Aspire4Rare:
A global guidance framework for rare disease policy

TABLE OF CONTENTS

Aspire4Rare: our ambition for rare disease

Significant progress in rare disease research, healthcare, and policy has been made in the last few decades. Recognition of rare disease policymaking e.g. UN Resolution on the Challenges of Persons Living with a Rare Disease and their Families, has brought rare disease to the forefront of public health. In parallel, discovery of new medicines and cures as well as establishment of clinical centres e.g. European Reference Networks (ERNs) have improved many lives.

Nevertheless, challenges remain for the 300 million people living with rare diseases worldwide. Issues such as lack of access to treatment and social care, the uncertainty that comes with a diagnostic odyssey, sense of isolation, and decreased quality of life still persist today. The restrictions imposed during the 2019 pandemic were a major setback in many areas of healthcare. The impact on access to care was particularly acute for those with rare diseases as access to care in situ was inconsistent and patchy at best.[1,2,3,4]

There is consensus that we need to strengthen and future-proof our health systems for the challenges ahead and withstand future shocks. Aspire4Rare is born in the spirit of reforming health systems for everyone's benefit, albeit with a particular focus on rare diseases given the added challenges that people living with rare diseases face. Aspire4Rare seeks to address the pre-existing challenges for the rare disease community, for instance geographic and societal inequalities, as well as tackle emerging issues around genomics, health data and workforce.

Past and/or existing initiatives including International Rare Diseases Research Consortium, the UN Resolution on Addressing the Challenges of Persons Living with a Rare Disease and their Families, as well as EU-level policies and initiatives such as Rare2030, European Partnership on Rare Diseases (2024-2031), the European Reference Networks, the European Joint Programme on Rare Diseases and Orphanet/ Orphacodes have outlined aspirational policy goals and recommendations for policymaking. Aspire4Rare strives to push these efforts even further, placing added emphasis on tangible, practical action.

To that end, Aspire4Rare is developed in collaboration with experts from across different disciplines in rare disease and healthcare. The result is a framework for systemic change. It includes ideal outcomes as well as examples of good practice from different health systems. Each outcome is accompanied by a set of practical measures that assesses the performance of a health system. Some measures are derived from existing rare disease literature as footnoted in the report; others are proposed new measures recommended by experts. These new measures aim to improve our collective understanding of whether policies and health systems are working for people living with rare diseases, and could be opportunities for future ideation and collaboration with stakeholders across the ecosystem. Finally, the good practice examples serve as a menu of tried-and-tested policy actions that policymakers can choose to adapt in their local context.

Although health systems vary from country-to-country, assessing their performance using a common framework can provide a structured approach to highly complex problems. Nevertheless, the framework's application should be context-driven and adapted to local systems. Such adaptation would build on the existing framework, facilitate knowledge transfer, and promote learning for the future.

[1](Soussand, et al., 2022)
[2](Zhang, et al., 2022)
[3](EURORDIS - Rare Diseases Europe, 2020)
[4](NORD – National Organization for Rare Disorders, Inc., 2020)

Acknowledgements

At UCB, we support the development of healthcare systems that cater to all those living with rare diseases by fostering collaboration within the healthcare community and leveraging data to drive transformations in healthcare policy. Together, we strive to develop holistic and sustainable systems for people living with rare diseases.

Aspire4Rare is a project co-created with a multi-disciplinary group of 9 experts in rare diseases from policy, health, research and patient advocacy backgrounds across Europe and the US:

Holm Graeßner, Managing Director of the Centre for Rare Diseases, Coordinator of the European Reference Network for Rare Neurological Diseases

Victor Maertens, Government Affairs Director for the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

Antoni Montserrat Moliner, Vice President at ALAN Maladies Rares

Alexander Natz, Secretary General of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

Vinciane Quoidbach, Research Project Manager – Public Health and Policy for the Value of Treatment at the European Brain Council

Maurizio Scarpa, Coordinator of the European Reference Network for Rare Hereditary Metabolic Diseases METABERN

Rachel Sher, Former Vice President of Policy and Regulatory Affairs for the National Organization for Rare Disorders (NORD) and Life Sciences and FDA Partner at Manatt, Phelps & Phillips

Jamie Sullivan, Vice President of Public Policy at EveryLife Foundation

Sheela Upadhyaya, consultant to the life sciences industry, specialising in rare diseases, co-chair Rare Disease Special Interest Group – Health Technology Assessment international.

The Aspire4Rare Framework

DEVELOPING THE FRAMEWORK

To achieve the desirable outcomes for rare disease, there is a general consensus that we must strengthen health systems. In this regard, the World Health Organisation's Health Systems Framework[5] provided a basis for conceptualising an approach to accelerate systems-level change to improve outcomes.

The WHO Health Systems Framework defines 6 core building blocks that make up a health system:

- **Leadership and governance**
- **Access to essential medicines**
- **Health information**
- **Health service delivery**
- **Financing**
- **Health workforce**

Together they function to achieve better population health, better quality of care, and better value for money.

