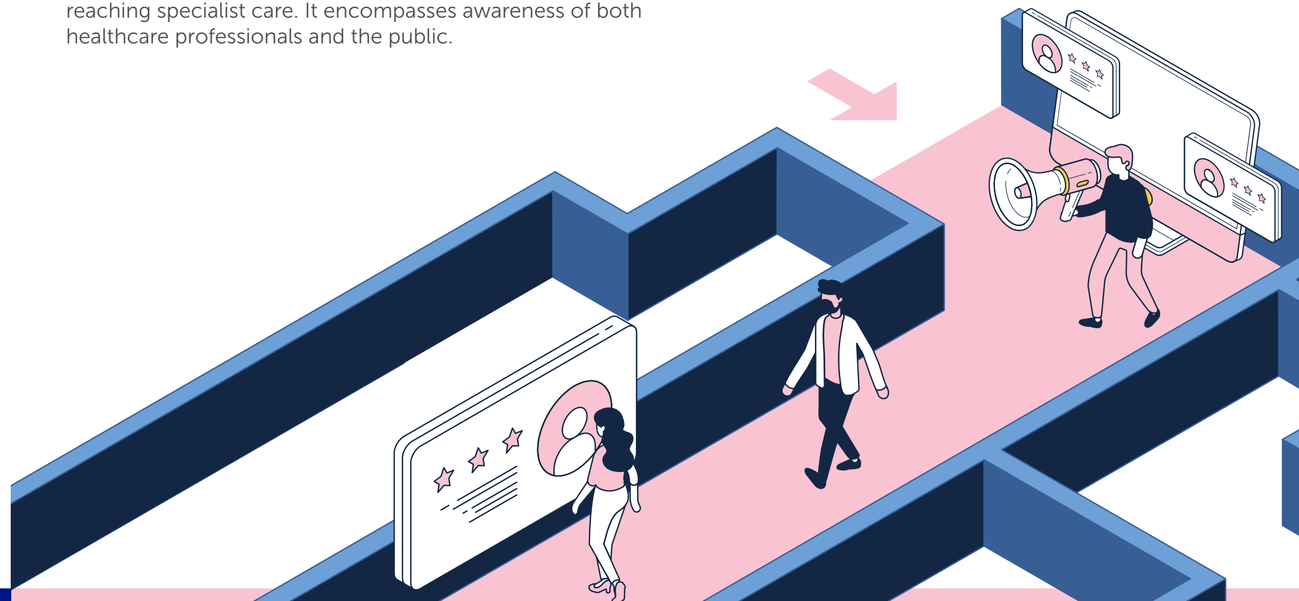
The report is broken down into multiple archetypes structured around specific aspects of the diagnostic odyssey. Diagnosis itself is not linear, and themes may be revisited multiple times during the journey. They also aim to encompass future advances in our understanding of rare disease.





Building Awareness to Support Referrals to Centres of Expertise

This archetype focuses on the critical early stages of the diagnostic odyssey – from experiencing first symptoms to reaching specialist care. It encompasses awareness of both healthcare professionals and the public.



Diagnosis Barriers in this Archetype

Limited Awareness and Training

Awareness and education for the public and relevant professionals is fundamental for diagnosis of rare diseases. People may not have considered they could have a rare disease. If they go to their doctor with symptoms, the doctor may also have preconceptions that lead them to dismiss the possibility of a rare disease or may attribute their symptoms to other factors. Improved public and healthcare professional (HCP) awareness could help people advocate for themselves and/or their loved ones to receive an accurate diagnosis. It should also address issues of trust in the healthcare system and where to find reliable sources of advice.

In an ideal world, everyone would be aware that unexplained symptoms could be a sign of a rare disease and that they do not have to suffer in silence. When they go to seek medical help, the doctor should be trained to consider the possibility of rare disease and be equipped with the information and resources to make specialist referrals.

Healthcare systems should establish coordinated referral pathways that ensure people with suspected rare diseases receive consistent, high-quality care throughout the diagnostic process, involving HCPs of all types.

> "Awareness needs to acknowledge the motivation of those being trained. A family doctor will not be motivated to learn about multiple genetic causes of muscle disease or epilepsy. What they need is to know how and when to refer."
>
> **Sameer Zuberi**



Non-Specific and Overlapping Symptoms

Statistically, most people who go to their doctor to ask about symptoms will have a common condition. However, rare disease symptoms can be like those of common diseases, and it can be difficult for HCPs and lay people to tell the difference. Patients may refrain from seeking medical attention and go undiagnosed because they do not realise their symptoms could be a sign of a rare disease and do not seek medical help, or because HCPs might not be able to identify or misdiagnose the symptoms.

This is particularly an issue for rare diseases that lack immediately visible symptoms. Invisible illnesses pose greater diagnosis challenges, and mild presentations of rare disease can be particularly challenging to identify and might not become apparent until later in life. The key is to ensure awareness of when to seek further expert input; especially where there is doubt about a diagnosis or a conclusion cannot be reached.

Referral and Specialist Consultations

When HCPs do recognise a possible rare disease, there may still be barriers to reaching a specialist who can provide a definitive diagnosis. Family doctors do not have to know about all rare diseases, although they would ideally know where to refer someone to or who to ask for advice. This information may not always be available to them, particularly in rural and underserved areas. The multisystemic impact of many rare diseases complicates understanding of where to refer, especially when there is no specialist service.

Misdiagnosis remains possible once someone has been referred to specialist care. A rare disease could be mistaken for a more common one, or a similar rare disease, resulting in a premature end to the diagnostic workup. Rare diseases with multiple subtypes are also challenging to diagnose, and the impact of identifying the wrong subtype could impact disease treatment and progression.

> "Obtaining a timely and accurate diagnosis is key. However, compassionate communication and ensuring a diagnosis-informed, competent medical and social follow-up is just as important. We owe patients not only the answer, but the support that must follow it."
>
> **Holm Graeßner**



Wider Systemic Barriers to Awareness

Wider social and cultural dynamics around characteristics such as age, gender, sexual orientation, socioeconomic status, geography, race, ethnicity, and physical impairments also affect the way healthcare systems operate. These dynamics exist in rare disease diagnosis as much as they do in common conditions, and people's experiences of the diagnostic odyssey are impacted by the way these characteristics interact. This concept is known as 'intersectionality', and provides a lens to consider how systemic biases affect people seeking a diagnosis.[24]

Additionally, priorities regarding diagnosis vary between individuals and communities based on the context they live in. For example, raising awareness of rare disease so that more people come forward to obtain a diagnosis is an important aspect of advocacy. However, some communities may wish to focus on ensuring that the (smaller) number of people who do seek diagnosis have clear reimbursement pathways for diagnosis, care and treatment. In other more rural/underserved areas, people may be even more likely to face difficulties securing a rare disease diagnosis, with having to travel long distances for healthcare and difficulty in disseminating information being the main barriers to uptake of health services.

Workforce and Patient Advocacy Resources

Allied healthcare professions can play a key role in addressing these awareness challenges. Repositories such as Orphanet[25] provide a vital database of rare disease information, resources, and contact points for clinicians and patient advocacy groups (PAGs). PAGs may also have their own resource directories. However, users first need to know that such resources exist in order to benefit from this information.

> "When I spoke to trainee neurologists during my hospital stays, none of them wanted to specialise in rare diseases because they saw no professional future in the field. I find that extremely concerning. We need to make practical study of rare diseases compulsory – not just a few lines in a textbook, but time spent in specialist departments and with patient associations. We cannot remain overlooked when a diagnosis is needed."
>
> **Isabella Curtis**





Action for Change and How to Measure It

These recommendations should be considered in the context of assessing priorities and system capacities for reform; they are not universally applicable across all healthcare systems and geographies. Stakeholders seeking to improve rare disease diagnosis should select actions that are suited to their resource levels and specific needs.

Limited Awareness And Training

- Strengthen awareness and capability across the care continuum by embedding mandatory rare disease training in medical education and continuing professional development (CPD), including structured placements with rare disease patient organisations so trainees gain insight into lived experiences and communication needs.
- Work with media and culture organisations to raise public awareness of rare diseases through integrating rare disease diagnosis stories into popular programming and the mainstream press, developed in conjunction with patient organisations to reflect their real-life experiences of the diagnostic odyssey.
- Relevant measurements:
  - Number of medical education and CPD courses integrating rare disease considerations.
  - Number of HCPs trained annually in rare disease awareness, disaggregated by primary/secondary care.
  - Percentage of people who are aware of rare diseases and of the associated diagnosis challenges.

Non-Specific and Overlapping Symptoms

- Improve early recognition in primary care and frontline settings by disseminating simple diagnostic "clues" and red flag symptom sets (e.g., Medics For Rare Disease's seven clinical clues)[39], tailored for non specialists and adapted for invisible or overlapping symptom presentations (e.g., the UK NHS's Genomics Education Programme[40]).
- Deploy digital clinical decision support tools (e.g., Electronic Health Record (EHR) integrated alerts, AI pattern recognition systems) to help clinicians identify when symptoms may indicate a rare disease and prompt appropriate investigation or referral.
- Relevant measurements:
  - Proportion of people diagnosed with a rare disease who had diagnostic investigations and first treatment given, or a non-treatment decision taken, within national maximum waiting times for such services.[41]
  - Presence/absence of the technical prerequisites for implementation (e.g., interoperable data).
  - Uptake of clinical decision support tools – proportion of clinicians reporting having used such tools in the past six months.

Referral and Specialist Consultations

- Establish clear, nationally agreed, tiered referral pathways that connect primary care and generalist services to centres of expertise and ensure consistent, timely routes to specialist assessment. This should be accompanied by fast-track referrals and telehealth options for suspected rare diseases among people living in remote, rural and/or underserved areas.
- Expand early access to multidisciplinary expertise (including diagnostics, genetic counselling where appropriate, and allied health professionals) to support accurate disease identification, reduce misdiagnosis risk, and ensure seamless transition across paediatric and adult services.
- Ensure systematic psychosocial and navigation support by providing newly suspected or diagnosed individuals with information about relevant patient advocacy groups and care networks at the point of referral or diagnosis.
- Relevant measurements:
  - Percentage of people living with rare disease reporting one or more misdiagnoses.[42]
  - Percentage of patients referred to a centre of expertise or national equivalent.
  - Percentage of recently diagnosed people living with rare diseases reporting having received information about patient advocacy and care networks.

Wider Systemic Barriers to Awareness

- Develop and implement policies to support rare disease specialists in remote and rural areas, which could include specific training and/or incentives or subsidies for practicing in such areas.
- Relevant measurements:
  - Percentage of people living with rare diseases in different categories of travel distance required to access rare disease care.[43]

"Every person living with rare disease should be able to trust the healthcare workforce to understand the unique profile of needs they might have. Every healthcare professional deserves to feel confident in their approach to rare conditions they may not have heard of. In order to achieve this the systems in which healthcare professionals train and work need to approach rare disease as one large and neglected patient population, not by teaching about a handful of single conditions in isolation."

Lucy McKay



Medics For Rare Disease Call-Out Box

Medics for Rare Disease is shaping a medical profession that can provide timely diagnosis and excellent care to people living with rare disease. It is a small charity[44] based in the U.K. that works globally to design and provide online and in person training about Rare Disease to medical professionals.[45,46,47] They work closely with other healthcare professional groups such as the Global Rare Disease Nurse Network and Rareminds. The charity's advocacy work informs national and global policy and it has a large network of Ambassadors[48,49] who support the charity with their lived experience insights.

Case Studies

MYASTHENIA GRAVIS

Initial Presentation

Myasthenia Gravis (MG) is an autoimmune neuromuscular disorder causing fluctuating muscle weakness[26]. It is often misdiagnosed as stress, chronic fatigue, or other neuromuscular conditions, delaying referral as a result of fluctuating, non-specific, and sometimes invisible symptoms and low frontline awareness.[27] People living with myasthenia gravis therefore experience long diagnostic delays[28], with just over a quarter of patients in a European study waiting over a year for an MG diagnosis, yet timely recognition and referral drastically improve outcomes.[29,30,31] This figure is significant in comparison to the International Rare Diseases Research Consortium's target of diagnosing all patients with a suspected rare disease within a year of coming to medical attention if their condition is known in the medical literature.[32] MG is a chronic disease, and people who are diagnosed and on effective treatment with regular follow-up can continue to live an almost-normal life – continuing to participate in work and maintain a social life.

Diagnostic Odyssey

One of the key issues in MG is ensuring that primary care professionals – nurses and GPs – are trained to identify potential cases and refer onward to specialist care. Over 40% of people living with MG have never been referred to a rare disease unit.[33,34] In the absence of this training, the patient will continue to search for answers over an extended period. People living with MG (especially young women, who are disproportionately affected by the condition[35]) often have to advocate strongly for themselves in order to receive a diagnosis, to overcome reticence or disbelief from clinicians and insist on receiving testing.

Self-advocacy is only possible if the person has the resources and references to support them in doing so. People who have not heard of the condition and do not know of anyone with the condition may struggle with getting doctors to understand them and take their concerns seriously.

> "The longest diagnostic journey I know in my community took ten years – a young woman whose symptoms were dismissed until her health deteriorated dramatically. A quicker referral to a centre of expertise would have changed everything."
>
> **Lutgarde Allard**



Opportunity for Change

Contact with specialist centres can also lead to contact with patient organisations, who can serve as a lifeline for people who have been newly diagnosed with MG. They share reliable knowledge and provide answers to questions in an accessible way, as well as being able to share information about disease symptoms and let them know what is available on the healthcare system. Such information is crucial for patient empowerment and wellbeing. As 66% of patients report not getting the help they need to access information and support, and only 40% have contact with an MG patient organisation, more work needs to be done to connect people living with MG with the organisations representing and supporting them.[36,37]

Outcome & Lessons

Patient advocacy groups provide mutual support and reliable information, as well as upholding the rights of people living with rare diseases. They are an essential part of the awareness-raising process, both through sharing knowledge and through working with other stakeholders in the healthcare system.

Front-line clinicians need to be able to detect potential symptoms of a rare disease in order to refer their patients onward, and so awareness schemes need to reach primary care professionals. Otherwise, the patient bears the burden of visiting multiple healthcare professionals and seeking second opinions until they find someone who refers them onward.

> "When you're diagnosed with a rare disease, you face two immediate enemies: ignorance and isolation. You've never heard of the condition, you have no social or cultural references to help you, and you feel you have no one to turn to. The single best thing my neurologist ever did was hand me a leaflet for the national MG patient association. It was my psychological salvation. Every neurologist should do the same – systematically – for every newly diagnosed patient."
>
> **Isabella Curtis**



Policy Implications

To support awareness of MG and early referral, healthcare systems should:

- Require trainee specialists to spend time working with a rare disease patient group and produce a written assignment following this placement, so they can learn about patient experiences and how best to interact with people living with the conditions they treat.
- Disseminate information to primary care professionals about potential signs of rare disease, such as the study by Medics For Rare Disease[38] identifying seven clinical clues that could point to an underlying rare disease.
- Implement pathways for timely referral of newly diagnosed people to MG specialist facilities, including systematic provision of information about patient advocacy groups.



Access to Technology

This archetype focuses on the technological barriers that prevent early and accurate diagnosis, even when patients reach appropriate care settings. There are two overarching topics within the archetype: infrastructure and training.

Call-Out Box: a note on Technology and Equity

Advances in genomics and AI enabled decision support can accelerate diagnosis where infrastructure, workforce capacity, and representative data are in place. However, it is vital to remember that there are persistent inequities in access to such tools and that they will not be imminently available everywhere. In many settings, the fastest route to better diagnosis remains system strengthening, training and referral pathways, access to essential tests, care coordination, and reliable information for patients and clinicians. This report therefore treats technology as an enabler, not a substitute for healthcare system design, and emphasises scalable options that can reduce diagnostic delay in systems with a range of resource levels.

Diagnosis Barriers in this Archetype

Specialised and Limited Testing

Specialised diagnostic tests (e.g., molecular diagnostics, genetic analysis, antibody testing) are often expensive and not widely available. In contexts where such testing is available, this does not mean the costs incurred will be reimbursed by the healthcare system. They can also be complex and time-consuming to order and interpret, which acts as a deterrent for HCPs considering their use. In some low- and middle-income countries (LMICs), whole genomic sequencing is not available through the healthcare system and people living with undiagnosed diseases have to depend on philanthropic initiatives for access.

Inequitable access to advanced diagnostics

In the diagnostic infrastructure context, access to technologies remains a pervasive challenge. In LMICs, limited in-country diagnostic infrastructure often requires tests – particularly advanced analyses such as genetic or antibody testing for certain rare diseases – to be sent overseas, increasing costs and turnaround times. As a result, healthcare systems may impose restrictions on HCPs' ability to order such tests, including requirements for prior authorisation from payers and the application of strict eligibility criteria to limit test volumes. These structural, financial, and administrative barriers collectively contribute to inequitable access to timely and accurate diagnosis.

Additionally, not all centres can offer advanced and expert diagnostic testing. People who can access specialist centres may benefit from tests that can provide answers in a matter of months, while others may have to wait years for their local hospital to reach a diagnosis.

Fragmented Systems and Pathways

Diagnostic methods, particularly advanced and/or innovative methods, are sometimes standalone services that are not well connected with the wider healthcare system. This increases access challenges, resulting in a fragmented system. People accessing technologies such as whole genome sequencing and whole-exome sequencing (WGS and WES) may fall through the gaps in accessing a specific care pathway. In turn, this would impede access to counselling, multidisciplinary team (MDT) review, and connections to therapy, registries and cascade genetic testing. Where cascade testing does take place, there can be a lack of support available to family members and a lack of guidance for HCPs.

Additionally, interoperability of systems and structures can mean that diagnostic results are in some situations not automatically captured in EHRs and registries. This can cause difficulties for patients, researchers and clinicians in access to further care and support, as well as in identifying people eligible for clinical trials. It also impedes use of AI tools if these cannot draw on the latest results from EHRs and connect to specialist and expert centres.

Continued from previous page

Technological and Logistical Challenges

Digital tools, such as AI clinical support systems, have the potential to pick up on patterns in health data that non-specialists may not have identified. This means they can provide a 'nudge' to a healthcare professional to consider specific rare diseases in the diagnostic process, which could be especially useful in cases of overlapping and invisible symptoms. These systems are specifically designed for this purpose and differ from those available to the general public. They remain fallible and operate only as a signpost for clinical judgement, not as a substitute for it.

They can also be technically complex to integrate into healthcare systems. Existing hospital IT systems may predate the development of these technologies and, therefore, compatibility with newer software may present an issue. Data transfer between such tools and hospital records may also be complicated if the systems use different standards that are not interoperable.

HCP Training and Complexity of Test Interpretation

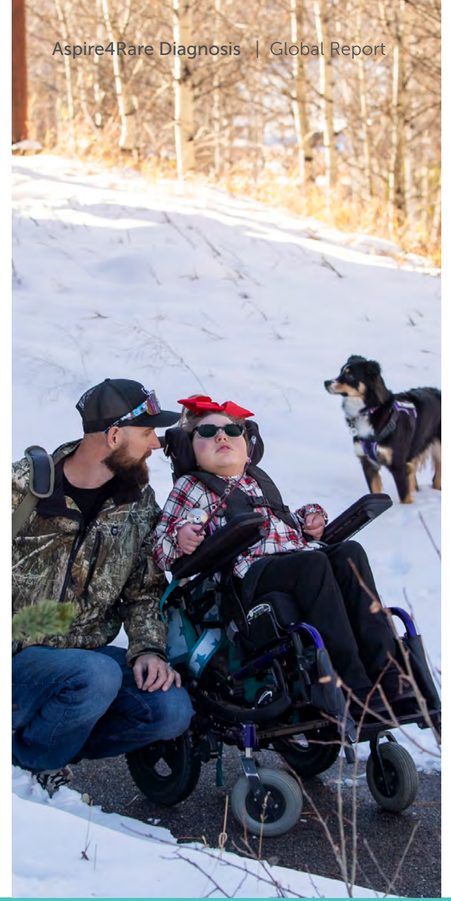
Rare disease diagnosis involves collating multiple pieces of evidence and tying it all together to a specific condition: as such, training in interpreting complex test results and making the rare disease link is essential. Expert input is key for understanding test results and avoiding misdiagnosis, and multiple experts should be involved for a full understanding of the specific patient.

Genetic diagnosis is one such mechanism of ensuring that the correct subtype of a rare disease is identified and the patient can get timely follow-up testing to monitor progression. However, access to such testing remains variable and genetic counselling is not always included in the diagnostic process. Without such analysis of gene screening results, people can be left to navigate the diagnostic odyssey without an expert guide.

For accurate interpretation of test results, systems should be capable of storing and collating different diagnostic information for HCPs who have the clinical expertise to tie it all together. This expert involvement is essential given the complexities involved – particularly in testing for multisystemic diseases and where the existing knowledge of a rare disease is not yet sufficient for reliable clinical application by non-content experts (such as if a variant of unknown significance is detected). Diagnostic tests and their timing also require expert input to minimise the risk of false negatives or positives, and to consider the specific windows for initial and (where necessary) repeat testing.

> "Digital health tools are not a luxury for rare disease – they are vital. Rare disease patients are, by definition, rare and dispersed across countries. Telemedicine and digital platforms can reach low-income countries and rural regions alike, connecting patients to expert centres and clinical trials they would never otherwise access."
>
> **Alessandra Ferlini**





Action for Change and How to Measure It

Overarching Measurements

- Impact of timely diagnosis and delayed diagnosis on the burden of disease – direct and indirect cost in national currency per patient per year.
- Reduced morbidity and mortality from rare disease diagnoses, improved lifespan and health span.

Specialised and Limited Testing

- Strengthen and standardise genomic testing infrastructure by designating central diagnostic laboratories for WGS/WES and establishing national rare disease genomic datasets to accelerate variant interpretation, discovery of novel genes, and translation from research to clinical practice.
- Relevant measurements:

  Availability and utilisation of advanced diagnostic technologies, including the number and share of molecular, antibody, and genomic tests (WGS/WES) performed domestically each year.

Inequitable Access to Advanced Diagnostics

- Guarantee equitable access to essential diagnostic technologies regardless of age by recognising antibody testing, advanced molecular diagnostics, and genomic sequencing as core components of rare disease differential diagnosis – ensuring they are reimbursed, available domestically where possible, and not limited to philanthropic or research settings.
- Develop public-private partnerships that offer funding for people living with rare diseases to access diagnosis, as part of an effort to secure early intervention and improve public health in general.
- Promote rare disease global networks for data sharing, promoting education, and fostering new collaborations.
- Relevant measurements
  - Reimbursement and accessibility of genetic testing per region/country, measured by the proportion of patients able to access recommended tests without out-of-pocket payment and the existence of clear national guidance on when WGS/WES is reimbursable.
  - Number and description of relevant public-private partnerships.
  - Amount of funding secured through PPPs, broken down by the contribution from each sector.

- Number of people living with rare diseases who receive financial support from these PPPs, broken down (if feasible without identifying participants) by age, gender, socioeconomic status, geography, ethnicity, and physical impairment.
- Number of healthcare providers in global rare disease networks.[82]
- Number of patient representatives in global rare disease networks.[83]
- Number of countries of origin of network members.[84]
- Number of training courses developed by these networks.[85]
- Number of trainees who completed those training courses.[86]

Fragmented Systems and Pathways

- Integrate diagnostic technologies into coordinated, end to end care pathways that link testing to counselling, multidisciplinary team review, cascade testing for families, registry participation, and timely referral into treatment or research pathways – reducing fragmentation and improving continuity of care.
- Establish clear national criteria and HTA-aligned guidance on when WGS/WES should be used as a first-line test, ensuring clinicians can order appropriate tests without administrative barriers and enabling consistent, equitable adoption across regions and providers.
- Relevant measurements:
  - Proportion of people undergoing diagnosis for a rare disease, or who have a suspected rare disease that remains undiagnosed, who report receiving clear and accurate information.[87]
  - Proportion of people with a newly diagnosed rare disease who report receiving clear and accurate information.[88]
  - Number of tests/consultations required before diagnosis.
  - Time from first consultation/test to final diagnosis.
  - Proportion of cases where genomic findings enable cascade testing or diagnosis in family members.
  - Equity of access to advanced diagnostics, including the percentage of people with rare diseases who report being unable to access genetic testing due to HCP reluctance, lack of information, geographic location, or socioeconomic barriers (disaggregated by contextually relevant equity indicators).
  - National criteria documents that have been issued and contain defined clinical indications for first-line WGS/WES use.
  - Percentage of relevant clinicians who are aware of and can correctly identify the indications in the guidance.
  - Percentage of clinicians reporting barriers to ordering tests.

Technological and Logistical Challenges

- Mandate interoperable digital systems for diagnosis by requiring all genetic and molecular test results to be automatically integrated into EHRs in a structured, interoperable format, enabling use in registries, MDTs, and AI-enabled tools while ensuring data quality, privacy, and connectivity with reference networks.
- Relevant measurements:
  - Proportion of test results successfully integrated into interoperable EHRs/registries.
  - Number of functioning national or disease-specific registries supporting data reuse and re-analysis.

HCP Training and Complexity of Test Interpretation

- Build workforce capability for modern diagnostics through funded training programmes for all types of HCPs in ordering, interpreting, and communicating complex diagnostic results. This will be accompanied by specialist expert review of test interpretation to prevent misdiagnosis and improve diagnostic accuracy.
- Secure long-term investment in genomic re-analysis and data infrastructure so that undiagnosed or inconclusive cases are systematically revisited as science evolves, supported by robust governance frameworks for AI-assisted diagnosis, data sharing, and use of national and patient-led rare disease registries.
- Relevant measurements:
  - Funding allocated to such training programmes.
  - Number of HCPs completing the training programmes, broken down by speciality, role, and local area.
  - Participation surveys about the usefulness and efficacy of the training programmes.
  - Quality and inclusiveness of diagnostic communication, tracked via the proportion of people living with rare diseases reporting that first symptoms were dismissed, attributed to psychological causes, or led to psychiatric misdiagnosis, as well as the share of cases where clinicians provided referral to patient advocacy groups.
  - Levels of investment in re-analysis and infrastructure.
  - Number and proportion of cases re-analysed each year and the number and proportion of resulting diagnoses.
  - Presence/absence of governance frameworks for:
    - AI support tools,
    - Data sharing,
    - and patient-led rare disease registries.

Case Studies

TK2d

Initial Presentation

Thymidine Kinase 2 Deficiency (TK2d) is an ultra-rare progressive, genetic, and often fatal mitochondrial disease with a severe impact on daily living and quality of life. Most patients are unable to walk, eat, or breathe independently. TK2d is characterized by a spectrum of severity that correlates broadly with age at symptom onset, with the most severe presentations beginning in infancy (age of onset ≤1 year) and associated with a median post-onset survival of one year.[50] Patients can present with progressive muscle and respiratory weakness, clinical features that closely resemble other neuromuscular disorders, making differential diagnosis difficult. Because TK2d is often overlooked in differential diagnosis and not integrated into targeted panels, broader approaches such as whole-exome sequencing (WES) or whole genome sequencing (WGS) are more likely to identify the condition in patients for whom TK2d is not initially suspected. Many patients only get access to WES or WGS as a last resort when no other explanation can be found for their symptoms. Delayed diagnosis in progressive diseases like TK2d can lead to irreversible damage and poorer health outcomes. Early diagnosis of TK2d is crucial as earlier symptom onset results in faster disease progression, and delays in diagnosis and treatment may lead to significant morbidity and mortality.

Diagnostic Odyssey

The availability of specialised tests and the complexity of ordering them compound these clinical challenges. In many healthcare systems, insurance approval[51,52] for genetic testing can be prohibitive. For example, some US insurers require that a treatment exists before approving testing[53] or the patient is responsible for a very large co-pay, creating a paradox that delays the identification of patients, diagnosis, and enrolment to clinical trials to develop such treatments. A study of the US Undiagnosed Diseases Network found that 88 of 206 patients[54] recommended for WES were not able to access genetic testing due to insurance (payer) barriers, delaying diagnosis by several years[55]. Some insurers and payer organisations also require prior authorisation for high-cost specialist testing, which further delays the diagnostic odyssey. Even when approval for testing is granted, laboratory turnaround time (TAT)[56] adds further months-long delays, and logistics issues can slow the process further. These obstacles are collectively detrimental in progressive diseases, where early intervention can significantly alter health outcomes.

Opportunity for Change

Innovative solutions have emerged to address these logistical hurdles:

- Patient advocacy groups, such as the United Mitochondrial Disease Foundation (UMDF), offer no-cost genetic testing and connect families to specialist clinicians.[57,58,59]
- The Children's Hospital of Philadelphia established in-house mitochondrial DNA sequencing, bypassing external insurance approval and reducing turnaround times.[60]
- In the UK, 13 genomic medicine centres integrated genetic testing into routine care, supported by trained nurses who guide families through testing and counselling.[61,62]
- Public-private partnerships like Screen4Care in Europe researches the potential of newborn genetic screening and predictive algorithms to flag rare disease patterns in electronic health records (EHRs) to accelerate diagnosis.[63]

However, disparities persist within and between healthcare systems at all national income levels. US data show disparities in genetic testing awareness – with those who were older, on a lower household income, and who belonged to an ethnic minority group having lower awareness.[64] In South Africa, genetic services are clustered in three provinces, leaving rural patients without access.[65] In Ghana, the Illumina iHope programme[66] offered WGS to only 10 children per year, highlighting the stark inequities in low- and middle-income countries.

Such inequities also exist in high-income countries, particularly for those who need to travel to access services but cannot afford to take time off work or find childcare, who rely on public transport, are underinsured, or already experiencing chronic illness.[67] Given the high need for multidisciplinary clinical management across most rare diseases, this inequity is a profound barrier to improved health outcomes for all people living with rare diseases and further highlights the postcode lottery effect.

> "Delay in referrals and diagnostic testing is the single biggest challenge across all rare disorders. Lack of awareness leads to late referrals – these are the challenges we observe every day. Widespread education is imperative, to decrease the time to diagnosis."
>
> **Zarazuela Zolkipli-Cunningham**



Outcome & Lessons

Such barriers to diagnosis represent a systemic inefficiency. Delayed diagnosis increases healthcare costs through unnecessary treatments and disease progression. Conversely, early diagnosis can reduce long-term costs: an Australian Genomics analysis estimated that implementing genomic sequencing for childhood mitochondrial diseases could save up to AUD 0.7 million annually.[68]

Key lessons:

- Insurance coverage for genetic testing must not depend on treatment availability.
- Centralised genomic services require strong referral pathways and tele-genetics options to avoid geographic inequities.
- Public-private partnerships and advocacy groups are critical for bridging funding gaps and improving access to diagnosis.
- Raised awareness by education and training facilitates consideration of ultra-rare disease.

Policy Implications

To address these barriers, healthcare systems should:

Mandate insurance coverage for clinically indicated genetic testing, regardless of treatment availability.

Encourage investment in infrastructure for in-house sequencing to reduce reliance on external labs and speed up turnaround times.

Support public-private partnerships to fund genomic testing and expand newborn screening programmes.

Develop national frameworks for equitable access, including telemedicine and travel support for people living with rare diseases in underserved regions.

Ensure there is a joined-up pathway for expert interpretation of genetic testing to identify the diagnosis.

Encourage investment in rare disease clinicians' education and training.

Case Studies

AI

Initial Presentation

The length of the diagnostic odyssey is a significant challenge worldwide. According to a retrospective Rare Barometer study[69], patient-related factors account for 10% of time to diagnosis, with the other 90% stemming from healthcare system delays. Tools like AI decision support systems have the potential to assist in shortening time to diagnosis. They can help people to describe their symptoms more effectively and prompt clinicians to consider rare diseases as possible explanations, therefore addressing both sides of the diagnostic odyssey.

Diagnostic Odyssey

The average time to diagnosis varies by country, with estimates as high as over six years.[70,71] This prolonged process has both human and economic costs.

For people living with rare diseases, a delayed diagnosis can delay access to the most suitable treatment and lead to avoidable complications. A survey of people living with rare diseases in 21 Latin American countries assessed the consequences of delayed diagnosis, with 36% experiencing worsening of disease, 35% not receiving treatment or support, and 24% having received inappropriate treatment.[72] For healthcare systems, there is a significant financial impact; avoidable costs of delayed diagnosis (through medical costs and productivity loss) have been estimated to be between 86 and 517,000 USD cumulatively for the years of delay.[73] In Germany, average inpatient costs for rare disease patients were 16,983 EUR, about 9.4x higher than other patients.[74]

By reducing the time to diagnosis, AI decision support tools have the potential to help alleviate these costs for the patient and for society.

Opportunity for Change

An example of such innovation is the AI support tool – DxGPT – designed to help people living with rare diseases to describe their symptoms and prompt clinicians to consider specific rare diseases.[76] A version of the tool is also used in the Madrid public healthcare system to help clinicians with rare disease diagnosis,[77,78,79] reflecting the potential of such tools to support clinical understanding of patient experiences.

Outcome & Lessons

DxGPT has shown positive impact in practice, helping narrow down potential rare disease diagnoses. In almost 60% of cases, its first suggestion matched the confirmed diagnosis. Additionally, in nearly 65% of cases, the confirmed diagnosis was among the top five suggestions.[80] It has also shown accuracy similar[81] to that of medical staff at a Barcelona paediatric hospital, further emphasising the potential of these tools to reliably prompt consideration of rare diseases in the diagnosis process.

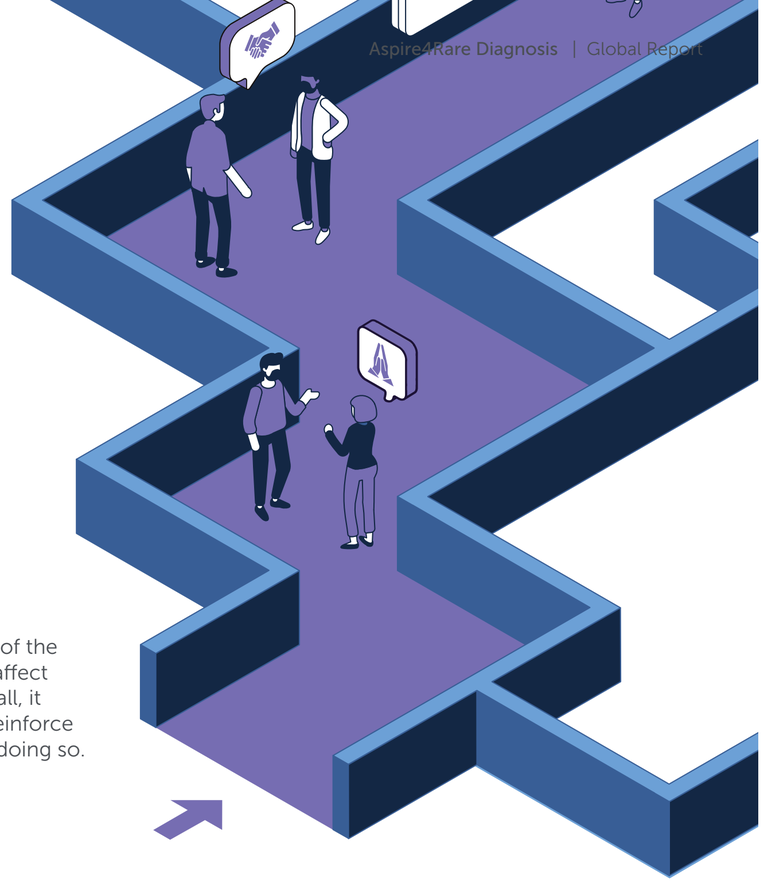
This success highlights the broader value of patient-led innovation and collaboration between the private and public sectors. The case of DxGPT illustrates not only the technological potential of AI decision support tools but also the critical importance of multi-stakeholder cooperation in addressing rare disease challenges.

Policy Implications

To make the most of technological developments like DxGPT, healthcare systems should:

> Work with civil society and the private sector to implement pilot projects of such technologies, collecting evidence about how they work in practice and supporting implementation elsewhere in the healthcare system.





Diagnosis in Social Context

This archetype places diagnosis into the context of the wider social, cultural, and systemic aspects that affect its meaning and its practical repercussions. Overall, it addresses non-medical factors that create and reinforce barriers for seeking a diagnosis and persisting in doing so.

Diagnosis Barriers in this Archetype

Genetic and Family Issues

These barriers are expressed differently in different national contexts. In some cases, people living with rare diseases have to advocate for genetic testing to be done and become inadvertent case managers in the process of navigating the diagnostic odyssey. In others, health literacy and social stigma are barriers to a diagnosis. Lack of awareness of the value of diagnosis and concerns around stigma can deter people from seeking care for potential rare diseases. They may not wish to share their medical histories because of concerns about discrimination, loss of health insurance, and being ostracised from their communities.

When testing does take place, it can be challenging to understand the results and their implications. Diagnosis can help with life and family planning, but family conflict can also arise following the discovery of a genetic disease. Such conflict can have disproportionate impacts on women, who are all too often simultaneously deprived of a voice in decision-making about diagnosis (whether for themselves and/or for family members). Fear of losing health coverage and lack of access to care coordination services can exacerbate these issues, with caregivers (who are often women) having to become case managers for relatives living with rare diseases in the absence of support services.

Patient Advocacy and Support

Patient advocacy groups play an essential role in supporting people living with rare or undiagnosed diseases and their families. System navigators can help shoulder the burden of the diagnostic odyssey, alleviating the pressure on family 'case managers' mentioned above, but usually have no formal role in the care pathway and become involved as a last-resort method of providing support.

A lack of well-resourced patient advocacy groups, psychological support, and training for teachers and community members can further isolate people living with rare diseases and their families. For people in remote and underserved areas, those with language barriers, and those who struggle with technology, it can be difficult to access specialist care, advanced testing, or even basic information about rare and undiagnosed disease.

People living with rare diseases may also not routinely have access to social work or genetic counselling within care pathways, even facing an absence of support professionals when they receive life-changing news. Adults living with rare disease, in particular, report feeling obligated to advocate for themselves as nobody else would do it for them. They face a double bind of fighting both the rare disease and societal perceptions of living with it.

> "Without policy, nothing can be realized. You can establish diagnostic criteria, develop treatments, and build welfare services – but the power to bring all of these together lies in policy. That is why advocating for change at the governmental level is not optional; it is essential."
>
> **Taro Higuchi**



Psychological and Emotional Impact

Diagnosis can take an emotional toll on both the person receiving it and their loved ones, underlining the importance of psychological support and education for the patient and their family members. Emotional responses can vary widely, and people may have multiple reactions to diagnosis. These can include (but are not limited to) fear and shock, as well as validation and relief at having an answer. People may also feel distressed about the delay in diagnosis or the burden of treatment.

Systemic and Socioeconomic Barriers

Socioeconomic status, geographic location, and public awareness significantly impact access to diagnosis. Disparities in quality of and access to healthcare lengthen the diagnostic odyssey and result in poorer outcomes for marginalised groups. These disparities extend throughout the diagnostic odyssey and beyond it, continuing to present barriers to follow-up care and connection to services post-diagnosis. Intersectionality is also key here, as barriers from multiple marginalised identities interact with each other.

The diagnostic odyssey's demands on time and money are difficult to navigate for all people living with rare diseases, and this is exacerbated for people in precarious or low-paid work. The impact of lost wages, travel and out-of-pocket costs, and delays to family and career decision-making, hit harder for those who do not have a strong safety net in place.

Community beliefs and social practices around life decisions, inheritance, disorders, and illness may also

Continued from previous page

go overlooked during the diagnostic odyssey. This makes it more complex for people living with rare diseases to engage with healthcare professionals on the issues that matter to them. This may be accompanied by mistrust of the healthcare system among ethnic minority groups, who may also be reluctant to seek care if diagnosis would run the risk of ostracisation from the community. Trusted community and faith leaders can play a key role, particularly in working with HCPs to sensitively manage testing in communities where consanguinity is more common.