Adapting this concept, we proceeded to develop a framework that reflects the unique challenges, characteristics, and conditions of the rare disease landscape. Rare2030, as a comprehensive set of rare disease policy recommendations aligned to the Sustainable Development Goals, served as inspiration for this process. Global rare disease experts, who form the Aspire4Rare expert panel (see p.2), were consulted on how they envision rare disease policies as captured in Rare2030 can be advanced. Their input was then incorporated in the final conceptualisation of the Aspire4Rare Framework (see on p.4.). They also provided insights into successful step-change in policy reforms as well as good practices – captured in this Report – that could offer inspiration to policy practitioners for policy design and implementation.

[5](World Health Organisation, 2007)

Emerging Themes in Rare Disease: Views from Experts

The advancements in rare disease policies are laudable and we ought to celebrate the successes achieved thus far. But there are still significant unmet needs, particularly as new technologies and biological discoveries uncover new paradigms of diseases and treatments. In late 2023, the Aspire4Rare expert panel came together to review and arrive at an optimal framework against which to assess and measure the effectiveness of rare disease policies, and the following themes arose from their discussion:

01 Rare diseases should be integrated into existing structures and health policies, whilst still distinct from other disease areas.

02 Patient perspectives need to be incorporated to guide policies and decision-making.

03 Raising the public profile of rare diseases can help improve understanding of the disease area and commitment to action.

04 Health system reluctance to reform needs to be addressed, particularly where it exacerbates geographic inequalities among people living with rare diseases.

05 Relevant health professions, such as genetic counselling, need to be recognised and effectively integrated into health systems.

06 Rare disease policy needs to be about living well with rare diseases and supporting continued research.

07 Supporting transition from child and adolescent health services into adult services is important in promoting optimised outcomes.

08 Improved data collection and centring of people living with rare diseases are both key in all building blocks.

> We need to find ways to work rare disease considerations into existing policies and structures. People living with rare diseases have lots of unique challenges, but they may also get diabetes and other non-communicable diseases.
>
> **Sheela Upadhyaya**

Crucially, the experts agreed that strategies are only useful if they can be and are implemented. For this reason, the Aspire4Rare approach depends not only on establishing the ideal outcomes for rare disease policy, but also understanding what needs to happen to achieve those outcomes, how health systems can assess their progress towards their individual ideal scenario, and what good practices exist to help realise their goals.

These observations were embedded in our initial health systems framework, and which culminated in the **Aspire4Rare Framework: Building Blocks for Change.**

A Framework for Access to Care for Rare Diseases

Building Blocks	Outcomes										
Leadership & Governance Guarantee public health prioritisation of people living with rare disease	Effective incentives spur research and innovation in rare disease	Value-assessment frameworks for rare diseases are aligned and harmonised	Rare disease is integrated into overall health policy	Rare disease policies are monitored and adapted based on outcomes achieved	Mechanisms exist for PLWRD to contribute to RD policy process	Actionable rare disease plans are implemented	Rare disease plans are long-term and are regularly adapted	National genomics programmes are implemented for rare disease care and research	The public understands what rare disease means	National governments collaborate on international disease registries	Regulatory approvals reference international clinical trial data
Innovative Ideas Become life-changing technologies and therapies		Health data related to rare disease diagnosis and care is accessible for research purposes	Researchers participate in consortia to share knowledge and expertise	Innovative research in rare disease is being advanced	PLWRD are able to participate in clinical research	Innovative ideas are translated to new technologies and treatments for rare disease	Researchers are inspired to work on rare disease	Advancements in rare disease research result from collaboration across disciplines	Innovative care for rare diseases is advanced throughout the life course	Payers engage in open dialogue early in the development process for innovative treatments	People living with rare diseases are able to access available treatments
Health Information Systems Accelerate access to and development of new ways to care for rare diseases	New technologies are harnessed to reduce complexity of diagnosis for rare diseases		PLWRD have access to multidisciplinary interoperable services throughout the patient pathway	Data is standardised for use across all care settings	PLWRD contribute to data and evidence on Patient-Reported Outcomes	Genomic data on rare diseases is consistently captured in an accessible database	RD patient registries are integrated into the healthcare system				
Health Services Work for people with rare disease	Early screening and testing lead to early or timely diagnosis	Health services provide the same high quality care to all PLWRD		PLWRD can access social care services	Rare disease pathways are adapted to individual needs	Service provision and coverage decisions take into account PROs and are value-added for PLWRD	Clinical standards for rare disease are harmonised across borders	There are mechanisms to support coordination between the health and social care systems for PLWRD	Caregivers are able to access support services	Young people living with rare disease experience a smooth, quality transition from paediatric to adult services	
Health System Financing Meets rare disease community needs	Financing accounts for and addresses inequalities in access to care	Health system financing decisions on rare disease coverage are open and transparent	PLWRD have access to reliable information on care funding options	Innovative rare disease care is affordable to PLWRD	Governments collect data about socio-economic impacts of living with a rare disease to determine funding allocations		Rare disease plans include funding for implementation or signpost to funding sources	PLWRD and those caring for them receive adequate financial and non-financial support	Health systems maintain quality of care at a sustainable cost	Public-private models of financing support research in rare disease	
Health Workforce Supports acess to high-quality care	PLWRD provide input into medical workforce training	Social services professionals are trained and equipped to support PLWRD	Medical education systems prioritise rare disease care	Healthcare professionals are trained to support people with the day-to-day realities of living with rare disease	PLWRD have easy access to specialist care	People living with undiagnosed and rare diseases have access to genetic testing and counselling					

Aspire4Rare Framework's Building Blocks for Change

Similar to the WHO Health System Framework, the Aspire4Rare Framework consists of 6 core building blocks and aspirations.

01
Leadership and governance guarantee public health prioritisation of people living with rare diseases

02
Innovative ideas become life-changing technologies and therapies

03
Health information systems accelerate access to and development of new ways to care for rare diseases

04
Health services work for people with rare diseases

05
Health system financing meets rare disease community needs

06
Health workforce supports access to high-quality care

DEFINITIONS

Building blocks
Overarching pillars of a health system fit for rare diseases. Each building block encompasses several measurable outcomes.

Outcomes
Taken as a group, outcomes clarify the concepts behind building blocks of a health system fit for rare diseases. These outcomes describe what health systems fit for rare can deliver to patients. Outcomes can be measured to assess a country's health system's preparedness for rare diseases.

Measures
Measures are used to assess an outcome. They are illustrated by specific best practice data points.

Good Practices
Good Practices will be used to illustrate outcomes in a very practical way. They will be published alongside the framework, in order to provide inspiration to policy practitioners and makers.

Each building block is characterised by discrete outcomes. Potential measurements or data points help assess and monitor progress towards each outcome and good practices provide a frame of reference for how health systems achieve those outcomes. These good practices can serve as inspiration and guide action among policymakers and health service practitioners as they look to attain the outcomes set out in the building block. The execution of the approaches, however, will need to be adapted to each individual system.

Data captured in this report is drawn from secondary literature, including policy documents and academic texts on rare disease policies and health system performance. Some of these measures are derived from existing rare disease publications as footnoted in the report. However, for some outcomes, ideal measurements to track progress are not yet available. In this regard, we have proposed potential ways to evaluate and measure outcomes. Some of these are crude -- instead of real – measures, as there are no established ways of measuring performance due to the complex nature of health systems.

How to use this document

This document is meant to be used as a toolkit for policy practitioners and makers as well as those in the rare disease advocacy community. The Aspire4Rare Framework is not a prescriptive tool, but rather, the recommended outcomes, measures and good practices serve as a reference and should be adapted and localised to a country's health system.

THE FRAMEWORK CAN BE UTILISED IN SEVERAL WAYS:

01
as a basis for discussion with implementation partners;

02
to inform policy learning and scenario planning;

03
as reference and input into operationalising rare disease strategies or plans.

THE NEXT SECTION OF THIS DOCUMENT WILL:

01
Define the aspiration for each building block

02
Describe the outcome(s) in each building block

03
Propose datapoints and progress measures to understand how well a system is achieving the outcome(s)

We recognise that different health systems are on different journeys, and the goal of the Framework is to work in conjunction with local priorities and objectives as well as social, cultural, and institutional contexts.

We invite readers to use this report to stimulate discussions that can further advance existing rare disease policies or plans, encompassing action within the community or broader healthcare ecosystem. It can be used to inform such exchanges and act as a reference point for dynamic assessment of what is working for the community and what must be improved. We also encourage and welcome feedback and ideas for collaboration to create tangible impact in the health system for the benefit of people living with rare diseases.

Building Block 1
Leadership and governance

This building block addresses the role of public policy in prioritising the health and wellbeing of people living with rare diseases. Health policymakers face multiple competing demands, and the voices and needs of people living with rare diseases can often be overlooked due to the lower prevalence of such conditions. Systematic effort and attention are required to ensure that rare diseases do not slip off the political radar.

OUR ASPIRATION

Leadership and governance structures, at all levels of government, drive forward regulations, strategies and policies addressing rare disease. Such actions are designed and implemented with input from people living with rare diseases, and authorities are accountable for their implementation and results.

To achieve this

- High-level recognition of the importance of rare disease as part of health policy overall is required, alongside implementation of long-term, up-to-date rare disease plans.
- An effective public health policy system has mechanisms for consulting people living with rare diseases on policies that affect them and monitors the outcomes of such policies to adapt them accordingly.
- It incentivises innovation and implements 1) national genomic programmes that support the integration of genomics into clinical practice, research, and education, and 2) promotes rare disease awareness among the general public.
- On the international level, national governments work together to coordinate and align disease registries, reference international trial data in their regulatory approvals, and align their value assessment frameworks, where applicable, for medicinal products.

01

OUTCOMES AND PROGRESS MEASURES

OUTCOME 1

Effective incentives spur research and innovation in rare disease

The incentive system should be well-implemented in practice, evidenced by both availability and uptake of a variety of regulatory, financial, and intellectual property incentives.

OUTCOME 2

Value-assessment frameworks for rare diseases are aligned and harmonised

Health systems may differ, though the challenges posed by rare disease remain constant. To ensure consistent access to rare disease treatments, all payers should assess the value of health technologies in a harmonised manner.