Diagnostic Biases and Stereotypes

Wider societal biases also have an impact on the process of seeking diagnosis. The process itself is not solely about the identification of a disease and a treatment process. For people experiencing it, it represents a fight for the right to life and to good health, to integrity, to social acceptance – and fundamentally, to be seen as a human being.

Implicit and unconscious biases around patient characteristics can affect thinking about which diagnoses are considered possible or likely. Certain genetic conditions can go underdiagnosed in specific ethnic groups due to historical research biases or assumptions that the person does not fit the 'profile' of someone who lives with that rare disease (such as mixed-race people living with sickle cell disease). Ageism can also slow time to diagnosis and affect treatment outcomes. Twenty common signs of ageing are also symptoms of adult-onset rare diseases.[89] People living with rare diseases have reported confusion between the effects of ageing and the effects of the disease, and facing dismissal from HCPs who attribute their symptoms to ageing.[90] Older people have also reported experiencing ageism, poor communication, and lack of tailored information when accessing health services[91] – which can negatively impact treatment outcomes.[92]

Gender bias can also contribute to misdiagnosis or under recognition of rare diseases. Again, historical research biases and misconceptions about disease presentation may prevent women from obtaining a correct rare disease diagnosis. Their symptoms may also be dismissed as psychological, which is particularly problematic in cases where mental health co-morbidities or symptoms overshadow or impede recognition of the physical symptoms of a rare disease. These barriers apply when women seek a diagnosis, but family roles can prevent them from doing so in the first place. Their health decisions are not always their own to make, and they may suffer in silence out of fear of abandonment should they be diagnosed with an illness.

Health Literacy and Communication Barriers

Health literacy and communication also present challenges in accessing a rare disease diagnosis. Rare disease communities are, by their nature, geographically disparate. The internet (particularly social media platforms) has provided people living with a rare disease the opportunity to connect with peers across borders, to exchange experiences and knowledge, which can also be of benefit to people seeking answers about a disease they suspect they have.

However, this requires skills (and typically knowledge of English) in using social media and searching for information online. It also comes with accessibility challenges where websites are not adapted to people with impairments or disorders. Without internet access and confidence in using technology, it is impossible to receive early triage or second opinions from distant specialists through telemedicine, to participate in a registry, or access post-diagnosis care from expert centres without having to travel.

Additionally, reaching out to experts online requires confidence in advocacy abilities and capacity to communicate in a language that may be different from one's own mother tongue. Translation services may speak the patient's language, but can face difficulty in reflecting the implications of a clinician's statements (particularly in the case of breaking bad news[93]) or struggle to encapsulate the way the patient views and describes symptoms, health, illness, and medicine in their cultural context.[94] This puts another layer between the patient and the HCP, with the accompanying increased risk of miscommunication and/or misunderstanding.

> "Access to diagnosis is not determined by availability alone. Families' decisions are shaped by stigma, gender roles, social expectations, and fears about discrimination in education, employment, and marriage prospects. These intersecting pressures often delay diagnosis even in well-resourced settings, showing that bias operates alongside structural health-system barriers. Addressing diagnostic delay therefore requires confronting bias as much as improving access."
>
> **Ritu Jain**



Action for Change and How to Measure It

Overarching Measurements

- Consequences of misdiagnosis and delayed diagnosis, measured by:
  - the proportion of people living with rare diseases experiencing inappropriate care or surgery, delayed access to appropriate treatment, worsening symptoms, or inability to make informed reproductive choices as a result of diagnostic delays.

Genetic and Family Issues

- Require rare disease clinics and multidisciplinary diagnostic teams to include social work, psychological support, and genetic counselling, ensuring that diagnostic pathways address emotional, familial, and practical needs alongside clinical assessment.
- Relevant measurements:
  - Impact of diagnosis on the health outcomes of people living with rare diseases, measured by:
    - the proportion of people living with rare diseases reporting post-diagnosis change in access to the most appropriate treatment, understanding of the disease, financial support, integration into school/work, social services, clinical trials, financial services (e.g., insurance), and their social lives.[117]
  - Availability and uptake of social and psychological support:
    - including the percentage of people receiving genetic counselling and psychosocial support at diagnosis.

Patient Advocacy and Support

- Formalise and fund patient navigation roles (including community navigators, rare disease nurses, and lay advocates) to support individuals and families through the diagnostic process, particularly in underserved, rural, and minority communities.
- Relevant measurements:
  - Proportion of people diagnosed with a rare disease who have a named healthcare professional.[118]
  - Proportion of people with a suspected rare disease that remains undiagnosed after diagnostic investigations, who have a named healthcare professional.[119]
  - Availability and uptake navigation support, including the percentage of people receiving formal navigation assistance.

Psychological and Emotional Impact

- Establish dedicated community based support programmes (e.g., transition support for youth leaving school, peer support hubs, outreach services) to address social isolation, educational disruption, and the psychosocial burden experienced during prolonged diagnostic odysseys.
- Relevant measurements:
  - Percentage of pupils and students with rare diseases reporting limited participation in school compared to others the same age, as measured by the Child and Adolescent Scale of Participation (CASP).[120]
  - Percentage of people living with rare diseases reporting limited community participation.[121]
  - Peer and community support connectivity, measured by:
    - the percentage of people living with rare or undiagnosed conditions who are in touch with a peer, patient group, or community network with the same or a similar condition – serving as a proxy for the reach and strength of patient advocacy organisations and community networks.

Systemic and Socioeconomic Barriers

- Embed culturally and socially informed diagnostic outreach by partnering with community, religious, and local civic leaders to co design awareness campaigns that reduce stigma, improve understanding of rare diseases, and encourage early engagement with health services.
- Relevant measurements:
  - Impact of social and cultural barriers on the diagnostic process:
    - including the percentage of people living with rare diseases reporting fluctuating, invisible, behavioural, cognitive, or sudden onset symptoms,
    - and how often these presentations contribute to misdiagnosis or delayed diagnosis across demographic groups.

Diagnostic Biases and Stereotypes

- Develop national guidance for age-inclusive diagnostic practices, ensuring older adults with atypical or evolving symptoms are appropriately considered for rare disease workup and supported to attend appointments, follow recommendations, and access diagnostic interventions.
- Collect data on equity of diagnostic access and experience.
- Relevant measurements:
  - Systematic disaggregation of time to diagnosis, referral patterns, number of HCPs consulted, and diagnostic outcomes by contextually relevant equity indicators.

Health Literacy and Communication Barriers

- Improve equity and accessibility of diagnostic pathways through targeted policies for populations with limited health literacy, linguistic barriers, or mistrust of healthcare systems – such as multilingual materials, interpreters trained in sensitive diagnostic communication, and community specific engagement models.
- Relevant measurements:
  - Accessibility and inclusiveness of diagnostic pathways:
    - travel time to specialist centres,
    - availability of transport support,
    - and mapping of non traditional stakeholders (religious leaders, community workers, rare disease nurses) who have been trained and actively support diagnosis.

Case Studies

SICKLE CELL DISEASE

Initial Presentation

Sickle cell disease is a group of rare inherited blood diseases[95], the most common of which is sickle cell anaemia.[96] The vast majority of cases are in sub-Saharan Africa,[97] although it is becoming more common in other regions as people migrate.[98] It is now the most prevalent genetic disease in France and the UK, which has required countries to develop specific pathways for people living with SCD, but gaps persist in availability of specialist care.[99]

Diagnostic Odyssey

People living with sickle cell disease have reported[100] differences in care across regions, particularly in less diverse areas where clinicians do not routinely suspect sickle cell or develop experience in diagnosing and treating it. Additionally, lack of awareness of sickle cell often means people living with the condition have to explain it to healthcare professionals while they are unwell and in pain, in general wards as well as in emergency care – which can have negative health impacts.[101] Stigma and discrimination are viewed as contributing to this situation by people living with sickle cell, including stereotypical perceptions of Black people and a perception that sickle cell is neglected in comparison to diseases that primarily affect White people.[102]

Opportunity for Change

European countries have increasingly begun screening for SCD, although not all have a national programme.[103] Barriers include:

- Lack of funding for these efforts; in the UK, clinicians had to volunteer for pilot programmes, eventually resulting in a national screening programme (from 2005 onwards) based on the evidence they generated.[104]
- Belgian SCD screening is only conducted in Brussels and Liège, Ireland's programme is not publicly funded, and Germany and Italy have conducted specific pilot projects.[105]
- Low participation of primary care paediatricians in a pilot project in Italy led to calls for SCD screening to be included in Italy's healthcare system.[106]

The universalisation of such programmes can reduce the chance of newborns going undiagnosed because their parents cannot access or are unaware of screening services.

Outcome & Lessons

The SCD case study illustrates wider issues in rare disease diagnosis – such as lack of awareness and geographic disparities – which interact with discrimination and stigma against ethnic minority groups. This double burden makes it even more difficult to receive a rare disease diagnosis, as rare conditions in a minority group remain under resourced and understudied.

Unwillingness to invest by healthcare systems places the burden of organising services on patient advocacy groups and individual clinicians, and means that only those connected to these networks early in life can access newborn screening pilots. Other people living with SCD may fall through the gaps[107] and go undiagnosed. In SCD, this can have potentially deadly consequences.

Overall, a cycle of underinvestment and lack of awareness results in underestimating the prevalence of SCD and reinforcing the perception that it does not require national-level intervention.

> "There are specific diagnostic challenges for ethnic minorities and older patients that we simply cannot ignore. Some communities carry an inbuilt mistrust of the healthcare system or face cultural barriers that make seeking a diagnosis feel like risking being ostracised. Older patients are too often told, 'it's because of your age' – and diagnostic support is simply not forthcoming."
>
> **Sheela Upadhyaya**



Policy Implications

To address inequalities for ethnic minority people living with rare diseases, healthcare systems should:

Engage and fund partnerships with patient advocacy groups and community organisations, ensuring culturally competent communication, co designed awareness materials, and improved trust with minority communities.

Mandate anti bias and cultural safety training for clinicians in emergency, primary, and paediatric care to reduce stigma-driven diagnostic delays and improve patient experience.

Assess whether screening programmes are truly providing population-wide coverage in a timely, equitable manner, including identification of any factors promoting or impeding access to screening.

As with rare diseases in general, create a decision-making culture that understands the difficulty in gathering accurate data and proactively works to close potential gaps in access to services, rather than assuming less information means there is less of a problem.

Case Studies

EHLERS-DANLOS

Initial Presentation

Ehlers-Danlos syndrome is a group of rare connective tissue diseases, which range in severity from mild hypermobility and skin flexibility to disabling and life-threatening complications.[108]

Diagnostic Odyssey

Young women with Ehlers-Danlos syndrome may have to consult multiple specialists over several years (an average of 4 years for men and 16 years for women)[109] prior to receiving an accurate diagnosis of Ehlers-Danlos syndrome. During the diagnostic odyssey[110], they may develop secondary complications[111] and experience significant psychological distress. Clinicians may attribute their symptoms to the distress associated with the diagnosis process, dismissing them as anxiety or attention-seeking and attributing their pain to psychological factors.[112] This causes frustration and feelings of being patronised and ignored among women living with Ehlers-Danlos.[113]

Opportunity for Change

Such frustration and loss of trust in healthcare systems can be avoided through implementation of consistent clinical pathways, use of technology, and support provision for people living with rare diseases. Systematic screening for young adults with ongoing joint pain, using validated screening instruments, and clinical support tools that flag combinations of symptoms can counterbalance the tendency to dismiss such symptoms as psychological.

This should then encourage consultation with colleagues and referral onward to specialist multidisciplinary care, where the person can be put in touch with care coordination services and patient advocacy groups. Such services can also provide people with mental health support throughout the diagnosis process if required, as a supplement rather than a substitute for further analysis. Baseline rare disease training for primary care providers would also help reinforce the importance of listening to and respecting the expertise of people living with rare diseases.

Outcome & Lessons

The risk of women's health concerns being overlooked or dismissed as mental health related, regretfully, exists in rare disease just as much as it does in common conditions. The lengthy history of attributing women's symptoms to hysteria has left its mark on diagnosis processes and, as such, great care is required to guard against downplaying physical symptoms and assumptions that the condition is psychological.[114] Such misdiagnosis can stigmatise people and have negative health impacts, leading them to disengage from the healthcare system and extending the diagnostic odyssey even further.[115]

> "The most critical failure is still the lack of knowledge – not only among GPs, but also among specialists. And when prejudice enters the room, especially toward young women, patients lose precious time they may never get back."
>
> **Lutgarde Allard**



Policy Implications

To tackle gender bias in the diagnosis process, healthcare systems should:

- Implement training and education for clinicians designed to counteract gender bias in medicine, and address the impacts of historical and present-day dismissal of women's experiences.[116]
- Integrate rare disease into efforts to tackle gender inequalities and support mainstreaming of gender considerations within their service provision.
- Signpost clinicians to seek support from other healthcare professionals when seeking an explanation for symptoms that have no clear diagnosis.

Dynamic Diagnosis Throughout the Patient Journey

This archetype focuses on the way diagnosis changes over time and in light of changes in other fields – for example, advancement in knowledge and science, different funding allocations, and the political environment. As previously mentioned, diagnosis is a long journey that does not always involve moving forward in a straight line; someone may wish to revisit their diagnosis in the future to secure additional answers.



Challenges

Non-Specific and Overlapping Symptoms

As the symptoms of rare diseases are not specific to those diseases, and overlap with the symptoms of more common conditions, often in the absence of specific biomarkers that can differentiate a common from a rare disease, patients often undergo multiple rounds of different diagnostic tests and seek clinical evaluation from multiple physicians. Some people may not get an accurate diagnosis for decades.

This increases the time, emotional, and economic burden involved in rare disease diagnosis and causes the patient (and caregiver where applicable) to miss more work and/or school. The experience of testing is often incredibly challenging emotionally, economically and socially, particularly when invasive procedures and long delays in the turnaround of results are involved.

Additionally, the way a rare disease presents may change over time and new features may lead to a revision of the original diagnosis. Disease progression during the diagnostic odyssey can result in unnecessary investigations and their associated risks, increased medical needs, complex symptoms, and higher morbidity and mortality if the correct treatment is not received.

Specialised and Limited Testing

Testing technologies and methods may change over time with improved understanding of the natural history of disease and the definition of the condition. Scientific advancements can also result in different testing methods as new markers and potential causes of disease are discovered.

However, changes in scientific understanding do not always lead to practical changes in diagnosis. Innovative testing methods may not be available or reimbursed, impeding access to these technologies in practice. As a result, people may remain undiagnosed or misdiagnosed despite the fact that the relevant tools exist.

Research and Knowledge Gaps

Diagnosis is not static; it involves ongoing reanalysis using new technologies as they emerge. This can result in diagnosis of cases that could not be solved with the technology available at the time of initial presentation. This is only possible with ongoing investment in research and healthcare system plans for periodically reviewing cases of undiagnosed disease.

However, historic consent may not cover techniques or scientific developments that were not available at the time. It is possible to seek consent for further study, although the challenge is identifying the patients who should be recontacted. If they cannot be reached, they may fall through the gaps and miss out on opportunities for further testing or research.

Psychological and Social Burden of Diagnostic Uncertainty

People living with undiagnosed diseases may experience ongoing uncertainty and struggle with a lack of recognition in society – accompanied by stigma and exclusion – in the absence of a confirmed diagnosis. This may prevent them from accessing health insurance reimbursement, support in educational settings and/or the workplace, welfare benefits, assistance by a third person, and assistive technology.



Continued from previous page

Additionally, diagnosis of a poorly understood rare disease may mean that the person still does not know what the long-term impacts of their disease could be and therefore faces anxiety and potential difficulty in accessing insurance coverage and financial services based on their medical history.

Systemic Gaps in Re-Evaluation

New discoveries about genetic variants of unknown significance and disease biomarkers are being made all the time, but reanalysis of patient data does not keep pace with this progress. There is an absence of structured provision for regular, reimbursed, reassessment of undiagnosed disease cases over time. Additionally, someone may remain undiagnosed or still have a misdiagnosis at the time of transitioning to adult care, potentially missing opportunities to identify a more suitable diagnosis.

As previously discussed, availability and reimbursement of diagnostic services and testing are often tied to the existence of a treatment. For those rare diseases that do not have a treatment, however, diagnosis still helps inform disease management and supports progress towards a disease. Should a treatment be discovered, it may also become urgent to identify those with the rare disease in question – which becomes much more difficult if testing was not reimbursable.

The Aftermath of a Diagnosis

The moment of receiving a specific diagnosis is a key event in the wider process of diagnosis. It is an event that may be repeated multiple times before the correct diagnosis is reached. In each case, the person living with the rare disease has to consider what the impact of this latest diagnosis may be on their daily life and capacity to carry out day-to-day tasks now and in the future. Those with caring responsibilities may worry about who can take on that role if they become unable to do so, especially those who do not have family members living nearby.

A specific diagnosis may also require monitoring for complications. Certain rare diseases make people more likely to develop specific types of cancer – such as Squamous Cell Carcinoma in Epidermolysis Bullosa [122] and lymphoma in Sjogren's disease[123] – and regular follow-up appointments to check for such complications can take place once the diagnosis is known. In such situations, the "second diagnosis may count for more than the first one."[124]

A diagnosis may also have far-reaching effects on other family members – who may also be a carrier of the rare disease. These can include impact on relationships, allocation of blame, and requirements for screening of relatives – including the ethical ramifications of testing in children. For the person living with the rare disease and their loved ones, however, this may also result in revisions of insurance coverage and reimbursement decisions that can cause gaps in access to healthcare while the situation is assessed and any changes to eligibility implemented.

> "Genomic sequencing is a cornerstone of rare disease diagnosis, yet too many patients still face barriers to access. Given the rapid evolution of scientific knowledge, systematic reanalysis of genetic data every few years should be considered a clinical necessity and integrated into routine diagnostic pathways."
>
> **Vinciane Quoidbach**



Action for Change and How to Measure It

Non-Specific and Overlapping Symptoms

- **Invest in advanced diagnostic technologies such as AI-based tools,** to provide support for clinical decision-making and data integration. This can contribute to timely rare disease diagnosis, enable systematic reanalysis of unresolved cases, and reduce diagnostic delays. Earlier and more accurate diagnosis may also improve healthcare system efficiency by reducing repeated inconclusive testing, inappropriate treatments, and avoidable disease progression.
- Relevant measurements:
  - Diagnostic pathway efficiency and revision, measured through indicators such as:
    - the average number of healthcare professionals consulted,
    - the percentage of patients diagnosed by their first specialist clinician,
    - the number of misdiagnoses received,
    - and differences in diagnostic timelines between genetic and non-genetic conditions.
  - Equity and demographic variation in diagnostic odysseys, tracked through disaggregated data on:
    - age at first symptoms,
    - number of clinicians seen,
    - misdiagnosis frequency,
    - referral patterns,
    - and the proportion of individuals reporting fluctuating or intermittent symptoms across contextually relevant equity indicators.
  - Burden and consequences of misdiagnosis, measured by:
    - the proportion of patients reporting delayed or inappropriate treatment,
    - lack of reproductive counselling opportunities,
    - worsening of symptoms,
    - or being treated for unrelated conditions prior to accurate diagnosis.

Specialised and Limited Testing

- **Decouple diagnostic access from treatment availability** by ensuring diagnostic tests (including genomic, biomarker, and specialist evaluations) are reimbursed even when no approved treatment yet exists, recognising diagnosis as a standalone health and social value.
- **Relevant measurements:**
  - The number of diagnostic test categories eligible for reimbursement, compared to the total number of clinically validated diagnostics available – tracked over time.
  - Comparison of time to diagnosis in rare diseases with and without specific approved treatments.

Research and Knowledge Gaps

- **Modernise consent and data governance policies** so that patients can be recontacted when new diagnostic insights, treatments, clinical trials, or diagnostic insights emerge–ensuring consent processes explicitly cover recontact, data reuse, and long term storage of diagnostic information. This is particularly essential for ensuring the long-term sustainability of biobanks. Clear policies on long-term storage, governance, interoperability, and ethically approved reuse of biological material (e.g., biopsy samples, DNA, and other biological materials) are essential to enable future diagnostic reanalysis, biomarker discovery, and access to emerging therapies as scientific knowledge evolves.
- **Establish harmonised rare disease registries (including patients without diagnosis and a suspected rare disease) at the regional and national level,** encompassing both clinical and patient-reported outcome data. These can support healthcare professionals in data capture, diagnostic decision-making, and ongoing monitoring. Registries capturing quality of life, diagnostic timelines, and patient experience could help better quantify the diagnostic odyssey, monitor equity of access, and assess the real-world impact of diagnostic improvements.
- Relevant measurements:
  - Percentage of active patient records with documented consent that specifically permits recontact when new diagnostic insights, treatments, or clinical trials emerge.
  - Proportion of national biobanks with formal policies covering long-term sample storage, interoperability with other repositories, and approved secondary use of biological materials.
  - Number of regions/countries with at least one rare disease registry that meets relevant interoperability and FAIR data standards.

Psychological and Social Burden of Diagnostic Uncertainty

- **Improve awareness and uptake of the existing disease code[137] for undiagnosed syndromes/ Syndromes Without A Name (SWAN)** so that these patients can be identified within the healthcare system for regular follow-up and research participation opportunities.
- **Invest in longitudinal research infrastructure—** including natural history studies, bio and data repositories, and biomarker research – to expand understanding of disease progression and enable earlier, more accurate diagnosis over time.
- **Relevant measurements:**
  - Accessibility of holistic diagnostic support, including:
    - reported difficulties in accessing education or workplace accommodations during diagnostic uncertainty,
    - availability of insurance coverage,
    - travel time to specialist centres,
    - and mapping of trained non traditional stakeholders (e.g., community leaders, rare disease nurses) supporting diagnostic processes.

Systemic Gaps in Re-Evaluation

- **Establish international guidelines and national frameworks for routine re evaluation of undiagnosed and previously diagnosed cases,** including scheduled genomic re analysis, MDT review, and clear pathways for referring complex or evolving cases back into specialist centres as science advances.
- Relevant measures:
  - Proportion of people with a suspected rare disease that remains undiagnosed after diagnostic investigations who have a documented plan for ongoing review and re-evaluation.[138]
  - Existence and implementation of national guidance on periodic re evaluation, including whether national/regional policies specify how often undiagnosed or complex rare disease cases must be reviewed and the percentage of cases actually receiving scheduled re analysis.

The Aftermath of a Diagnosis

- **Guarantee flexible access to social, educational, and employment support** for individuals with undiagnosed, fluctuating, or progressive rare diseases, ensuring that eligibility for accommodations does not depend on having a confirmed diagnosis.
- **Provide tailored mental health and psychosocial support** throughout the diagnostic odyssey, with specific provisions for individuals experiencing prolonged uncertainty, repeated misdiagnosis, or major life impacts associated with evolving disease.
- **Strengthen financial protection mechanisms,** including safeguards to maintain insurance coverage during diagnostic workup and for undiagnosed individuals, and create a nationally mapped overview of benefits and entitlements to support navigation.
- **Relevant measurements:**
  - Post diagnosis impact on quality of life and access to services, including the percentage of people reporting:[139]
    - improved access to appropriate care,
    - clearer understanding of disease progression,
    - access to social services,
    - integration at school or work,
    - participation in clinical trials,
    - and ability to obtain financial or social support.

Case Studies

MOGAD

Initial Presentation

Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease (MOGAD) is a recently defined autoimmune condition affecting the central nervous system.[125] Its diagnostic criteria[126] were only established in 2023, and research into its underlying mechanisms is ongoing. Because of its novelty and overlapping symptoms with other neuroimmunological disorders, patients rarely receive a definitive diagnosis at first presentation.

Diagnostic Odyssey

When patients first experience symptoms (such as swelling of the optic nerve or inflammation of the spinal cord), clinicians often consider multiple possibilities:[127, 128, 129] commonly Multiple Sclerosis (MS), Neuromyelitis Optica Spectrum Disorder (NMOSD), Acute Disseminated Encephalomyelitis (ADEM)[130], or Transverse Myelitis.

A 2023 multinational survey[131] of 204 patients found that 55.4% received an incorrect diagnosis before MOGAD was confirmed, most often MS or NMOSD. Limited access to antibody testing compounds this challenge; in a Latin American study,[132] half of the patients who did not meet the 2023 diagnostic criteria lacked access to MOG-IgG titration, making confirmation difficult.

Opportunity for Change

Advances in diagnostic technology have transformed this landscape. New forms of MOG antibody testing[133] and improved imaging techniques[134] now enable clinicians to revisit earlier assumptions. A 2025 real-world study across six countries found[135] that 64.2% of patients had prior misdiagnoses and **required a median of 12 assessments and tests before confirmation**. Crucially, all patients ultimately underwent antibody testing – a step that was unavailable or inaccessible for many at the start of their journey.

This limited sample cannot be extrapolated to all patients in all regions, however, as barriers to antibody testing persist. In Japan, for example, MOG-IgG antibody testing by cell-based assay is not currently covered by public health insurance reimbursement, rendering it effectively inaccessible for many patients in routine clinical practice. Therefore, these patients remain undiagnosed or misdiagnosed and the true number of people living with MOGAD is underestimated.

Outcome & Lessons

This case illustrates[136] that **diagnosis is dynamic, not static**. It evolves with scientific progress and requires systems that support re-evaluation. Such scientific progress also needs to be translated into real-world impact so everyone living with a rare disease can benefit from it. In MOGAD, the transformative advances set out above are not available to all patients. Guidance is not always consistently implemented and accurate diagnosis remains challenging. For patients, delayed diagnosis means prolonged uncertainty, inappropriate treatments, and missed opportunities for clinical trial participation. For healthcare systems, it underscores the need for:

- **Regular review of undiagnosed cases** as knowledge advances.
- **Reimbursement for re-testing as technology becomes more accurate**, even when no treatment exists.
- **Education for clinicians and patients** on the role of new tests and evolving criteria.

> "A diagnosis is not just a label – it is the beginning of a patient's new life journey. It opens the door to treatment, to prognosis, to understanding. For rare disease patients, that door is too often locked."
>
> **Taro Higuchi**



Policy Implications

Dynamic diagnosis demands a shift from a "one-and-done" mindset to a continuous diagnostic cycle. Healthcare systems should:

- Implement frameworks for periodic reassessment of undiagnosed cases.
- Fund antibody and genetic testing as essential diagnostic tools.
- Ensure interoperability of electronic health records to integrate new findings.
- Provide mental health and social support for people living with rare diseases navigating prolonged uncertainty.

Case Studies

TK2d (II)

Initial Presentation

Thymidine Kinase 2 Deficiency (TK2d) is an ultra-rare, progressive, and often fatal mitochondrial disease caused by mutations in the TK2 gene.

Most people living with TK2d see their primary care physician or paediatrician for their symptoms and are then referred on to specialist care (most often neurology) and subsequently genetics. However, some people see multiple specialities for their different symptoms and only receive a TK2d diagnosis after red flag symptoms affecting multiple organs lead to a genetics referral.

Diagnostic Odyssey

During this process, many metabolic and non-genetic tests will have been done without identifying a diagnosis. The person may then undergo genetic testing. In some countries, whole-exome sequencing or whole genome sequencing (WES/WGS) may be performed in the first instance while others focus on a panel of genes. Such panels can miss TK2d variants as they may be too narrow to identify mitochondrial diseases effectively or may not be up-to-date with the latest clinical knowledge.

Where people do undergo genetic testing and there is no conclusive result, there is a lack of regular, systemic provision for re-analysing their cases. Some countries consistently schedule follow-up visits to review undiagnosed cases, while others only do so case-by-case. There are various reasons why re-testing may be done:

- To take account of improvements in understanding of disease-causing variants and of testing methods
- A panel test is not sufficient to cover all the relevant genes or not the best fit for the symptoms expressed
- Laboratory technology was not sufficient to give reliable results at the time of testing
- New discoveries about relevant genes or testing technology could provide answers
- The person has new or worse symptoms, the disease is progressing, or starts to affect additional organs
- The person has red flag symptoms or findings that warrant further investigation
- Previous testing was negative but the clinician still strongly suspects rare disease
- Previous testing was inconclusive and advances in knowledge could provide more information following a re-test
- Family history or the diagnosis of a relative prompts further testing

Outcome & Lessons

Ideally, the follow-up process should be well-established in advance and fast-tracked in the event of symptom change, new treatment, or access to a clinical trial. Laboratory databases would automatically update so clinicians have access to the latest variant information and changes to gene panel contents, and payers would accept re-testing where there is disease progression or new evidence.

In practice, re-analysis is often only done where there are symptom changes, disease progression, or new/updated clinical guidelines. Alerts to new variants are also inconsistent and may mean clinicians miss the updates, delaying re-testing. Payers often require a new clinical justification and to sign off on reimbursement before the re-testing can go ahead. Some laboratories offer free re-analysis, but usually only once. Insurance may not cover re-testing, and some insurers require other options to have been tried and failed before accessing re-testing.

Laboratories may also not have sufficient capacity to cope with re-testing demand on top of day-to-day tasks, and the genetics workforce also has limited capacity to handle a long waitlist. Access to the expert analysis required to identify specific genetic diseases can also be a challenge for laboratories. People may also be unaware that they could be re-analysed and/or may not wish to participate. Those who take part should be supported to access and engage with the testing process. Delays to referral, missing test results, and logistical delays increase the risk of the person disengaging.

Someone may also disengage due to not wishing to undergo so many tests, as well as being worried about privacy, finances or travel barriers. They may even become lost to follow-up, making it impossible for them to be recontacted for access to new treatments or clinical trials.

> "The major obstacle doesn't only lie in the diagnostic technologies themselves, but also in the interpretation of the results. Whole genome sequencing is only as useful as our ability to read it in the context of a patient's clinical presentation. We need multidisciplinary teams and clinical translation specialists working together."
>
> **Sushan Luo**



Policy Implications

TK2d is emblematic of wider issues impeding dynamic diagnosis of rare disease through re-analysis and re-testing, and healthcare systems should resolve them by:

Supporting research into identifying potentially disease-causing variants and in explaining variants of uncertain significance.

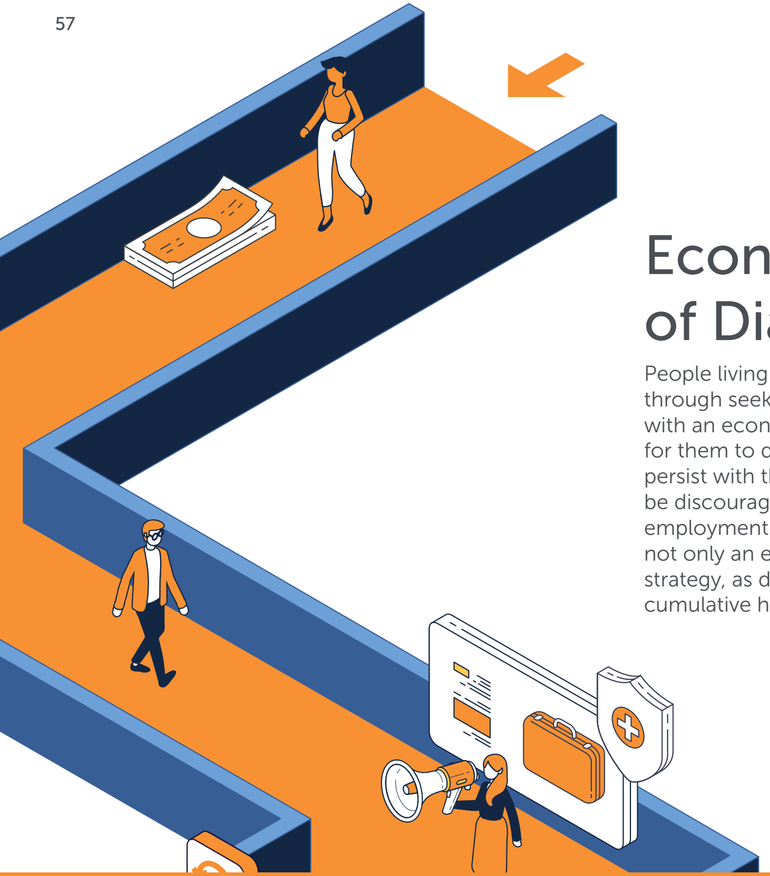
Promoting use of wider-ranging genetic testing to reduce the risk of overlooking conditions that do not often appear on panels.

Implementing referral and escalation pathways to support test result and health record sharing, minimising the need for repeating previous tests and multiple specialist appointments, while facilitating timely access to comprehensive genetic testing.

Simplifying insurer and/or payer requirements for stepwise testing and/or pre-authorisation of WES/WGS.

Ensuring that policies designed to safeguard patient privacy boost confidence in genetic medicine without becoming a barrier to diagnosis.

Developing programmes that provide financial and logistical support to complete (re-)testing for people who are at risk of being lost to follow-up.



Economic Aspects of Diagnosis

People living with rare diseases want to find answers through seeking out a diagnosis, but this also comes with an economic impact that can make it more difficult for them to do so. Some in the rare disease community persist with the diagnostic odyssey, while others may be discouraged by fear of insurance discrimination or employment stigma. Addressing these economic barriers is not only an equity imperative but also a system-efficiency strategy, as delayed diagnosis often results in higher cumulative healthcare costs and avoidable morbidity.

Challenges

Socio-Economic Factors

Socio-economic barriers are structural determinants that can prolong the diagnostic odyssey or prevent individuals from seeking diagnosis altogether. Income level, education, and employment status significantly shape access to specialist care, advanced testing, and follow-up services.

Additionally, marginalised populations – including those living in rural or remote areas, ethnic minorities, and individuals with limited health literacy – consistently experience longer diagnostic delays and poorer health outcomes, and reduced access to care.

Being diagnosed with a rare disease, or even just seeking an explanation of symptoms, carries a risk of being judged or discriminated against. People may also be reluctant to seek an explanation of their symptoms because of concerns about stigma and discrimination affecting their access to the workplace and to financial services.

People living with rare diseases have reported that being affected by a rare disease has limited their professional choices and opportunities, as well as reporting their suspicions that employers are reluctant to hire them as a result of impairments associated with their conditions.[140] In this context, some in the rare disease community may be deterred from diagnosis-seeking by wider structural economic insecurity.

Specialised and Limited Testing

When people do seek testing and diagnosis, there is no guarantee that their insurance or healthcare system will reimburse them for it. It is known that in many healthcare systems, genetic and specialised testing are not automatically reimbursed, creating significant financial barriers.

Travelling to seek diagnosis, especially when living in rural, remote, or island regions, also contributes to higher costs with no guarantee of reimbursement. Travel will be necessary because of the importance of centralising rare disease care for consistency and quality purposes, and highly specialised testing cannot be delivered everywhere.

However, for some people living with rare diseases, the nearest specialist centre could be in another country entirely. Cross-border healthcare is not always available through telemedicine, and healthcare system frameworks may not allow reimbursed care delivered in or from another country. Without coordinated policy mechanisms, access to advanced diagnostics becomes dependent on geography and personal financial capacity rather than clinical need.

Referral and Specialist Consultation

Misdiagnosis and delayed diagnosis increase healthcare costs due to unnecessary treatments and disease progression, while early and accurate diagnosis can reduce long-term costs and improve outcomes. Delayed referral is not only a clinical inefficiency but also an economic one.

When specialist consultation access involves travel or telehealth usage, people facing conflicting work schedules, accessibility barriers or limited digital literacy – whether personally or their carers – may find it harder to access such care. Remote monitoring of disease can be effective for some people living with rare diseases, only when accompanied by proper training, accessible technology, and structured clinical guidance.

Continued from previous page

Patient Advocacy and Support

Patient advocacy groups often serve as a critical bridge between individuals and the healthcare system, providing guidance, peer support, information, and practical navigation during the diagnostic odyssey. In many countries, healthcare systems rely on patient organisations to fill systemic gaps without adequately supporting them.

These organisations are often run by members of the community,[141] who also care for themselves or their loved ones, and therefore may not have the resources or capacity to support everyone who needs their help. As a result, their capacity is frequently limited by volunteer burnout, unstable funding, and lack of institutional support.

Even larger patient associations can face challenges in securing the financing they need to hire enough staff, produce knowledge-sharing resources, and provide services.

Coverage and Reimbursement Hurdles

When diagnostic testing is costly, inconsistently reimbursed, or administratively complex, individuals are forced to weigh the personal financial risks of seeking answers. In such contexts, diagnosis becomes not only a clinical pathway but a financial calculation. Fear of insurance implications, employment discrimination, or uncovered testing costs can discourage timely diagnostic pursuit. This is not a reflection of patient indifference, but of system-level uncertainty about whether a diagnosis will translate into tangible support.

The structure of the healthcare system also affects payer and public perceptions of what constitutes an acceptable cost for rare disease diagnosis – with substantial differences between public health and insurance-based systems. Some systems, such as those in Europe, may offer cross-border healthcare that facilitates the movement of knowledge instead of people living with rare diseases.

> "Life insurance policies remain clueless about the prognosis of many rare diseases. Add in the effect a diagnosis can have on job prospects and economic security, and you begin to see how the social and economic dimensions of rare disease are just as urgent as the clinical ones."
>
> **Derek Yach**





Action for Change and How to Measure It

Socio-Economic Factors

- Ensure full implementation and financing of national rare disease laws and action plans: End the current situation in which families must pursue legal action to receive coverage for diagnosis or treatment that is guaranteed by law.
- Relevant measurements:
  - Percentage of people living with rare diseases and their family members who are unemployed, compared to the general unemployment rate.[158]
  - Percentage of people living with rare diseases and their family members citing the following factors as a reason for being unemployed:[159]
    - difficulty managing symptoms/medical appointments,
    - lack of work accommodations,
    - difficult labour market,
    - negative attitudes and stigma from potential or previous employers,
    - lack of training/career counselling/job guidance,
    - fear of losing financial benefits,
    - and caregiving responsibilities.
  - Percentage of people living with rare diseases reporting having experienced discrimination in employment because of their disease or impairment[160]
  - Percentage of people living with rare diseases who state the disease has:[161, 162]
    - Limited their professional choices,
    - Caused a decrease in their income,
    - Led them to reduce or to stop their professional activity,
    - Limited their chances of getting a job,
    - Limited their chances of promotion,
    - and prevented them from accessing higher education.
  - Economic inequity indicators within the diagnostic odyssey, including:
    - disparities by gender, ethnicity, geography, national income, and welfare system type in relation to:
    - access to testing,
    - access to specialist consultations,
    - out-of-pocket expenditure levels,
    - and access to financial protection mechanisms.

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Specialised and Limited Testing

- Harmonise and pool diagnostic resources across regions: Centralise expertise, promote consistent newborn screening and referral pathways, and foster testing standards to reduce inequality and improve diagnostic efficiency.
- Relevant measurements:
  - o Affordability and financial accessibility of diagnostic testing, measured by:
    - the percentage of people living with rare diseases who needed a genetic or advanced diagnostic test but could not access it due to cost or lack of availability (disaggregated by contextually relevant equity indicators).

Referral and Specialist Consultation

- Reform telemedicine access to rare disease specialists: Remove administrative, technical, and financial barriers to virtual cross regional consultations so expertise can reach people living with rare diseases, not the other way around.
- Relevant measurements:
  - Long-distance access to diagnostic services, tracked through:
    - the proportion of people living with rare diseases who accessed genetic testing, other diagnostic tests, or specialist advice (virtual or in person) in another region or country, disaggregated by contextually relevant equity indicators.
    - Time to referral for genetic testing services (virtual or in-person).