OUTCOME 3

Rare disease is integrated into overall health policy

People living with rare diseases may also be living with other, more common health conditions. Health policies should take these interactions into account, such as through clinical guidance or integrating rare disease into action plans on other health issues.

OUTCOME 4

Rare disease policies are monitored and adapted based on outcomes achieved

In the absence of monitoring mechanisms, it is impossible to tell whether policies are working as intended. As such, health systems should develop methods of monitoring outcomes throughout the rare disease patient journey and undertake regular assessment of whether it works effectively for people living with rare diseases.

OUTCOME 5

Mechanisms exist for people living with rare diseases to contribute to rare disease policy process

People living with rare diseases are the experts on their own lives. Policies and decisions that do not take this expertise into account may reach incorrect conclusions and may even be counterproductive. Seeking their contributions must not become a tick-box exercise, but instead serve as a genuinely influential factor in decision-making.

OUTCOME 6

Actionable rare disease plans are implemented

Rare disease plans need to be well-funded, and it is, furthermore, essential to develop objective measurements of progress and assess implementation.

OUTCOME 7

Rare disease plans are long-term and are regularly adapted

Rare disease plans have important ambitions across the rare disease patient journey, such as early or timely diagnosis, access to innovative treatment, quality of life, training for healthcare professionals, and data collection. However, all too often, they then go unimplemented and eventually expire without much change being made. Rare disease plans should be regularly updated – at least every few years – and involve a review of which goals were not met, and why.

OUTCOME 8

National genomics programmes are implemented for rare disease care and research

National genomics programmes can be a lifeline for people living with undiagnosed or unnamed rare diseases, providing them with a greater understanding of what has caused their condition – and potentially a diagnosis that could be treatable. Successful implementation of a national genomics programme requires strong leadership, substantial funding, regulatory guardrails and standards, infrastructure and manpower and multiple stakeholder collaboration.

OUTCOME 9

The public understands what rare disease means

Public awareness of rare disease is important to keep up the momentum of recent decades, to show policymakers that the public wants to see further progress. Additionally, increased public awareness could encourage people with unexplained symptoms to visit their doctors, and facilitate early detection by education workers or relatives of symptoms among children.

OUTCOME 10

National governments promote collaboration on international disease registries

As previously mentioned, rare disease communities can be spread out across large geographical areas. When national governments facilitate cooperation on cross-registry analysis, such as through supporting semantic interoperability of registries, the likelihood of finding individuals living with the same rare disease increases. This, in turn, facilitates the formation of advocacy and support groups, as well as a larger pool of potential research participants.

OUTCOME 11

Regulatory approvals reference international clinical trial data

Increased consistency in product assessment processes helps facilitate sponsor applications for marketing authorisation in multiple markets, as there are fewer different requirements to be addressed. More importantly, where the population of people with a particular rare disease is too low for a separate national study, regulators can rely on data from larger rare disease communities overseas to inform their decision-making.

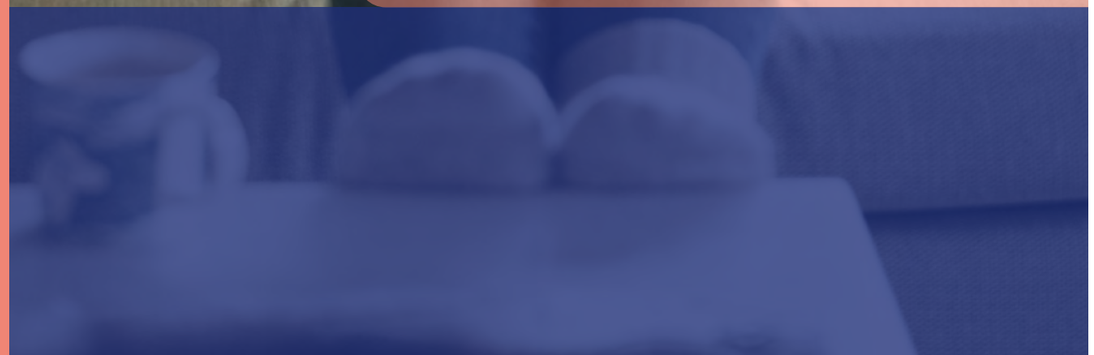
> Sometimes, countries are fine with the principle of rare disease policies but are reluctant to change the way they do things in practice. It can be difficult for countries with differing regional policies to make the changes people living with rare diseases need.
>
> **Maurizio Scarpa**

MAKING ASPIRATION A REALITY

EXAMPLE	OUTCOME	DETAILS	MORE INFORMATION
Rare Disease Advisory Councils (RDACs)	Mechanisms exist for people living with rare diseases to contribute to rare disease policy process	26 US states have passed laws setting up RDACs – 11 state governors have signed RDAC legislation since 2020 RDACs allow stakeholders to make formal recommendations to state leaders on rare disease policy issues e.g. Medicaid benefits, health insurance regulation	NORD – National Organization for Rare Disorders, 2023. *Rare Disease Advisory Councils (RDACs)*. [Online] Available at: https://rarediseases.org/wp-content/uploads/2023/07/NRD-2301-RDAC-Sell-Sheet_FNL-1.pdf
genomDE - German strategy for genomic medicine	National genomics programmes are implemented for rare disease care and research	The German genomDE consortium brings together 14 of the most important nationwide initiatives in genomic medicine for data utilisation and sequencing in medicine. Germany launched this initiative in October 2021, working to include patients, set up the data infrastructure needed, and establish a legal basis for genome sequencing for rare diseases and cancer. A pilot project will run from January 2024 for at least five years, integrating genomic medicine into the German health system. GenomDE also includes the national platform for medical genome sequencing to be used by the pilot project.	TMF – Technologie- und Methodenplattform für die vernetzte medizinische Forschung e. V., 2024. *genomDE*. [Online] Available at: https://www.genom.de/

There are good, ongoing, efforts to integrate patient input into decision-making and value-assessment frameworks, rather than being tacked on at the end.

Jamie Sullivan



Building Block 2
Innovative ideas

This building block focuses on innovative ideas. Due to the nature of rare diseases, research is limited by a lack of funding, critical mass in terms of population size essential for carrying out studies with clinical significance and commercial potential.

OUR ASPIRATION

Innovative ideas become life-changing technologies and therapies

To achieve this

- Incentives need to be in place to promote research and innovation in rare diseases.
- Developed treatments reach people living with rare diseases in a timely manner.
- Rare disease health data should be made accessible for research purposes.
- Researchers should participate in consortia to exchange knowledge and ideas.
- Support - whether financial or regulatory - is available to advance innovative research.
- There is investment in translating research into medicinal products, which would result in additional authorised orphan and advanced therapeutic medicinal products (ATMPs).
- Researchers would find a supportive legislative environment and would work together across disciplines to advance knowledge of rare diseases.
- Payers would engage in early dialogue with the developers of innovative treatments, to speed up approval and marketing of new medicinal products.

02

OUTCOMES AND PROGRESS MEASURES

OUTCOME 1
Effective incentives spur research and innovation in rare disease

A system of incentives should support and promote ideas and innovative developments that benefit people living with rare diseases.

OUTCOME 2
Health data related to rare disease diagnosis and care is accessible for research purposes

To translate innovation into action, researchers need to have access to health data for secondary use purposes via well-governed processes.

OUTCOME 3
Researchers participate in consortia to share knowledge and expertise

Given the variation of rare disease prevalence across geographies, knowledge sharing networks – that could be facilitated through public-private partnerships – are key for exchange of ideas and collaboration to develop better understanding of rare diseases.

OUTCOME 4
Innovative research in rare disease is being advanced

In addition to promoting and supporting research and development in rare diseases, it is vital to monitor the progress and outcomes of that research.

OUTCOME 5
People living with rare diseases are able to participate in clinical research

If people living with rare diseases find it prohibitively difficult to participate in clinical research, there will be limited progress towards greater scientific understanding and its translation into treatments. As such, policymakers should facilitate rare disease community participation in research studies addressing the barriers that prevent participation.

OUTCOME 6
Innovative ideas are translated to new technologies and treatments for rare disease

Scientific discoveries about the nature and progression of rare diseases can potentially lead to new ways of addressing symptoms, or even curative treatments. For this to be the case, governments should ensure they provide support for and investment in translational research.

OUTCOME 7
Researchers are inspired to work on rare disease

Dedicating a career to researching rare diseases and developing treatments is a substantial commitment, and one with no guarantee of success. To generate more robust research, we need to draw more researchers into the field of rare disease.

OUTCOME 8
Advancements in rare disease research result from collaboration across disciplines

Given the complexity of rare diseases and their multifaceted impacts on the body, research is most effective when it involves a breadth of expertise.

OUTCOME 9
Innovative care for rare diseases is advanced throughout the life course

Rare disease statistics, taken together, paint a picture of the health journeys of people living with rare diseases. Diagnostic, prevalence, and natural history measures tell us how many people live with a disease, when it begins, how it progresses, and what its effects are – integrating first-hand reports of outcomes by people living with rare diseases. If this information is unavailable, it will be impossible to enact effective reforms.

OUTCOME 10
Payers engage in open dialogue early in the development process for innovative treatments

The complexity of rare diseases affects the process of approving and reimbursing treatments using conventional health economics assessment frameworks. It is important for developers and payers to engage early about what kind of evidence they should produce to secure rapid approval for – and therefore rapid access to – innovative treatment for people living with rare diseases.

OUTCOME 11
People living with rare diseases are able to access available treatments

Where treatments for rare disease have been developed, they become available to the people living with that rare disease within a reasonable timescale.

People living with rare diseases need centres of excellence connecting with their local doctors and paramedical healthcare professionals, so that an individual patient-centred network will be built, knowledge be accumulated and used for the benefit of the patient.