Patient Advocacy and Support

- Establish publicly funded patient navigation and case coordination services: Provide support for insurance authorisation, reimbursement steps, organising specialist appointments, and care coordination – especially critical for low income, rural, and underserved groups.
- Provide sustainable public investment in patient advocacy groups (PAGs): Recognise and fund PAGs as essential partners of the diagnostic ecosystem that deliver peer support, referral guidance, education, and help people navigate diagnosis and coverage systems.
- Relevant measurements:
  - Access to essential support services during the diagnostic odyssey, including the proportions of people living with rare diseases, disaggregated by contextually relevant equity indicators, who received:
    - adequate psychological support,
    - adequate care coordination/navigation support,
    - and adequate financial support.

Coverage and Reimbursement Hurdles

- Mandate insurance coverage for clinically indicated diagnostic tests: Ensure genetic, molecular, and advanced diagnostic testing is reimbursed so that the ability to pay does not determine whether someone receives a diagnosis.
- Relevant measurements:
  - Percentage of people living with rare diseases who reported that they or their family members had to cover some or all of the costs of tests and assessments.[163]

Case Studies

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Initial Presentation

Duchenne Muscular Dystrophy (DMD) is a rare genetic muscular condition which is diagnosed based on the clinical picture, family history and laboratory testing, with genetic testing as a gold standard.[142]

Diagnostic Odyssey

DMD has been **associated with high costs of delayed diagnosis,** both through medical costs and loss of productivity, amounting to nearly 100,000 USD per patient.[143] Reducing these diagnostic delays could potentially allow for reduced complications, in turn reducing the direct and indirect costs of DMD.[144] However, families have historically reported that they had to make a financial contribution to secure that diagnosis – which they saw as high or very high cost in 10% of cases.[145] Diagnosis delays mean missed opportunities for genetic counselling, starting the care pathways, and access to clinical trials and approved treatments.[146]

Opportunity for Change

Time from symptom onset to DMD diagnosis varies substantially between countries – ranging from 4.7 months in Germany to 26.4 months in the USA (potentially because of the size of the country, urban/rural disparities, lack of DMD knowledge among primary care providers, and (to a lesser extent) insurance coverage barriers).[147] Performance in the USA remained static over a 15-year period.[148] Muscle biopsy testing has been shown to be a very invasive method of diagnosing DMD,[149] and genetic testing is preferred in order to avoid invasive procedures and facilitate clinical trial enrolment. However, these techniques may not always be available for infrastructure or workforce reasons.



Outcome & Lessons

Integrating DMD considerations into routine childhood checkups can help detect the condition early, through encouraging clinicians to order relevant testing in children with developmental delay symptoms.[150, 151] As direct and indirect costs increase with disease progression in DMD,[152] earlier diagnosis and earlier intervention could help slow this progression[153] and the loss of muscle and motor skills,[154] mitigating some of the disease burden and the cost to the healthcare system.

Regrettably, diagnosis delays persist despite the availability of cost-effective tests and increased understanding of DMD. This understanding has not been disseminated widely enough to the public and primary care clinicians,[155, 156] and therefore, the condition is not always considered when assessing children with motor difficulties.[157] This is an example of the ways in which the Aspire4Rare archetypes interact with each other. Cost-effective diagnosis tools can reduce the economic impact of the diagnostic odyssey on families and healthcare systems, but only if they are effectively integrated into daily practice.

> "Healthcare systems should consider the efficiencies to be made if diagnosis is made more streamlined. By optimizing diagnostic pathways, we don't just improve patient outcomes – we ensure more efficient use of resources and release capacity to support other severe, debilitating conditions."
>
> **Sheela Upadhyaya**



Policy Implications

In this regard, healthcare systems should:

Integrate rare disease considerations into scheduled health checks for children and young people, as a way of raising awareness among primary care clinicians and encouraging them to include rare diseases in their regular analysis.

Implement suspected rare disease pathways that set out which tests to order and provide reimbursement for those tests, and have clear guidance on which first-line investigations to order and when to refer to Centres of Expertise.

Invest in the training and infrastructure necessary for access to these tests, in partnership with other regions or countries if required.



Standardisation of Diagnosis Process

This archetype focuses on consistency and systematic approaches to diagnosing rare disease. It has two key elements: clinical guidance and data harmonisation. Rare disease strategies are useful in supporting consistency across geographies, as they set out common baseline goals. Local areas can then implement shared priorities in line with their own needs and resource levels. These strategies also facilitate consistency in policy implementation and knowledge uptake – for example, through supporting the practical application of diagnostic guidelines (where available).

Challenges

Limited Awareness and Training

Diagnostic guidelines for rare diseases may not exist yet or lack wide dissemination. Even when guidelines exist, they may not be consistently implemented in clinical practice. Clinical guidelines, however, are also subject to fragmentation where different recommendations are made for the same disease, depending on the local clinical practice. They may also become outdated if no specific structures are put in place to routinely update them.

In addition to guideline dissemination, it may be useful to explicitly recognise gaps in rare disease education within undergraduate and postgraduate medical training. Limited exposure during medical education can contribute to delayed suspicion, misdiagnosis, and inconsistent referral to specialist centres.

> "We cannot accept a system where a child suspected of having TK2d receives a diagnosis in under three months at a specialized centre, while the same child seen at a peripheral hospital may wait years. Geography and socioeconomic status should never determine a patient's fate."
>
> **Serena Massucci**



Specialised and Limited Testing

Diagnostic processes are often fragmented, with inconsistent criteria and resource use across regions and healthcare systems. Specialised services may only be available in large academic centres to centralise expertise, and there can be a postcode lottery in referrals to tertiary care centres and newborn screening disease coverage.

Depending on which European country a baby is born in, they could be screened for anything from 2 to 48 diseases.[164] Where newborn screening does take place, ensuring an established infrastructure would be essential, to avoid lack of a coordinated diagnostic process in place following a positive result.

Technological and Logistical Challenges

Many rare diseases lack clear diagnostic criteria and standardised ICD10 codes on disorder level, impeding accurate diagnosis, tracking, and service planning. With the revision process leading into the ICD-11 disease identification system, 5,400 of the rare diseases listed in the Orphanet database have a unique identifier – 10 times more than under ICD10.[165]

Furthermore, rare diseases may not always be consistently recorded using the same disease code within electronic or manual health records. Different countries or institutions utilise different coding systems, despite the existence of Orphanet as a facilitator of consistent classification of diseases across care settings and countries.

Effort is ongoing in the ICD-11 update to integrate and standardise rare disease coding, although more work could be done in this area,[166] and practical uptake should be monitored and measured. It is also important to ensure that, when a diagnosis is obtained, this is correctly codified and updated in the patient's health records.

Integrating advanced diagnostics into routine clinical practice is also hindered by technical complexity and lack of interoperability. Diagnostic laboratory methodologies, clinical diagnostic criteria and clinical interpretation may vary from one organisation to another, and different countries will have different regulation and approval systems in place for diagnostic criteria, testing, and access to treatments.

Referral and Specialist Consultations

In the absence of a standard, consistent diagnostic process, referrals to a specialist centre will be inconsistent. Transitioning newborn screening programmes from pilot projects to population-level, for example, requires health ministry support to become part of the public healthcare system and secure consistent follow-up through routine care pathways.

Continued from previous page

Call-Out Box for Rare Disease Coding

Disease codes are used to classify and record medical conditions, with a specific number allocated to each disease. There are different coding systems, and ICD-11[167] is the latest global classification of disease, maintained by the WHO. These codes mean the same disease is recorded the same way across different healthcare systems, which supports accurate patient records and monitoring of disease prevalence.

In rare disease, consistent disease coding increases the visibility of these diseases for healthcare system planning purposes and makes it easier to identify health records for research. The ORPHAcode system is specifically designed for rare diseases and can be used in addition to other general coding systems. Orphanet is working to include specific rare disease codes in the ICD-11, while diseases not included can be referenced using ORPHAcodes.[168] ORPHAcodes are designed to work with and refer to other disease coding systems – for example, Dravet syndrome has an ORPHAcode of 33069[169] and an ICD-11 code of 8A61.11.[170]

Inconsistency in Guidelines and Clinical Pathways

In common diseases, clinicians typically develop sufficient expertise to discern how to tailor the care pathway to meet patients' unique needs. However, in rare diseases, one healthcare professional or institution will never see enough patient cases to develop the level of expertise required to facilitate precision medicine.

Systematic approaches, clinical guidelines, and structured care pathways would help support non-specialists by providing guidance. An ideal collaboration model would allow direct communication with specialists, helping to ensure coordinated care and avoid gaps in the diagnosis and treatment of rare diseases.

Furthermore, global efforts with expert representation from across countries would be the best approach to clinical guideline development and to prevent duplication of efforts by multiple research groups and medical societies. Supporting institutions to implement rare disease guidelines will require investment in training, funding, and oversight. At the same time, personalised medicine should be encouraged given the broad clinical heterogeneity across rare disorders.

Data Fragmentation and System Gaps

By the nature of rare disease, there are usually not enough people living with rare diseases in a single country to gather sufficient data for research purposes. Therefore, data need to be drawn from the wider global population of individuals living with the same rare disease. If different healthcare systems use different data standards, it is time-consuming and expensive to make them compatible with each other. It is also important to establish consistent, interoperable, disease codes for each rare condition.

People living with rare diseases tend to be more willing to share their health data than the general population,[171] given the fact that rare disease communities are inherently small and spread across borders. Establishing datasets that are large enough to act on will therefore involve cross-border data transfer and storage.

Differences in data privacy regulations between countries often complicate the startup and management of global registries for specific rare diseases. Sharing data between institutional and national systems also requires use of a common or mutually intelligible data format, and standardisation challenges persist in this area. Harmonised rare disease registries, including both clinical registries and patient-reported outcome registries, could support standardisation of diagnostic processes, improve monitoring of diagnostic pathways, and help assess quality of life and diagnostic odyssey outcomes across populations.

Resource Gaps and Implementation Barriers

Despite efforts to reduce inequalities and provide a more consistent care experience for people living with rare diseases, disparities persist between and within countries.

Prioritisation of rare disease policies differs across countries. Some regions still need to focus on establishing the baseline infrastructure and reimbursement policies before they consider adopting the standard processes of other countries that may be further established.

It may not be possible to implement a single global standard for genetic testing that works for all countries regardless of income. As such, recommendations for policy change in rare disease should provide opportunities and options for countries with differing economic capabilities and ways of allocating limited resources.

Action for Change and How to Measure It

Disclaimer: We appreciate that there may be region-specific limitations and barriers related to available resources within a region, state or country. Partnership with neighbouring countries would be encouraged in the global effort of equitable access to care.

Limited Awareness and Training

- Improve knowledge sharing between rare and non-rare disease experts, ensuring clinicians and patient groups can access updates on new diagnostics and learn from other rare conditions and innovations beyond the rare disease field.
- Relevant measurements:
  - Number and membership size of shared platforms, networks, or communities of practice that enable ongoing exchange of diagnostic updates, innovations, and lessons learned across disease boundaries.
  - Number of formal cross-disciplinary educational events, training programmes, joint grand rounds, webinars, or conferences held per year:
    - Participation figures disaggregated by:
    - rare disease clinicians,
    - non-rare disease clinicians,
    - researchers,
    - and patient groups.

Specialised and Limited Testing/ Resource Gaps and Implementation Barriers

- Ensure universal, consistently funded newborn screening and integrate validated rare disease screening tools and family history protocols into routine care. Additionally, broadening screening panels and integrating newer diagnostic technologies could improve cost efficiency and scalability. Technological innovation could also help make expanded screening more sustainable and accessible across different healthcare system contexts.
- Harmonise laboratory testing protocols by adopting internationally standardised methods for test performance and interpretation, supporting quality, comparability, and insurance coverage.
- Relevant measurements:
  - Performance of standardised care pathways, including:
    - care pathway outcomes (e.g., proportion of patients receiving diagnostic assessment within recommended timelines),
    - diagnostic yield indicators (e.g., rate of confirmed diagnoses),
    - and patient reported outcomes linked to the quality and consistency of diagnostic processes.

Technological and Logistical Challenges

- Embed telemedicine and clinical decision support tools into everyday practice to reduce regional disparities and strengthen early suspicion of rare diseases within the limitations of clinical practice and licensing.
- Relevant measurements:
  - Availability of holistic services linked to diagnosis and follow-up, measured by:
    - the proportion of patients who were offered psychological support, care coordination, and follow up services (e.g., support within 10 working days of referral, home visiting, care passports) across demographic groups and diagnosis contexts (virtual/in-person).

Referral and Specialist Consultations

- Expand multidisciplinary diagnostic models by funding reference networks and clinics that offer coordinated, single visit assessments supported by care coordination roles.
- Relevant measurements:
  - Equitable access to specialist diagnostic services, tracked through:
    - Percentage of patients appropriately referred to rare disease centres,
    - Percentage of referred patients with confirmation of diagnosis,
    - and percentage of patients with access to genetic testing (where deemed appropriate).

Inconsistency in Guidelines and Clinical Pathways

- Standardise diagnostic pathways and criteria, ensuring their consistent application through nationally agreed algorithms, clear diagnostic criteria, and harmonised reporting standards for next generation sequencing.
- Relevant measurements:
  - Development and uptake of standardised diagnostic tools, measured by:
    - the number of Clinical Practice Guidelines,
    - diagnostic algorithms,
    - consensus statements,
    - and other decision making tools.
  - developed, updated, adopted, and used across expert networks across rare disorders.
  - Timeliness and consistency of diagnostic reporting, including:
    - pathology turnaround times
    - and the proportion of patients receiving essential diagnostic documentation such as alert cards.

Data Fragmentation and System Gaps

- Facilitate the adoption of Orphacodes and interoperable data standards to enable consistent recording, tracking, and use of diagnostic information.
- Relevant measurements:
  - Implementation of standardised coding and tracking systems, reflected in:
    - consistent use of rare disease coding (e.g., Orphacodes / ICD-11)
    - and the proportion of patients accurately recorded and traceable across the healthcare system.

Case Studies

PHENYLKETONURIA (PKU)

Initial Presentation

Phenylketonuria (PKU) is a rare inherited metabolic disorder[172] in which the person has difficulty breaking down the amino acid phenylalanine because of an enzyme deficiency. High levels of phenylalanine (Phe) in the blood are linked to neurological symptoms, and untreated PKU can cause irreversible brain damage.[173]

Diagnostic Odyssey

Detecting this disease early makes it possible to avoid such damage, and so it is generally diagnosed through newborn screening.[174] Delayed diagnosis, however, is still possible in people who were born before screening was implemented or who were born in countries without universal PKU screening.[175] The main treatment for PKU is a restricted diet to minimise Phe levels, with some medications available, and early intervention means the majority of people living with PKU can retain normal intellectual ability and a good quality of life.[176]

Opportunity for Change

Since the discovery of a quick and cost-effective method of screening for PKU in 1963,[177] it has been available in many countries for over fifty years.[178] This newborn bloodspot screening, however, is not universally available around the world.

Some countries are yet to implement it, while others have only done so recently or may have organizational gaps in the screening programme.[179] Switzerland and Ireland, for example, are among the earliest adopters of PKU screening (1965 and 1966, respectively), while Malta began screening in 2018 and Mauritius implemented nationwide screening in 2019.[180] As of 2021, Malta did not have mandatory PKU screening in place.[181]



Outcome & Lessons

PKU is a rare disease that can be routinely and easily screened for, with multiple available pharmaceutical and non-pharmaceutical treatment options. As such, although unmet needs do persist among people living with PKU, it demonstrates what is possible when scientific developments become the standard diagnosis procedure. Where PKU diagnosis is delayed, it is primarily due to geographical gaps in screening coverage or being born prior to the introduction of screening.[182]

> "The science, policy frameworks and patient evidence are increasingly available. The next step is to translate them into healthcare system reform: ensuring equitable access to genomic testing, embedding psychosocial support throughout the diagnostic pathway, and recognising rare disease diagnosis as a public health priority."
>
> **Vinciane Quoidbach**



Policy Implications

The following policies can help healthcare systems secure true universal access to diagnosis for rare diseases like PKU:

Collaboration between countries for laboratory use can assist low-income countries in implementing universal screening for PKU.[183]

Areas with small populations or insufficient resources to carry out newborn screening can similarly benefit from partnering with their neighbours.[184]

To facilitate such partnerships, bilateral and multilateral agreements on governance frameworks and implementation models should address practical challenges including data privacy regulations, informed consent limitations, and logistical difficulties related to cross-border biological sample exchange.

It is critical that positive results are followed up, and the patient is referred to specialist care.[185]

However, awareness and education efforts for healthcare professionals should also stress that delayed diagnosis of PKU remains possible among those who have not had access to screening programmes.[186]

Case Studies

DRAVET SYNDROME

Initial Presentation

Dravet syndrome[187] is a rare, severe developmental and epileptic encephalopathy that typically begins in a normally developing infant around the age of 6 months with prolonged seizures, often associated with fever, or illness. Within a few years, most children will have therapy-resistant epilepsy and moderate or severe intellectual disability. Yet, despite increasing awareness and the availability of genetic testing, diagnostic delays and misdiagnoses remain widespread, exposing families to avoidable harm and uncertainty. The majority of medicines normally used to treat seizures provide limited clinical benefit in Dravet,[188] and some treatments can even exacerbate them.[189]

96.2% of parents of children with Dravet syndrome reported[190] that symptoms began in the child's first year of life. However, neurological examinations, scans, and tests may appear to have normal or non-specific results,[191, 192] which can lead clinicians to decide these symptoms reflect simple or complex febrile seizures or more common childhood epilepsies.[193] If Dravet syndrome diagnosis is not considered, opportunities for early intervention may be lost.

Diagnostic Odyssey

As such, the diagnostic odyssey for people living with Dravet syndrome is often long and complicated. A 2024 caregiver survey showed that 72.7% of participants had experienced at least one misdiagnosis, and only 6.6% received a diagnosis from the first doctor consulted. 65.1% had to consult with 2-4 specialists, and 22.8% saw more than 5 specialists.[194] As this disease begins in infancy, each additional specialist visit represents more time taken off work for the parents, often repeated unnecessary investigations and an increased burden of care coordination. Nineteen point eight percent (19.8%) of respondents sought help abroad during the diagnostic process, and 31.2% had to privately fund the diagnostic tests received[195] – adding to the bureaucratic and economic challenges these families face in the diagnostic odyssey.

The length of the diagnostic odyssey varies across countries. In the 2024 survey[196], conducted in Poland, 23.5% of participants received a diagnosis in the first year of their child's life, 45.3% between 1 and 3 years old, 22.7% between 4 and 10 years old, and 8.5% after the age of 11.[197] A literature review of articles on Dravet syndrome diagnostic outcomes from Europe, Asia, North America, South America, Africa, and Oceania found an average age at diagnosis from 1.6 to 9.2 years old.[198] Such delays lead to avoidable harm and inappropriate care. 67% of caregivers in the 2024 study reported their relative had taken unnecessary or contra-indicated medicines as a result of misdiagnosis, for example sodium-channel blockers which may exacerbate seizures. Additionally, 32.1% experienced unnecessary hospitalisations, 15.1% received unnecessary tests, treatments or surgeries, and 58.4% believed the overall delay negatively affected their child's health.[199]



Call-Out Box on the Use of/ Implementation of Diagnosis Guidelines

Although clinicians are likely to encounter people living with a rare disease in the course of their careers, the diseases are individually rare. It is not possible for most clinicians to develop practical experience in diagnosing and treating rare diseases in the same way they would do with more common ones. However, those clinicians working in centres that handle national or regional rare disease referrals do have the opportunity to see many patients with those specific conditions – and can work together to share their experiences with others in the form of guidelines.

These are often written by medical societies, and so may not be widely accessed by non-members of that society. It is also possible that medical societies in different countries may duplicate this work for their national context, reinforcing geographic inconsistencies in diagnosis processes for the same disease. The European Reference Networks have sought to address this issue through creating clinical pathway recommendations[216] together. Dissemination of these recommendations from specialist to generalist practice remains challenging. In France, National Diagnosis and Care Protocols (PNDS, in French)[217] are good-practice reference points for rare diseases, created by specialist centres and hosted by the Haute Autorité de Santé (a public body responsible for Health Technology Assessment). These are accompanied by summaries directed at general practitioners,[218] with guidance on the actions they can take.