Holm Graeßner

MAKING ASPIRATION A REALITY

EXAMPLE	OUTCOME	DETAILS	MORE INFORMATION
Undiagnosed Disease Network	Innovative care for rare diseases is advanced throughout the life course	A study funded by the US National Institutes of Health involving twelve clinical sites across the USA that aim to improve diagnosis and care for people with undiagnosed diseases. The clinical sites offer a medical and research evaluation by multiple specialists, which often includes genetic testing of the study participant and potentially family members. Following the evaluation, the participant's usual healthcare provider gets the evaluation information and can use it to inform treatment decisions and long-term care. The study also shares the stories of participants who consent to have this information posted online, in the hope of finding others who have similar symptoms or genetic changes.	Undiagnosed Diseases Network, 2024. *Finding Answers through Sharing.* [Online] Available at: https://undiagnosed.hms.harvard.edu/participants/ Undiagnosed Diseases Network, n.d. *Frequently Asked Questions*. [Online] Available at: https://undiagnosed.hms.harvard.edu/about-us/faqs/
Solve-RD	Researchers participate in consortia to share knowledge and expertise	EU-funded project aiming to solve rare diseases with yet unknown causes and improve diagnostics by sharing knowledge about genes, genomic variants, and phenotypes through a consortium of ERN participants, RD research and diagnosis infrastructures, patient organisations, and leading experts	Solve-RD, 2023. *Solve-RD - solving the unsolved rare diseases.* [Online] Available at: https://solve-rd.eu/

Building Block 3
Health information systems

This building block addresses the potential of technological advancement and health data collection to improve the lives of people living with rare diseases.

OUR ASPIRATION

Health information systems accelerate access to and development of new ways to care for rare diseases

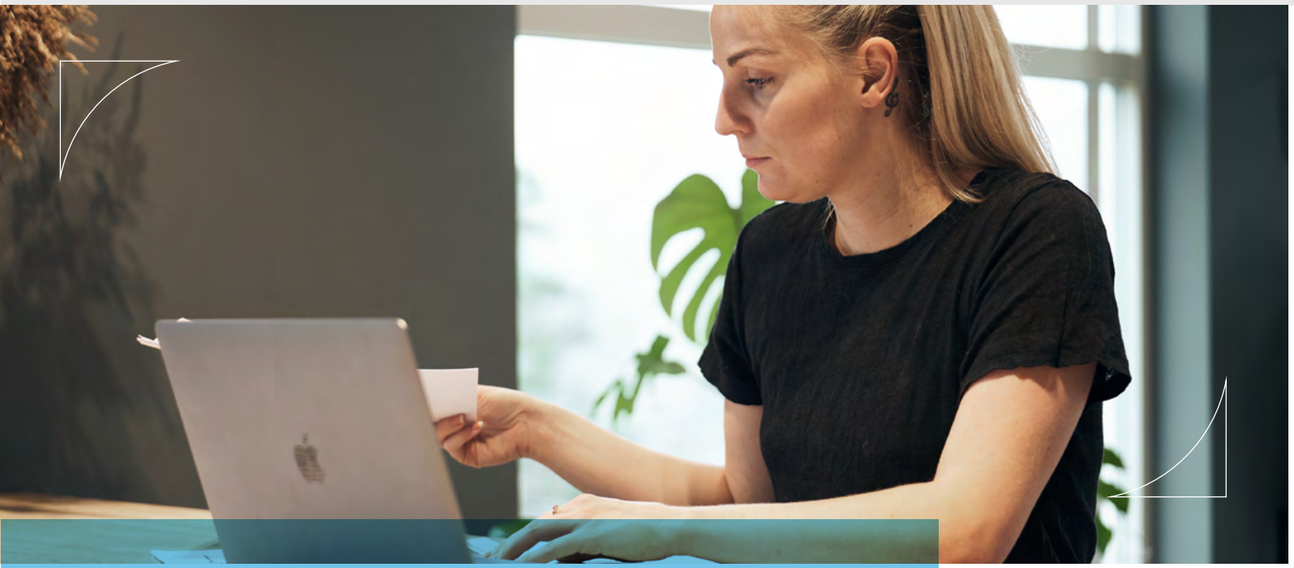
To achieve this

- This includes access to telemedicine and use of big data to support diagnosis, standardisation of data across care settings, consistent capture of genomic data, and integration of registries into the health system.
- People living with rare diseases contribute to data and evidence on Patient Reported Outcomes (PROs) which are used in practice nationwide.

There are substantial overlaps between information systems and the other building blocks, with good data often constituting the basis for promoting innovation and improving health services.

- Health data accessibility for research purposes is also measured here, from a technological implementation and data storage perspective.
- The digital aspects of access to multidisciplinary, interoperable services such as e-prescriptions, and the existence of legislation for health system digitalisation, also fall under this building block.

03



OUTCOMES AND PROGRESS MEASURES

OUTCOME 1

New technologies are harnessed to reduce complexity of diagnosis for rare diseases

The COVID-19 pandemic and its aftermath required a digital transformation in extremis. It ushered a new era for the use of digital technology in healthcare, such as, utilising big data for epidemiological monitoring purposes. Digital technology is an enabler: people living with rare diseases now have new avenues to seek specialist care anywhere in the world, while researchers are able to use algorithms to improve our collective understanding of rare disease. Genomic sequencing, as mentioned in other building blocks , is another key technological tool in efforts to tackle the diagnostic odyssey.