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Opportunity for Change

Genetic testing, alongside clinical recognition, is key for shortening the diagnostic odyssey in Dravet syndrome. Over 85% of cases are associated with disease-causing changes to the SCN1A gene,[200] and so, clinical guidelines recommend genetic testing for suspected Dravet regardless of the patient's age.[201] 87% of people whose children had a positive genetic test found it helpful in explaining their child's epilepsy, and 55% said it led to a change in treatment. 69% of those whose treatment changed reported fewer seizures, and 34% of this group saw their child's developmental progress improve. From a medical professional position, clinicians reported testing confirmed a clinical diagnosis in 45% of cases and allowed a diagnosis to be made earlier in 48% of cases. It also avoided additional investigations (67% of cases), changed the treatment plan (69%), and helped with medication choice (74%).[202]

In 99% of cases, genetic testing helped doctors manage Dravet syndrome.[203] Unfortunately, access to this testing is inconsistent. Families experience challenges in accessing genetic counselling and long waits for testing and interpretation of results. Some healthcare system delays occur even when testing is recommended, where clinicians delay ordering the tests until multiple seizure types or developmental delays are evident.[204] At that point, valuable time has been lost.

The impacts of delayed diagnosis can persist into adulthood. A UK genomic study found that some people with unexplained chronic epilepsy were not diagnosed with Dravet syndrome until they were adults, with a median age of 44.5 years at genetic confirmation.[205] This illustrates persistent, systemic gaps in diagnostic pathways for children and adults living with Dravet syndrome.

Efforts are being made in the Dravet community to fill in these gaps. Guidance exists both internationally[206] and in Europe[207] to develop life-long care pathways, setting out a clear framework for diagnosis and management. These documents formally integrate genetic testing early on in the care pathway and integrate wider support services. Additionally, a study from the Boston Children's Hospital has demonstrated the impact guideline implementation can have on outcomes for people living with Dravet syndrome. Following new consensus guidelines in 2018, there was a significant decrease in the time between first seizure and genetic testing, compared to those who had their first seizure before 2018.[208] Practices in this hospital also reflected a more holistic approach to Dravet syndrome, with all patients receiving a seizure action plan and the majority being evaluated for developmental delay and neurodevelopmental conditions.[209]

> "The high cost of genetic testing is an overwhelming barrier. Many samples collected in Latin America must be sent to high-complexity laboratories in Europe or the United States for analysis, and regional healthcare systems often prevent specialists from ordering these tests freely because of the expense."
>
> **Nohora Ramirez**



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Outcome & Lessons

These experiences of misdiagnosis and avoidable harm in Dravet syndrome carry key lessons for clinicians and decision makers. It is essential to pick up on the red flags[210, 211] of Dravet syndrome early to differentiate it from self-limited febrile seizures. However, the preventable harm arising from delayed diagnosis is a structural issue which cannot be addressed by individual clinicians. Misdiagnosis, repeated referrals, and exposure to contraindicated medicines[212] arise systematically and predictably across geographies.

Nationally consistent pathways should be designed and implemented to tackle these dynamics, and genetic testing should form part of standard clinical pathways for infants with prolonged or recurrent febrile seizures.[213, 214] They should also include counselling, psychosocial support, information resources and care coordination, so people living with Dravet syndrome are not left to handle the diagnosis alone. Additionally, pathways also need to be in place for detecting Dravet syndrome later in life – including for adults[215] with long-standing epilepsy.

> "Rare disease diagnosis is the stress test that no healthcare system wants to take – and every healthcare system is failing. It reveals with painful clarity that where you live, what you earn, and who you are still determine whether you receive a timely diagnosis or endure years of preventable suffering."
>
> **Maurizio Scarpa**



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Policy Implications

To ensure the best possible outcomes for both children and adults living with Dravet syndrome, healthcare systems should:

- Implement "Dravet suspicion triggers" across primary, emergency, and paediatric services to prompt early referral and genetic testing.
- Establish rapid-access genetic testing pathways for infantile onset epilepsy or following the first prolonged febrile or afebrile seizure.
- Ensure every suspected or confirmed case has a named care coordinator, reducing fragmentation.
- Mandate bundled diagnosis support packages, including genetic counselling and psychological support.
- Create an adult epilepsy genomics pathway to identify missed or late-diagnosed cases.
- Monitor diagnostic timeliness as a performance indicator across integrated care systems.



Advancing Research to Provide Answers

This archetype looks at translating research into practice and making sure insights from clinical practice translate back into research (and vice versa). Where research teams and clinicians work in silos, this can result in missed opportunities for mutual learning. Often, new findings and approaches are not disseminated to the wider primary care community and to affected people living with rare diseases.

By definition, diagnosing specific rare diseases will be an infrequent occurrence in the course of a medical career. Clinicians can expect to develop personal experience of diagnosing common conditions but will be more reliant on literature and the experiences of others when it comes to rare diagnoses. Therefore, carrying out and disseminating clinical research on rare disease diagnosis are essential in training the wider workforce.

Challenges

Research and Knowledge Gaps

The clinical diagnostic, phenotype and natural history of rare diseases is less understood as compared to more common disorders. Causal genetic etiologies are not yet known for a substantial fraction of rare diseases. Likewise, clinically meaningful diagnostic biomarkers are less likely to be established. In general, further research is needed to advance better understanding in the rare disorder field.

As such, HCPs are less likely to be trained in the interpretation of diagnostic test results of a rare disease diagnosis.

Genetic and Family History Factors

Careful collection of family history and genetic information is important for diagnosing rare diseases. It can help identify inheritance patterns, support earlier and more accurate diagnosis, and determine whether a person may be eligible for specific treatments or clinical trials. In community settings, family history data can also serve as a useful complement to the electronic health record.

Rare diseases may have different sub-groups of patients with differing symptom severity and symptom combinations. Data collection on the various symptoms over time facilitates a more complete understanding of the natural history of disease and identification of sub-groups of patients that diverge from the standard disease course. Knowledge of these subgroups can improve clinical diagnosis by helping clinicians recognise atypical forms of the disease and make more accurate diagnostic assessments.

Referral and Specialist Consultations

Tight collaboration between research clinicians and generalist healthcare professionals is essential for integrating advances in rare disease research into everyday care. This requires well-defined referral pathways, reciprocal communication, and shared access to relevant clinical information. In the absence of these links, people living with rare diseases may return from expert centres to local healthcare systems that are unaware of their diagnosis and unsure of how to best treat or support them.

Limited Awareness and Training

Research findings are often not translated into clinical practice due to a lack of data sharing, insufficient funding, and limited documentation of rare diseases. Standardised diagnosis criteria based on the latest high-quality evidence and dissemination of knowledge through medical education is necessary, to ensure research advances benefit patients in real-world settings.

When research is conducted in the same clinical setting in which standard care is delivered, it becomes easier to link research activity with routine patient management. This can improve the collection and use of real-world evidence, including patient-reported outcomes, which remains underused in both research and clinical care for rare diseases. To ensure that new knowledge is translated into practice, there must also be investment in processes for regularly reviewing and updating clinical guidelines in light of emerging evidence.

Technological and Logistical Challenges

As technology advances, training helps people get accustomed to using it and implementation frameworks define its role in systems of working. In the absence of planning and education, it is difficult to promote uptake of the latest innovations (such as AI and genetic testing). To bridge the gap between research and clinical diagnosis, investment in diagnostic infrastructure and respective workflows is key – alongside data sharing, multidisciplinary teams, and advocacy for such investment.

However, we must also remember that biases built into existing data will also be built into AI-powered tools. As of 2016, people of European ancestry accounted for 81% of individuals in genomics studies. In comparison, people of Asian ancestry accounted for about 14%, and people of African ancestry around 3%.[219] Research funders must address this imbalance, as it has worsened for some groups over the almost 10 years since.[220]

Additionally, standard diagnostic pathways may not reflect the realities of rare diseases, where small patient populations, variable presentations, and limited validated tools can make diagnosis difficult. In practice, diagnosis often requires combining multiple forms of evidence, including clinical assessment, family history, longitudinal data, and genetic findings. These challenges are even greater in ultra-rare conditions, where the scarcity of cases can make it difficult to define and apply clear diagnostic criteria.

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Gaps in Translating Research Knowledge

From a researcher perspective, funding gaps can arise between discovery and implementation of findings. If grant funding comes to an end before the healthcare system has adopted the new diagnostic approach, it is difficult to maintain the infrastructure and project knowledge for long enough to translate the research into clinical practice without an additional source of funding to bridge the gap.

On the clinical side, the inherently low prevalence of rare disease cases, and the low likelihood of encountering one in practice, exacerbate challenges in translating research knowledge. As there are fewer opportunities to learn about rare disease developments as part of day-to-day work, interested individuals may proactively seek them out while the wider clinical community engages less actively with rare diseases.

> "The resolution of challenges in rare disease cannot be done in isolation. It requires all system players – primary care, specialists, policymakers, educators, researchers – to come together and deliver on their responsibilities. And the lessons we learn here will have impact far beyond rare disease, informing how we tackle other complex healthcare challenges."
>
> **Sheela Upadhyaya**



Call-Out Box

Additionally, the World Medical Association's 2024 Declaration of Helsinki[221] has spelled out that exclusion of individuals, groups and communities in situations of vulnerability, with distinctive health needs, can reinforce or even worsen health inequalities. As such, the Declaration states that the harms of research inclusion and research exclusion must both be considered and balanced against each other. Participants must also stand to benefit from the results of such studies, which should respond to their needs and priorities.

This represents an effort[222] to address delayed access to effective treatments among such individuals, groups and communities and actively include research participants in designing and planning research studies. People living with rare diseases have long advocated for their involvement throughout the research process, and this recognition presents another opportunity to design and participate in medical research of importance to individuals, groups and communities living with rare diseases.

Action for Change and How to Measure It

Research and Knowledge Gaps

- **Invest in natural history studies and high quality rare disease registries** to improve understanding of disease progression, refine diagnostic criteria, and accelerate discovery of diagnostic biomarkers.
- **Build local research capacity** by investing in training programmes for clinicians and scientists, enabling locally driven solutions and more effective engagement with policymakers and communities.
- Relevant measurements:
  - Research activity and collaboration within expert networks, measured by the number of studies, data collection initiatives, and peer-reviewed publications involving expert network members that contribute to improved understanding of rare disease diagnosis, including diagnostic pathways, biomarkers, genotype–phenotype correlations, and validation of diagnostic tools, and that acknowledge their contribution.
  - Growth and completeness of rare disease registries, including the number of new patients uploaded to expert network managed registries and the proportion of all patients within the network who are represented in those registries.

Genetic and Family History Factors

- **Expand global equity in genomic data generation,** including targeted funding to increase African genomic representation through international, multi country research partnerships.
- Involve people living with rare diseases and their families in all aspects of the research process from design to implementation.
- Relevant measurements:
  - Genome Wide Association Study Diversity Monitor.[266]
  - Percentage of people living with rare diseases that report positive experiences of research participation.[267]
  - Percentage of people living with rare diseases who feel insufficient dialogue between patients, scientists and clinicians is a main barrier to rare disease research.[268]

Referral and Specialist Consultations

- **Create pathways for undiagnosed patients to transition into research pipelines,** ensuring those who exhaust standard diagnostic routes are systematically assessed through advanced or research based methods.
- Place undiagnosed disease programmes on a stable financial footing and integrate them into the wider healthcare system to facilitate referral.
- Support cross-border engagement between undiagnosed disease programmes, to maximise the opportunity of finding answers and identifying other patients with the same condition.
- Relevant measurements:
  - Integration of research into diagnosis pathways, assessed through indicators such as:
    - the percentage of undiagnosed cases referred into
    - research programmes,
    - registry supported diagnostic re analysis,
    - or advanced investigative workflows.

Limited Awareness and Training

- Cooperate with NGOs, charitable funds, and the private sector to supplement public funding for rare disease through additional investment.
- **Increase inclusion of underrepresented populations** in research by reducing participation barriers, embedding community engagement, and addressing diagnostic bias in study design and recruitment. Complementary, national, large-scale genetic diagnosis programmes can benefit a wider group of people living with rare diseases.
- Relevant measurements:
  - The proportion of people with a rare disease that are eligible for clinical research and are offered the opportunity to take part.[269]

Technological and Logistical Challenges

- **Develop secure, curated data repositories for rare disease research,** enabling ethical storage, aggregation, and reuse of diverse datasets to support discovery and improve diagnostic accuracy.
- **Address infrastructure gaps in diagnostics, providing hospitals and research centres with the equipment, funding, and know-how they need to facilitate genetic and non-genetic rare disease diagnosis. This should also provide for adoption of new, more accurate, technologies.**
- Relevant measurements:
  - Use of standardised coding systems in research and clinical practice, tracked through:
  - adoption of Orphacodes (or ICD 11 equivalents) for coding and classifying rare disease cases across centres participating in research pipelines.

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Gaps in Translating Research Knowledge

- Promote innovative approaches to developing and validating rare disease diagnostic tools, and ensure that regulatory, health technology assessment, and reimbursement frameworks are adapted to the realities of small patient populations, heterogeneous presentations, and limited evidence bases.
- Provide for reimbursement of advanced diagnostic techniques to facilitate the establishment of undiagnosed disease programmes.
- Relevant measurements:
  - Knowledge generation and translation into practice, measured by:
    - updates to diagnostic guidelines informed by research findings,
    - uptake of research generated biomarkers or diagnostic tools,
    - and the percentage of clinicians using evidence derived from registry based or network based research.

Case Studies

UNDIAGNOSED DISEASES/SYNDROMES WITHOUT A NAME (SWAN)

Initial Presentation

Some people living with rare diseases have conditions that cannot (currently) be diagnosed. These may be referred to as undiagnosed rare diseases, or as Syndromes Without A Name (SWAN).[223] Some of these conditions are ultra-rare and may not have been seen before, while others have been documented but clinicians may not be aware of them.[224] It is also possible someone may have symptoms that are not 'usual' for their rare disease.[225] Additionally, sometimes technology is not advanced enough to determine what is causing someone's symptoms or we may not know if changes identified through genomic testing can cause disease.[226]

> "We need to distinguish between the clinically undiagnosed and the circumstantially undiagnosed. Some patients remain without a diagnosis despite being fully sequenced – because the biomarkers, the definitive gene, the interpretation capacity simply don't exist yet. Others haven't been diagnosed because they can't afford the test or can't access it. These are fundamentally different problems requiring fundamentally different solutions."
>
> **Kelly du Plessis**



Diagnostic Odyssey

The lack of a specific named diagnosis exacerbates the uncertainty involved in living with a rare disease, in the absence of information and community[227, 228] where specific rare disease groups may provide support with some aspects of the condition but not others.[229] It also exacerbates the burden of care coordination given the number of specialists and referrals involved,[230, 231] and impedes access to support pathways designed for those with a named condition.[232, 233] There is also substantial frustration and emotional impact involved in the diagnostic odyssey, with new tests bringing validation that something was wrong but disappointment when they did not provide answers.[233] Arriving at participation in undiagnosed disease projects often involves recognition that all other options have been exhausted.[235]

Opportunity for Change

Such undiagnosed disease projects can help provide answers by reassessing cases in the light of new knowledge. Solve-RD,[235, 236, 237] for example, reanalyses genomic data[239] to find new diagnoses in previously undiagnosed cases.[240] It involves over 300 clinicians, laboratory geneticists and translational researchers based in 12 European countries and Canada. Its reanalysis infrastructure allowed for a genetic diagnosis in 8.4% of families, around 500 diagnoses in a cohort of 6,000 families, and ad-hoc review in parallel diagnosed an additional 4.1% for a total diagnostic yield of 12.6%.[241] Several countries have implemented undiagnosed disease research networks that can support diagnosis. The Undiagnosed Diseases Network International was based on the United States Undiagnosed Diseases Network[242], and multiple other similar initiatives exist globally: Western Australia[243], Italy[244], Japan[245], France[246], United Kingdom.[247, 248] The patient-led Undiagnosed Disease movement is also introducing positive healthcare changes for undiagnosed rare disease patients. The US-based Undiagnosed Diseases Network Foundation offers a Patient Navigation Programme which assisted over 206 patients through the diagnosis process in 2024[249].

Additionally, Objetivo Diagnóstico in Spain is an association of undiagnosed people[250] that works with the national undiagnosed cases programme[251] and has an agreement[252] with the CIBER de Enfermedades Raras (CIBERER) network of research groups and clinics to allow its members to participate in the CIBERER clinical database of cases[253] without a genetic diagnosis after all avenues have been exhausted.

The Undiagnosed Hackathon is a Wilhelm Foundation programme[254] to bring together multidisciplinary teams to examine case studies of people who have gone through existing testing pipelines without a diagnosis. The first edition involved 10 cases with 40% receiving a diagnosis, and the second involved 42 cases with 24% receiving a definitive diagnosis and 21% a likely diagnosis requiring follow-up, for a total of 45%.[255]

Outcome & Lessons

Undiagnosed disease programmes have real potential to help people bring their long diagnostic odysseys to an end. However, to make this a reality, access issues must also be addressed. People who participate in such programmes have exhausted all the other options open to them – and not all options are open to them.

For example, a study of US Undiagnosed Diseases Network (UDN) patients[256] who experienced insurance coverage barriers to whole-exome sequencing (WES) found that a substantial proportion could have been diagnosed earlier if it had been financially possible to access clinical WES.

Identifying potentially disease-causing results on genomic testing also requires prior research into the significance of variants. In under-resourced areas, such research is less likely to have taken place. The information we have on variants will therefore be skewed towards groups who live in well-resourced areas.

The Rare Disease Working Group of the Human Heredity and Health in Africa Consortium (H3Africa) is frequently contacted by international researchers and clinicians. H3Africa has been able to tell Canadian clinicians about the novelty and rarity of variants in their dataset in order to support diagnosis in patients of African origin, but underrepresentation makes it harder to reach a molecular diagnosis in this group and risks misclassification of variants as (potentially) pathogenic because they are not present or are rarely found in reference databases.[257]

Efforts have been made to expand the amount of data available for research. In South Africa, the Nngwe Project[258] is a government-funded network of professionals working on improving care for people living with rare diseases. The project provides them with resources, training, and infrastructure to support their work.[259] As of November 2024[260] it has enrolled 131 participants (individuals being tested, family members, and controls). 109 have been enrolled in a biobank for long-term research, and over 30 clinicians and researchers contributed directly. The European Commission-funded Share4Rare online platform[261] attracted users with 622 unique conditions from over 200 countries[262] and this led to 8 studies including more than 50 rare diseases[263], including one for the undiagnosed community[264], 22 registries, and 22 new research proposals.[265]

> "Living in diagnostic limbo – where your condition is 'suspected,' 'possible,' or 'not yet classifiable' – is not a bureaucratic inconvenience. It is a source of chronic stress, identity confusion, and social invisibility. Yet almost no system provides mental health support for those in the middle of that journey."
>
> **Stelios Kympouropoulous**



Policy Implications

In order to give people living with undiagnosed rare diseases/Syndromes Without A Name the best chance at diagnosis, healthcare systems should:

- Provide for reimbursement of advanced diagnostic techniques.
- Ensure that undiagnosed disease programmes have a stable financial footing and are well-integrated into the wider healthcare system to facilitate referral.
- Support cross-border engagement between undiagnosed disease programmes, to maximise the opportunity of finding answers and identifying other patients with the same condition.
- Instigate and invest in efforts to identify genomic variants of potential significance, particularly in partnership with underrepresented communities.
- Remove bureaucratic barriers to rare disease community support services for people without a named condition.

Regional Call-Outs

Aspire4Rare Diagnosis – Europe Lens

Each region contributes distinct insights that enrich the global diagnosis framework. In Europe, the evolution of the European Reference Networks (ERNs) and broader EU-level initiatives serves as a real-world example. These efforts address the challenges found across several archetypes, particularly in awareness, access to expertise, technology adoption, dynamic diagnosis throughout the patient journey, and standardisation. This callout distills the most relevant European developments and policy needs, showing how regional experience can shape practical, scalable solutions within the Aspire4Rare Diagnosis framework.



Executive Summary

The European Reference Networks (ERNs) have been life changing for people living with rare diseases in the European Union and beyond. They bring specialist knowledge directly to patients instead of requiring people to travel across borders, and they underpin research that expands understanding of rare diseases and informs the development of diagnostic and care pathways.

In practice, ERNs help operationalise timely diagnosis by linking primary care clinicians to Centres of Expertise, enabling virtual multidisciplinary case review, supporting registries and natural-history research, and promoting more consistent diagnostic pathways across countries.

To sustain and strengthen this impact, ERNs require long term, stable funding in the EU budget and in national financing frameworks, ensuring Europe can continue to advance innovation and equity in rare disease diagnosis.

The Challenge

Around 30 million people in Europe[270] live with a rare disease, dispersed across countries and regions. This means individuals may be far from specialist expertise or peers with the same condition, reinforcing the need for cross border clinical cooperation.

The creation of the **European Reference Networks**[271], connecting specialist centres with each other and the wider healthcare system, aimed to meet this need. Such networks can tackle the issue of low patient numbers by bringing the wider community together. This provides a platform for expertise-sharing, data collection, research, and patient advocacy – all of which support timely diagnosis.

Their impact, however, depends on strong national implementation: patients must be referred into ERN-linked expertise in time, clinicians must be supported to participate, and recommendations must flow back into local care pathways, health records, and follow-up services.

This is especially important for undiagnosed adults and for people transitioning from paediatric to adult services, where expertise and continuity are often lost.

However, funding lines for the European Reference Networks (ERNs) have been spread across various EU programmes. ERN coordinators have reported sustainable funding access is one of their top two challenges, and they face the burden of repeatedly applying for Commission funding calls. This is a particular challenge for the ERN registries, which are vital for understanding and researching rare diseases.[272]

Additionally, virtual consultations with rare disease experts are often considered to be 'voluntary' and the time spent on them is not reimbursed – making it much more difficult for clinicians to take part. National-level funding is also essential for ERNs to carry out their work.[273, 274]

The Benefits

The ERNs have reviewed over 2650 patients[275] through their central Clinical Patient Management System – which represents almost 3000 people who got access to European expertise without having to travel. 416,000 people were referred to the ERNs in 2024, a 160% increase on 2018[276] – demonstrating a growing awareness and accessibility of these networks over time. 100% of ERNs received a satisfactory result in the 2024 evaluation of their work – with 92.42% of these receiving an 'excellent' or 'very good' rating.[277]

It must be noted that these results took place in a period of great stress for the healthcare system. ERNs were integral in supporting[278] people living with rare diseases during the COVID-19 pandemic: providing helplines, producing advice for other clinicians, and conducting studies on vaccination in people living with rare diseases. They also came together to support 2 million Ukrainians living with a rare disease, receiving almost 300 referrals in the first three months of Russia's full-scale invasion, establishing a framework for advising Ukrainian clinicians, and evacuating children with rare cancers.[279]

Beyond case review volumes, ERNs help standardise diagnostic approaches, connect patients to registries and research, and create value even where no disease-specific treatment yet exists–through diagnostic validation, better care planning, family counselling, and readiness for future clinical trials. They also provide a structure for revisiting unresolved or evolving cases as diagnostic criteria and scientific knowledge change.





Call to Action:

01 **Recognise and reward** the exceptional work of the ERNs – demonstrated even during pandemic and conflict – through strengthened support at both EU and national levels.

02 **The European Union should ringfence funding** for ERNs and rare disease activities on an ongoing basis,[280] ensuring long term sustainability.

03 **Member States should complement this by embedding ERNs into national diagnostic pathways:** reimbursing clinician participation in virtual consultations, integrating ERN outputs into interoperable records and registries, supporting referral and return pathways between local services and Centres of Expertise, and maintaining continuity across paediatric and adult care.

Aspire4Rare Diagnosis – Latin America and the Caribbean Lens

Each region contributes distinct insights that enrich the global diagnosis framework. In Latin America and the Caribbean, a highly heterogeneous region in terms of healthcare system capacity and access to diagnosis, expert groups of clinicians and patients have generated evidence on rare disease diagnosis and proposed pragmatic approaches adapted to available resources. These efforts address the challenges found across several archetypes, particularly regarding the social context and the economic aspects of diagnosis. This callout describes these initiatives, showing how regional experience can shape practical, scalable solutions within the Aspire4Rare Diagnosis framework.



Executive Summary

As part of the Enfermedades Raras en el Caribe y América Latina[281] (ERCAL) initiative, in Latin America and the Caribbean, a highly heterogeneous region in terms of healthcare system capacity and access to diagnosis, medical and research experts from Argentina, Brazil, Chile, Colombia, and Mexico work together to address the gaps and barriers to accessing genetic testing for the diagnosis of rare diseases in Latin America and the Caribbean. Such expert panels serve as a platform for further action across the region, and can provide relevant lessons for other resource- constrained settings, although implementation remains highly country-dependent.

On the patient advocacy side, the Ibero-American Alliance for Rare, Orphan or Infrequent Diseases[282] (ALIBER) brings together more than 700 associations working to promote the rights of people with rare diseases. Formed through cooperation between Spanish and Latin American rare disease patients, it facilitates the advocacy work of Spanish-speaking rare disease communities through expertise, knowledge, and good-practice sharing.

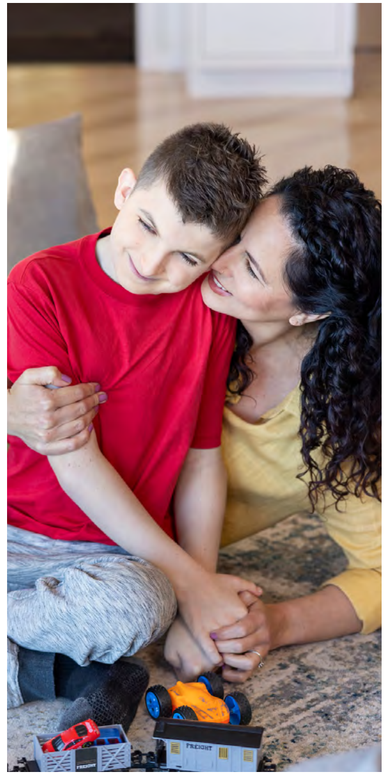
The Challenge

Around 40-50 million people live with a rare disease in Latin America and the Caribbean, 3-4 million of whom come from indigenous and underserved populations. The definition of a rare disease is inconsistent across the region. Some countries define a rare disease as affecting less than 5 in 10,000 individuals, and others have their own specific ones. There are still countries in the region that lack a formal definition,[284, 285, 286] making it much more complex to determine how prevalent rare diseases really are.

It can take 5-10 years for people living with rare diseases in Latin America and the Caribbean to secure a diagnosis,[287] and the average time to diagnosis among all respondents to an ALIBER survey was 5.9 years.[288] Increased knowledge and awareness of rare diseases has not substantially shortened the diagnostic odyssey, with people still facing significant delays even in better-recognised conditions.[289]

Newborn screening disparities also persist, with five categories of activities: well-established growing programmes, long-established programmes seeing national growth, more recently established programmes beginning to grow, some screening activity, and little or no screening. Across Latin America and the Caribbean, coverage and the scope of screening programmes vary significantly between countries, and many healthcare systems still face challenges not only in screening but also in confirmatory diagnosis, referral, and follow-up. Most Latin American countries fall into the second category,[290] and the situation is improving over time.[291]





The Benefits

ERCAL[292] and the Americas Health Foundation have convened consensus meetings of regional experts from Latin America and the Caribbean on rare disease diagnosis. The first focused on barriers and challenges to newborn screening and early diagnosis,[293] and the second on access to genetic and specialised molecular testing.[294]

Such expert panels, involving practicing rare disease clinicians and researchers, are also acutely aware of any resource constraints they may face in their setting. ERCAL-associated experts, for example, identify the difficulties involved in following up on testing results in rural areas and the major differences in healthcare system resource levels within the region. In this sense, their conclusions can also potentially help the rare disease community in other resource-limited regions identify context-relevant approaches, while recognising that implementation remains dependent on national healthcare system capacity.[295]

These meetings take place with the support of grants from philanthropic organisations,[296, 297] helping to alleviate the resourcing challenges involved in such projects. They culminate in the publication of consensus articles on the discussions and potential solutions. This can serve as a platform for further action, both through bringing together experts from the region and drawing attention to areas requiring improvement.

ALIBER has also sought to address the lack of detailed information about the Latin American rare disease community, carrying out a study on the health and social needs of people living with rare diseases and their families. ENSERio LATAM, by its Spanish initials, was inspired by a similar series of ENSERio studies conducted in Spain from 2009-2017.

It collected the experiences of people living with rare diseases from across Latin America through a questionnaire.[300] Respondents came from 21 Latin American countries,[301] the vast majority of whom were either living with a rare disease themselves or were caregivers of a person living with a rare disease.

As such, the rare disease community in Latin America has data on the length of the diagnostic odyssey that they can use as a basis for advocacy – 68% of participants waited over a year for diagnosis, with 20% of participants waiting ten years or more. Those who experienced delayed diagnosis waited an average of 8.9 years to diagnosis, with the average across the sample being 5.9 years.

They also have data reinforcing the consequences of delayed diagnosis – the most common impact being the worsening of the disease (36%), followed by not having received support and/or treatment (35%). 24% stated that they had received inappropriate treatment, and 15% required mental healthcare. These findings highlight the systemic impact of delayed diagnosis across the patient journey.

In working together with the Spanish rare disease community, they could compare and contrast their experiences – determining that the Latin American diagnostic odyssey was considerably longer and affected a larger share of the rare disease community. This underscores the need for region-specific approaches to diagnosis and care.



Call to Action:

01 Latin American countries should establish an expert group to propose a shared, consistent definition of rare diseases, including medical societies, patient advocacy groups, and researchers, while allowing for national adaptation, to facilitate service provision and comparative studies.[302, 303]

02 The implementation of the UN Resolution on Rare Diseases should encompass provision of universal healthcare, so that everyone living with a rare disease can access equitable quality health and social care,[304] including financial protection and sustainable access to diagnosis and treatment.

03 All stakeholders should cooperate to develop and disseminate accessible information about newborn screening programmes and early rare disease diagnosis, as well as to follow-up on the testing results in rural and underserved areas.[305] This should include strengthening referral pathways, confirmatory diagnosis, and long-term follow-up systems.

04 Expanding the number of diseases included in Latin American national screening programmes would also improve health and wellbeing in current and future generations.[306] This will also require collaboration with the private sector to strengthen access to diagnosis, innovation, and capacity-building efforts.

05 Countries should recognise the role of patient advocacy groups as a liaison between the rare disease community and other stakeholders, representing the experiences of people living with rare diseases to the public and private sectors,[307, 308] and ensure their meaningful participation in policy design, implementation, and monitoring.

06 Countries should, in their region and beyond, learn from other countries' experiences and resources they have produced in order to reduce duplication of effort when developing their own rare disease diagnosis policies,[309] while adapting these approaches to national healthcare system contexts.

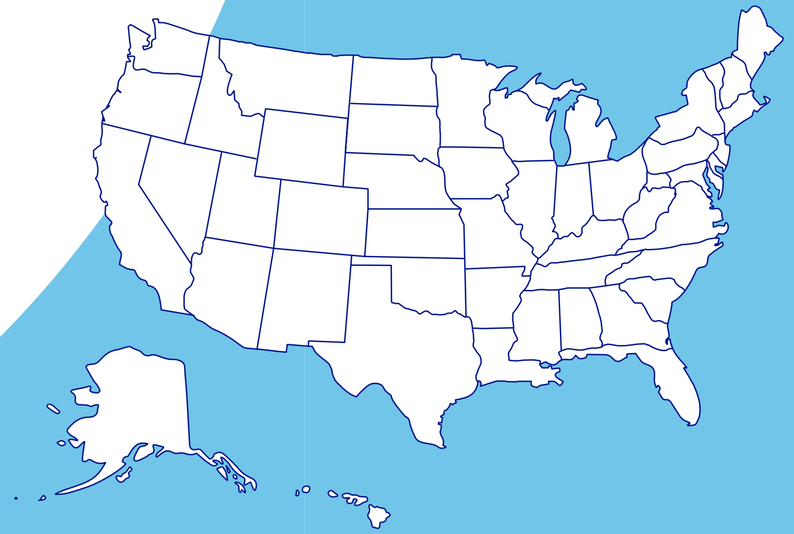
07 Patient advocacy groups can also benefit from replicating initiatives carried out by other members of the rare disease community, particularly where data collection has been done by others who share the same language.

08 Pilot projects for rare disease diagnosis can be useful to demonstrate impact for policymakers, and the funding required can be provided by third sector and/or private sector organisations,[310] provided that clear evaluation metrics, sustainability plans, and pathways to scale are defined from the outset.

09 Policymakers who seek to introduce such pilot projects for rare disease diagnosis need to include planning for the long-term sustainability and funding of these projects, should they be successful.[311]

Aspire4Rare Diagnosis – US Lens

Each region contributes distinct insights that enrich the global diagnosis framework. In the US, the rare disease community has advocated for reform to address workforce shortages in genetic specialists through facilitating licensing across states and improving coverage and reimbursement for genetic services, including telehealth. These efforts address challenges across several diagnosis archetypes, particularly access to specialist knowledge, diagnosis within social context, and standardization of diagnostic pathways. This callout sets out the key barriers and potential solutions for improving access to genetic medicine in the United States, demonstrating how regional experience can inform practical, scalable solutions within the Aspire4Rare Diagnosis framework.



Executive Summary

The majority of rare diseases are genetic,[312, 313] and timely access to genetic expertise can mean the difference between an extended diagnostic odyssey and an accurate diagnosis.

In the United States, genetic diagnostic services are primarily delivered by two distinct provider types: medical geneticists (physicians) and certified genetic counselors (CGCs). These roles differ in training, licensure, scope of practice, and reimbursement pathways, which have resulted in unique challenges that impact patient access to genetic services. Furthermore, geographic disparities and workforce shortages limit timely access to both medical geneticists and genetic counselors, particularly in rural and underserved areas.[314]

Telehealth has proven capable of mitigating some access barriers, but access to these services relies on a variety of policy factors, including geneticist provider licensure across state lines, coverage for telehealth services, and direct reimbursement for genetic counseling services delivered by genetic counselors. The Interstate Medical Licensure Compact makes it easier for healthcare professionals to become licensed in multiple states and to provide telehealth services. However, misalignment across these policy areas continues to constrain diagnostic access for people living with rare diseases.[315]

The Challenge

Workforce shortages and geographic disparities

In 2019, the National Organization for Rare Disorders (NORD) found that 36% of survey respondents received a rare disease diagnosis within the first year, in line with the goals[316] of the International Rare Diseases Research Consortium (IRDiRC). Of the survey respondents, 28 percent reported waiting seven or more years for a diagnosis.[317]

As of 2019, US states averaged seven genetic counselors and two medical geneticists per 500,000 people.[318] This aggregate figure masks significant regional inequities in access to genetic expertise. Of the 3,141 US counties, only 17% have at least one certified genetic counselor. Nearly 99% of genetic counselors live or work in densely populated urban areas, leaving many rural regions with limited or no local access to genetic services.[319] Although 71% of US residents live within a 30-minute drive of a genetic counselor, only 6% of individuals in non-metropolitan areas have comparable access.[320]

Medical geneticist organizations have also raised concerns about future workforce sustainability. While the genetic counselor workforce is growing overall, the medical geneticist workforce faces near-term strain, with a sizable proportion of clinicians expected to retire within the next decade[321] and approximately half of medical genetics residency positions going unfilled each year.[322]

Social determinants of health and access to genetic services

The social context of diagnosis further exacerbates workforce-related access challenges. Counties with in-person access to genetic counselors differ markedly from those without such access across multiple social determinants of health, including income, education, insurance coverage, and employment status. Household income shows a particularly strong correlation: counties with in-person genetic counselor access have a median household income approximately USD 10,000 higher than those without.[323] These disparities compound delays in diagnosis for individuals living with rare diseases in lower-income or underserved communities.

Licensure barriers affecting cross-state care

Licensure requirements for medical geneticists present additional obstacles to accessing genetic services across state lines and more broadly, via telehealth. The Interstate Medical Licensure Compact[324] makes it easier for physicians to apply for a license in the 42 participating states, D.C., and Guam, and has helped to expand the reach of existing providers through increasing the number of licensed physicians in participating states (particularly those with large rural and underserved populations).[325]

During the COVID-19 public health emergency, temporary interstate licensure flexibilities[326] allowed medical geneticists to provide care, including via telehealth, to patients in multiple states without securing separate licenses.[327] These measures helped direct limited specialist capacity to areas of highest need. However, most of these licensure flexibilities have since expired.[328] As a result, medical geneticists seeking to provide cross-state telegenetics care must once again navigate complex, state-specific licensing processes.[329] Only 21 states (plus Puerto Rico, D.C., and the US Virgin Islands) have permanent provisions for telemedicine licensing.[330]

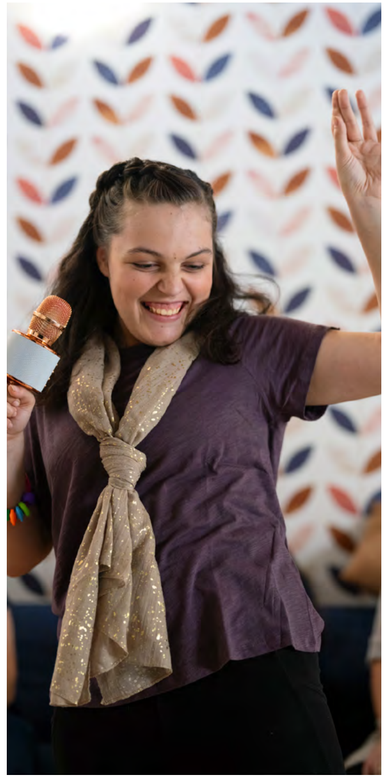
Recent policy efforts like the Accelerating Kids' Access to Care Act,[331] which streamlines Medicaid enrollment for out-of-state providers, signal growing recognition of the need to reduce cross-state barriers for patients with rare diseases, particularly children.

Coverage and reimbursement barriers

Medicare currently does not provide direct reimbursement for genetic counseling services delivered by genetic counselors, regardless of whether services are provided in person or via telehealth.[332] By contrast, genetic counseling services delivered by physicians may be reimbursed when billed under physician fee schedules.

During the COVID-19 public health emergency, Medicare temporarily expanded coverage for telehealth services, enabling patients and providers to acclimate to remote care delivery. Some Medicare telehealth flexibilities have since been extended through December 31, 2027.[333] While these extensions support better access to specialists, they did not resolve the absence of direct Medicare reimbursement for genetic counselors.

Taken together, these dynamics create a compounding access challenge. Declines and geographic maldistribution in the medical geneticist workforce constrain the delivery of genetic diagnostic services, while coverage and reimbursement gaps mean that even where certified genetic counselors are available, patients may not be able to access their services. Expanding coverage and reimbursement for genetic counseling services delivered by genetic counselors represents a critical step toward broadening timely access to genetic expertise and could, over time, help extend the reach of genetic services, including through telehealth-enabled models of care.



The Benefits

Addressing the full set of access barriers to genetic services – including workforce shortages among medical geneticists, geographic inequities, and coverage and reimbursement gaps affecting genetic counselors – has the potential to significantly improve the timeliness, equity, and quality of rare disease diagnosis in the United States. Strengthening the genetic workforce and ensuring sustainable reimbursement pathways would better align available expertise with patient need, particularly for individuals in rural and underserved communities.