OUTCOME 2

Health data related to rare disease diagnosis and care is accessible for research purposes

Health data systems should facilitate access to health data for secondary use purposes, via standardised data collection and storage infrastructure.

OUTCOME 3

People living with rare diseases have access to multidisciplinary, interoperable services throughout the patient pathway

The information systems aspects of this outcome involve ensuring digital infrastructure is set up in a way that facilitates individualised, multidisciplinary care networks for people living with rare diseases.

OUTCOME 4

Data is standardised for use across all care settings

Standardised, consistent data is vital for health system operation in general, particularly so in the rare disease space. Rare diseases must be defined and coded in compatible ways at the national and international levels to ensure a common understanding among researchers and clinicians. Furthermore, rare disease considerations should be an integral aspect of national strategies on both health data and overall data policy – and vice versa, with rare disease plans in place that include references to health data. Standards for genetic and genomic data are also essential in recording consistent genomic sequencing results and identifying potential variants of scientific and clinical interest.

OUTCOME 5

People living with rare diseases contribute to data and evidence on Patient-Reported Outcomes

In line with the principle that people living with rare diseases are the experts on their own needs, it is essential for health data to include measures of importance to them. Capturing PROs is a method of integrating what matters to people living with rare diseases into studies used to inform treatment development and policymaking.

OUTCOME 6

Genomic data on rare diseases is consistently captured in an accessible database

Biobanks and genomic databases are examples of effective ways to capture genomic data, and have been implemented in both the US and Europe. In countries without genomic databases, an opportunity to identify relevant genes and use the information to inform diagnostics and possible treatments is lost.

OUTCOME 7

Rare disease patient registries are integrated into the healthcare system

Not all patient registries can be linked directly to health systems, as they vary greatly in structure and interoperability. Ideally electronic health records would automatically be connected to registry data – with patient consent – so that the data can effectively follow the patient. In the event this is not possible, interoperability between the healthcare system's records and external registries and providing patients with the possibility to allow secondary use of their health data is essential.

Patient advocacy groups have a critical role to play in collecting the data needed to make effective policy for people living with rare disease.

Rachel Sher

To understand the causes of rare disease and support those travelling to access care, we need to share data across borders.

Antoni Montserrat Moliner

MAKING ASPIRATION A REALITY

EXAMPLE	OUTCOME	DETAILS	MORE INFORMATION
National DIMDI project "Kodierung von Seltenen Erkrankungen" (Rare diseases coding)	Data is standardised for use across all care settings	The German Federal Ministry of Health funded a project which checked whether every rare disease in the Orphanet database was included in its ICD-10 framework. If they were not, they got added and assigned to a category there. The project also cross-checked all German ICD-10 codes that were already mapped to rare diseases with Orphanet's coding. Each rare disease entry has both a connected Orphacode and ICD-10-GM code, allowing compatibility with rare disease codes in other parts of Europe, and its own unique Alpha-ID Code. For example: Fibrodysplasia Ossificans Progressiva has the ICD-10-GM code of M61.19 and Orpha number 337, with a unique identifier of I32050.	Federal Institute for Drugs and Medical Devices, n.d. *National DIMDI project "Kodierung von Seltenen Erkrankungen" (Rare diseases coding)*. [Online] Available at: https://www.bfarm.de/EN/Code-systems/Terminologies/Alpha-ID-SE/national-dimdi-project/_node.html
The Duchenne Registry	Rare disease patient registries are integrated into the healthcare system	Established 2007 by Parent Project Muscular Dystrophy (PPMD) Organisers from US government agencies, IT development industry and academic institutions Funded by PPMD, which oversees the Registry Patient-led and managed Registries support advocacy on what matters most to the community – and facilitate trust in the context of decision-making on whether to share highly sensitive and personal data.	Parent Project Muscular Dystrophy, 2024. *The Duchenne Registry*. [Online] Available at: https://www.duchenneregistry.org/

Building Block 4
Health services

This building block encompasses the entire care pathway for people living with rare diseases. Health services should facilitate early detection of rare disease, preventing people from having to undergo the diagnostic odyssey and permitting care and treatment to be put in place. Fundamentally, health services should aim to support living well with rare diseases.

OUR ASPIRATION

Health services work for people with rare disease

To achieve this

- Early screening and testing contribute to early or timely diagnosis, which is a prerequisite for consistent provision of high-quality, multidisciplinary care in health and social care systems.
- There are support services in place for those who care for people living with rare diseases. Such pathways are flexible enough to accommodate individual needs, and service provision decisions add value for people living with rare diseases and are responsive to Patient Reported Outcomes.
- Internationally, experts agree on consistent clinical practices across borders to facilitate travel for care.

04

OUTCOMES AND PROGRESS MEASURES

OUTCOME 1

Early screening and testing lead to early or timely diagnosis

Newborn screening (NBS) saves lives by identifying cases early enough to provide treatment, which can stop or even prevent disease progression. It is an essential service for any health system seeking to address rare diseases. For conditions not screened at birth, genomic and genetic testing can provide diagnostic answers – although it is not always available. It is also key to monitor the prevalence of misdiagnosis and delayed diagnosis, to determine if (and how many) people are falling through the cracks.