Within this broader context, telegenetics represents a critical mechanism for extending the reach of existing providers when supported by appropriate licensure and payment policies. Federally funded Regional Genetics Networks[334] report that telehealth enables patients in rural and underserved areas to connect with medical geneticists without traveling long distances. As of 2023, 82% of genetic counselors reported offering audiovisual telegenetic services, reflecting both provider readiness and the growing role of telehealth in genetic care delivery.[335]

Patient experience data further underscore the value of telehealth-enabled genetic services. During the COVID 19 pandemic, 92% of people living with rare diseases who were offered telehealth appointments reported positive experiences, and 70% expressed a desire to retain telehealth as an option for future care.[336] Telehealth can also help reduce the substantial travel burden associated with rare disease diagnosis, which has required nearly 40% of surveyed patients to travel at least 60 miles to access care.[337]

Rare disease–specific telemedicine carve outs could further close access gaps, as diagnostic services often require highly specialized expertise that may not be available within local or even state healthcare systems.

Patient advocacy organizations continue to emphasize that sustaining these benefits will require broader structural reform. The EveryLife Foundation for Rare Diseases[338] has called for direct Medicare reimbursement for genetic counseling services delivered by certified genetic counselors, while the National Organization for Rare Disorders[339] has articulated guiding principles to preserve patient choice between in person and telehealth based care.

Importantly, telehealth alone cannot resolve access inequities unless paired with efforts to address workforce sustainability, licensure alignment, and coverage and reimbursement gaps that currently limit patient access to genetic expertise.



Call to Action:

01 **Secure direct Medicare reimbursement for genetic counseling services delivered by certified genetic counselors.** Establishing direct reimbursement is a foundational step toward expanding access to genetic counseling, including via telehealth, and would reduce out-of-pocket cost burdens for patients.

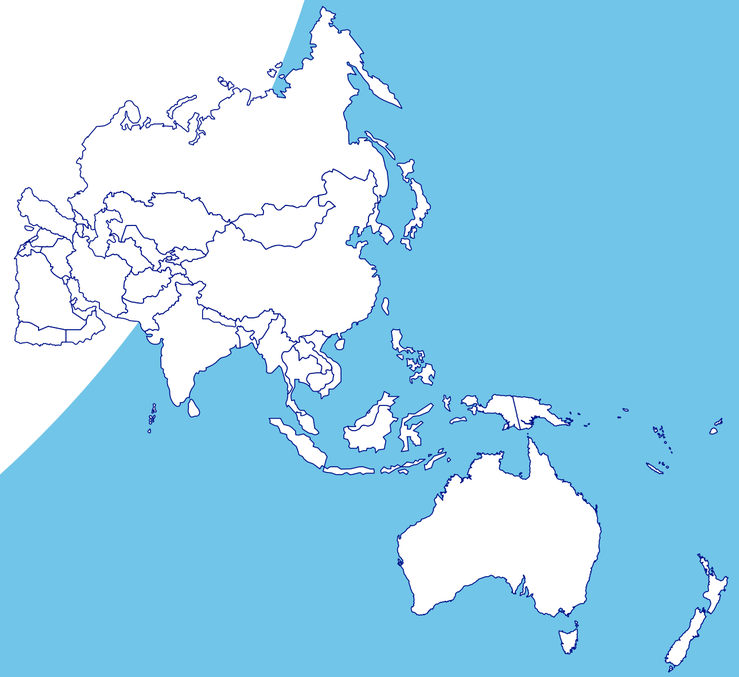
02 **Enact permanent, harmonised telehealth reforms across all states.** This includes encouraging broad participation in the Interstate Medical Licensure Compact, reducing cross-state licensure barriers for medical geneticists, and maintaining reimbursement parity for telehealth services where appropriate.

03 **Strengthen the long-term genetic workforce.** Develop strategies to incentivize specialization in genetic medicine, support training pathways for medical geneticists, and encourage placement in underserved and rural areas to improve geographic equity.

04 **Reduce the financial burden of rare disease diagnosis.** Improve payer coverage for genetic tests and related diagnostic services to address the high upfront costs that frequently prolong diagnostic odysseys for people living with rare diseases.

Aspire4Rare Diagnosis – Asia-Pacific Lens

Each region contributes distinct insights that enrich the global diagnosis framework. In Asia-Pacific, significant challenges and disparities persist for people living with rare diseases — and diagnosis is not a cure-all in this regard. At the same time, specific reforms and actions in a diverse range of countries demonstrate that improvement is possible across emerging and higher-income economies alike. These efforts address the challenges found across several archetypes, particularly diagnosis in social context, economic aspects of diagnosis, and standardisation of the diagnostic process. This callout describes the rare disease landscape in Asia-Pacific and highlights some key examples of good practice, showing how regional experience can shape practical, scalable solutions within the Aspire4Rare Diagnosis framework.



Executive Summary

The Asia-Pacific region faces significant challenges in addressing rare diseases. It encompasses 60% of the global population,[340] with substantial heterogeneity across the region. There are immense healthcare system disparities, including but not limited to, in patient advocacy, resource allocation and utilisation, awareness, and access to rare disease expertise. Limited access to diagnosis and treatment, coupled with substantial out-of-pocket costs, can place significant financial strain on patients and families. In some cases, the expense and stigma associated with diagnosis and the absence of accessible treatment discourage people from seeking one.

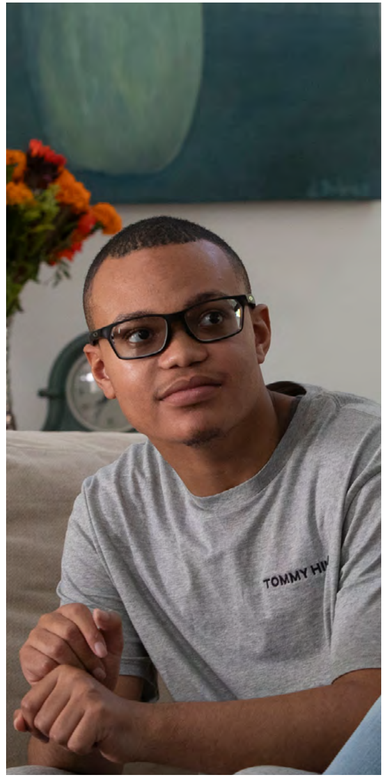
Rare disease advocacy efforts in the region exist in the context of resource constrained gaps in access to basic healthcare. This is all the more acute for people living with rare diseases. Additionally, the heterogeneity of the region – staggered levels of healthcare development, specialist availability and access, and the diversity of cultures, religions and languages – represents an underestimated barrier to accessing healthcare. For example, in countries with multiple different languages across states, those who can afford to travel to access care may experience communication difficulties with healthcare professionals.

Amid these challenges, however, several countries have made concrete improvements to policies and plans supporting people living with rare diseases to secure a diagnosis and access care.

The Challenge

Over 258 million people live with a rare disease in Asia-Pacific[341], and the out-of-pocket costs of medical care are substantial across the region.[342] Between 71 and 120 million people in South-East Asia and between 67 and 114 million people in the Western Pacific live with a rare disease.[343] 47% of respondents to a survey of clinicians in Asia-Pacific stated that improvements to financial support were the single action that would most benefit people living with rare diseases, and they identified diagnosis as the biggest challenge they faced in rare disease. Funding for diagnosis and funding for treatment were their second and third highest priorities for national rare disease policies.[344]

Several countries in the region also provide examples of good practice, across different resource levels. Notably, national wealth is not a prerequisite for or a guarantor of progress – higher-income and emerging markets alike are taking actions in the rare disease space.[345]





The Benefits

Taiwan provides an interesting example of rare disease progress while moving from middle to high-income status.[346] Its Rare Disease and Orphan Act, adopted in 2000 as the world's fifth law of its kind[347], defines rare disease and facilitates prevention, early diagnosis, research, and access to treatments and specific diets.[348] 20 years on, the Act has increased availability and accessibility of treatments and improved the situation of people living with rare diseases in Taiwan.[349] In sharp contrast, Singapore spends 4.43% of its sixth-highest GDP in the region[350] on healthcare while failing to recognise rare diseases in national insurance healthcare plans and relying on a charitable Rare Disease Fund (including only eight conditions[351]) for care coverage.[352]

Geographic differences also present a challenge for rare disease diagnosis in Asia-Pacific, especially in remote, rural, and island areas. The Philippines has thousands of islands[353] and has also implemented a newborn screening network, funded through national insurance, of over 7000 facilities, 7 regional laboratories, and 14 regional specialist follow-up clinics that can reach out to global experts.[354] This programme has reached 94.6% of newborns and covers 29 conditions[355] and has helped almost 300,000 babies through early detection and care.[356]

Japan, South Korea and Australia all have advanced, mature rare disease systems that have regional and international partnerships,[357] although these countries also experience geographic disparities and gaps in coverage for the rarest conditions.[358] All three countries have also implemented undiagnosed disease programmes, bringing together national and international experts to identify ultra-rare and previously unknown diseases.[359, 360] In Japan's case, researchers have discovered the underlying genetic changes associated with rare diseases for over 1,000 people living with a rare disease and identified new conditions.[361]

China and India provide examples of internal disparities, with substantial differences in rare disease service provision between regions.[362] Both countries have also begun to implement networks of rare disease centres, although these are generally concentrated in urban areas and few in number (especially given these are the two most populous countries in the world[363]) and this expertise does not filter down into the generalist healthcare system.[364]

Malaysia's rare disease commitment has been strengthened with the announcement of the 2025 National Policy for Rare Diseases.[365] Being implemented in phases, the plan focuses on early detection, clinical and allied health expertise development and a national rare disease database.[366, 367] RD diagnosis remains constrained by diagnostic capacity, specialist shortages and incomplete registry infrastructure. Although challenges remain, the focus is on integrating and strengthening existing efforts alongside forward-looking ambitions under the National Action Plan.



Call to Action:

01 Challenge the misconception that only higher-income countries can successfully start to address rare disease issues; barriers and solutions exist in a wide variety of economies.

02 Partnerships within and between countries can help to address rare disease challenges, provided that the burdens do not fall on people living with rare diseases.

03 Patient advocacy groups are a vital way for people living with rare diseases in the region to find support, share information, and partner with national healthcare systems towards supportive policies and practical changes.

04 Putting legal frameworks and binding rare disease plans in place can be a useful early action in geographies that do not yet have them.

05 Legislation, however, is a starting point for further action in ensuring the tools are in place for diagnosis and for access to treatment.[368]

06 Engagement with a wide variety of stakeholders is key to convince them to support reforms and to design actions that align with the priorities and needs of people living with rare diseases.[369] The cultural, linguistic and religious diversity of the relevant geography should be reflected in the composition of stakeholder engagement groups.

07 Community and government support for rare disease actions is essential, particularly where the programme involves public participation and/or requires financing support.[370]

08 Cross-border relationships involving guidance and training for implementing rare disease reforms can support the implementation of such programmes and give them space to develop independently.[371]

Aspire4Rare Diagnosis – Africa Lens

Each region contributes distinct insights that enrich the global diagnosis framework. In Africa, the Human Heredity and Health in Africa (H3Africa) initiative has facilitated collection of genomic data to help fill knowledge gaps and support rare disease diagnosis in people with African ancestry around the world. These efforts address the challenges found across several archetypes, particularly regarding access to knowledge and advancing research to provide answers. This callout describes the initiative and the lessons learned from it, showing how regional experience can shape practical, scalable solutions within the Aspire4Rare Diagnosis framework.



Executive Summary

In Africa, the global challenges people living with rare diseases face are exacerbated by healthcare system prioritisation of communicable diseases, limited access to next-generation sequencing (NGS) technologies, and chronic underrepresentation of African populations in genetic research. This results in knowledge gaps, as global genomic studies remain predominantly Eurocentric, leaving individuals of African ancestry underserved in diagnostic and research efforts.

The H3Africa initiative has demonstrated the benefits of strengthening local genomic research capacity. By fostering skill-building, infrastructure development, and international collaboration, H3Africa has enabled the reclassification of genetic variants and improved rare disease diagnosis in Africa and around the world. These efforts underscore the importance of diverse, representative datasets to develop solutions for rare disease diagnosis and establish equitable access to genomic medicine.

The Challenge

Around 50 million[372] people live with a rare disease in Africa, and the issue of healthcare system focus on communicable diseases, particularly in the low- and-middle-income African countries, exacerbates the difficulties people living with rare diseases face during the diagnostic odyssey.[373]

This is also the case for access to next-generation sequencing (NGS) technologies. Most of the international support available for accessing NGS in Africa is for testing pathogens,[374] rather than people, as part of efforts to detect emerging diseases of international concern. Barriers to access include lack of infrastructure, funding, and political support, as well as healthcare system structure issues.[375]

These barriers to access have led to substantial underrepresentation of African participants in genetic research. People of African ancestry comprise around 2% of people taking part in genome-wide association studies, with almost 80% of participants being of European ancestry.[376] The risk of such a Eurocentric perspective is that the European experience could be considered to be the universal 'default' for predicting disease risk and identifying genetic causes of rare disease, which facilitates misdiagnosis for individuals and communities who do not 'fit' that perception.





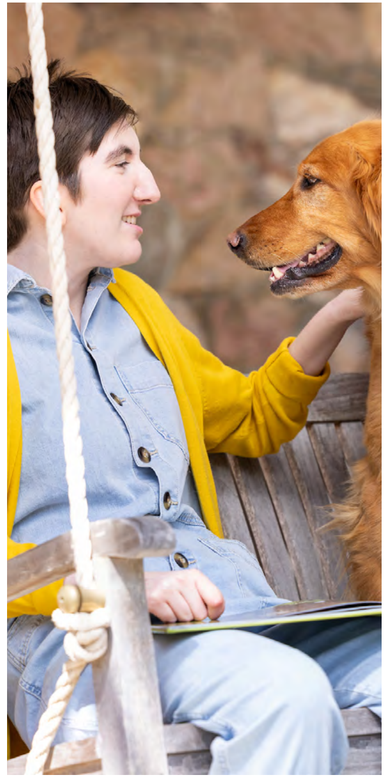
The Benefits

H3Africa, funded by the US National Institutes of Health and the UK Wellcome Trust, has supported research into communicable and non-communicable diseases across the continent.[377] H3Africa involves direct research grants to principal investigators, infrastructure and network development, and training programmes.[378]

It focuses on more common diseases, which resulted in skill building and infrastructure development for genomic research and NGS[379] that could be deployed in the rare disease space. H3Africa has submitted variants it has identified through these projects to the ClinVar[380] genetic database, supporting their reclassification though providing evidence that these variants did not cause disease.[381] In this way, upskilling of African researchers can support studies involving NGS and improve understanding of disease-causing variants in local populations.

This additional knowledge on basic science could then support clinicians in understanding the significance of genetic variants in people with African ancestry and facilitating potential rare disease diagnoses. For example, H3Africa's Rare Disease Working Group has used African datasets to help explain variant prevalence to Canadian clinicians treating people of African origin.[382] More representative datasets, therefore, can help improve rare disease diagnosis worldwide.

Such initiatives also help researchers form partnerships with their international counterparts – both in other African countries and further afield – and exchange experiences and knowledge.[383] H3Africa has also provided grants for studying community engagement, informed consent, and the wider factors that matter to local communities when deciding whether to take part in research.[384] As of March 2020, there were over 50 funded projects within the H3Africa Consortium, over 500 members, and the equivalent of 170 million USD in investment.[385]



Call to Action:

01 Policymakers should develop strategies to increase the diversity of samples in genetic reference databases. This will facilitate diagnosis through more accurate classification of variants, which may have been considered new or rare but turn out to be commonplace in people from groups traditionally underrepresented in research.[386]

02 Policymakers should develop and implement national frameworks to manage the ethical issues and social contexts of genomic medicine and research expansion.[387]

03 Patient advocacy groups should participate in initiatives and discussions around data sharing for research purposes and how to protect sensitive data as part of encouraging people to take part in studies.[388]

04 International expertise-sharing and financial investment partnerships can support improved understanding of rare diseases and genetic variants in underrepresented groups, which helps people living with rare diseases who share that ancestry – regardless of where they are in the world – find answers about their health.[389]

05 Local and international funding agencies should therefore invest in such partnerships in order to fill the gaps in knowledge about African genomic data and increase the diversity of research participants, from smaller local studies to large datasets that support precision medicine[390] or continent-wide genomic sequencing.[391]

06 Such partnerships should be collaborative and support local capacity and expertise-building, with local scientists taking the lead on conducting research and responsibility for data governance and storage.[392] Data collection and use should also provide benefit to the local communities who have agreed to share their data.[393]

07 Policymakers and clinical staff should include patient, community and research group representatives in planning and delivery of genomics studies.

08 Education and skills training should also form part of these partnerships, upskilling participants to develop a technically highly-skilled genomics workforce.

09 Local leadership is also essential in building trust among the communities taking part in research, and communities should be included in the study design process so that any research projects are responsive to community needs, values, cultures, and perceptions about genetic studies.[394]

10 Researchers should ensure that potential participants have access to explanatory materials in a language and format they understand, to facilitate informed consent.[395]

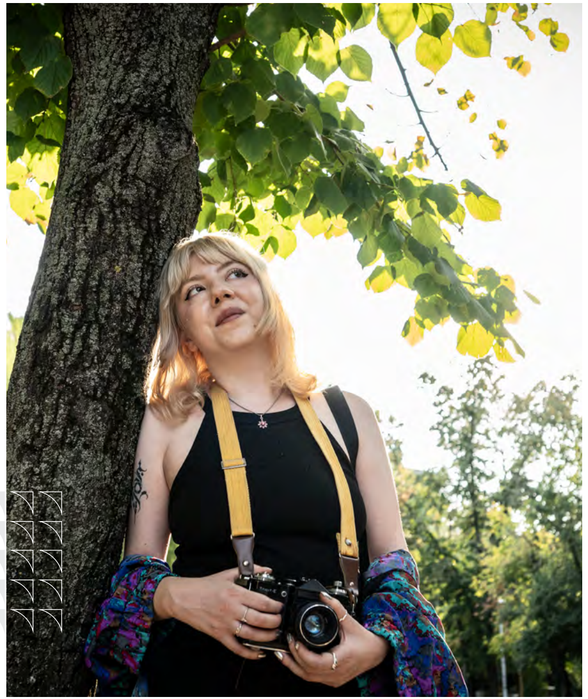
11 Partners providing training and education resources[396] on rare disease related topics should ensure they are also offered in languages other than English, to expand their geographic reach.

Glossary

TERM	DEFINITION
Antibody testing	Checking for the presence of substances that the body makes to fight disease
Biobanks	Stores of large amounts of biological samples for research into the causes of disease
Biomarkers	A biological marker – which can indicate a particular disease is present
Cascade testing	The process of testing the family members of someone with a genetic condition to see if they have also inherited it
Causal genetic etiologies	Assigning of genetic causes of disease
Differential diagnosis	Diagnosing a disease by listing the possible causes of the symptoms and gathering information and data to decide on a particular diagnosis
Disaggregation	Breaking down data into particular categories e.g., responses from different income categories
Genomics	The study of genomes (all the DNA of an organism)
Genotype	Genetic information

TERM	DEFINITION
Interoperability	The ability of a system to work with other systems
Longitudinal data	The collection of data over a specific time period
Metabolic disease	Diseases affecting how the body turns food into energy
Mitochondrial disease	Diseases affecting how cells produce energy
Molecular diagnostics	The process of looking at biological samples to see if there is evidence of a disease in genes and/or proteins
Morbidity	The impact of a disease on a population
Pathogenic	Causing disease
Phenotype	The physical expression of genetic information
Registries	Collections of data and information about people living with a specific rare disease, which can help support research
Syndromes Without A Name	Diseases that are so rare they do not have a specific name of their own

TERM	DEFINITION
Variant of unknown significance	A change in a gene that is not well-known enough for doctors and scientists to tell if it could be linked to disease
Whole-exome sequencing	The process of checking the parts of DNA that contain instructions for making proteins
Whole genome sequencing	The process of checking the whole DNA sequence of an organism



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