OUTCOME 2

Health services provide the same high-quality care to all people living with rare diseases

Networks of experts that work together to provide clinical advice, diagnosis, treatment, and follow-up of people living with rare diseases have the potential to support local healthcare professionals (HCPs) with particular rare disease cases – improving consistency of care quality regardless of where the person lives.

OUTCOME 3

People living with rare diseases have access to multidisciplinary, interoperable services throughout the patient pathway

The services perspective on this outcome centres on the implementation of multidisciplinary care in practice; for example, service users' views on rare disease health services, and guidance for caring for people living with rare diseases in emergency and other medical situations. It further encompasses referral to support services and follow-up processes.

OUTCOME 4

People living with rare diseases can access social care services

Sickness and disability benefits should be responsive to rare diseases, providing fast-track decisions where necessary and ensuring people living with rare diseases have access to the financial support they need. Rehabilitation services also fall under social care, and can be measured in relation to the prevalence of unmet rehabilitation needs among people living with rare diseases. Specific support staff based in rare disease centres who can assist with coordination of non-medical needs can also be of great benefit.

OUTCOME 5

Rare disease pathways are adapted to individual needs

Ideally, each person living with rare diseases would take a well-established path through a hospital or other health centre. Such a path would be flexible enough to adapt to their unique needs, rather than one-size-fits-all, and should become a formal patient journey process. Where care pathways are not tailored to the person's needs, they may have to pay out-of-pocket to meet them.

OUTCOME 6

Service provision and coverage decisions take into account patient-reported outcomes (PROs) and are value-added for people living with rare diseases

Health services cannot be truly patient-centric without the input of those who use them. As such, they must include rare disease patient organisations in official rare disease diagnosis and treatment projects – in both organisational and leadership roles. Furthermore, countries should use Patient-Reported Outcome Measures (PROMs) and other outcomes meaningful to patients in practice – including in clinical outcome assessments, clinical trial endpoints, and for specific diseases. As previously mentioned, this means collecting and recording information that matters to people living with rare diseases and allows procurement decisions to depend on the value of medicinal products to people living with rare diseases.

OUTCOME 7

Clinical practices for rare disease are harmonised across borders

If travel for rare disease care becomes necessary, those who make the journey should be able to rely on the same baseline standard of care at home and elsewhere. Those who do travel for care should have access to information in a language they understand, and benefit from a specific policy setting out their right to participate in decision-making about their own care. Whether travel or telemedicine, authorities should document any barriers to care standards, update health data records, and provide follow-up appointments in their place of residence and there should be mechanisms in place for ensuring that personal data and follow-up appointments are available in their place of residence.

OUTCOME 8

There are mechanisms to support coordination between the health and social care systems for people living with rare diseases

It should be routine practice for clinics, social services, and community providers to work together on coordinating rare disease care – and for people living with rare diseases to participate in these processes and structures.

OUTCOME 9

Caregivers are able to access support services

Those who care for people living with rare diseases face various challenges, including loss of access to the labour market or reduced working hours. This, in turn, causes both personal financial impact and a reduction in productivity. Through providing respite care and/or financial assistance, governments can support caregivers to avoid poverty and – where possible – remain in or re-join the workforce.

OUTCOME 10

Young people living with rare disease experience a smooth, quality transition from paediatric to adult services

When asked to think of a person with rare diseases, many people imagine a newborn or young child. In the absence of guidance and solid frameworks for transition from paediatric to adult rare disease health and social care services, it is possible for young people living with rare diseases to become 'invisible' in society's eyes. If they drop off the radar, they face the real risk of disruptions to care and treatment upon moving into adulthood.

> Health services need to support people living with rare diseases throughout their lives. Especially during transitions of care, which come with a risk of treatment non-adherence and related health problems
>
> **Vinciane Quoidbach**

MAKING ASPIRATION A REALITY

EXAMPLE	OUTCOME	DETAILS	MORE INFORMATION
Innovation and Value Initiative and the EveryLife Foundation for Rare Disease - Rare Disease Initiative partnership	Service provision and coverage decisions take into account PROs and are value-added for people living with rare diseases	A partnership between the Innovation and Value Initiative and the EveryLife Foundation for Rare Diseases to develop new approaches to patient-centred outcomes research (PCOR), comparative effectiveness research (CER) and HTA via roundtables and a final report with recommendations.	Innovation and Value Initiative, 2023. *Partnering with Rare Disease Patients to Identify Meaningful Approaches to Health Technology Assessment.* [Online] Available at: https://thevalueinitiative.org/rare-disease-initiative/
Implementation of a coordinated transition process from paediatric to specialised adult care for people with Phenylketonuria (PKU)	Rare disease pathways are adapted to individual needs Young people living with rare diseases experience a smooth, quality transition from paediatric to adult services	Supporting successful follow-up, positive social outcomes, therapeutic adherence, and good, stable metabolic control with multidisciplinary teams	Mütze, U., Thiele, A.G., Baerwald, C. et al. Ten years of specialized adult care for phenylketonuria – a single-centre experience. Orphanet J Rare Dis 11, 27 (2016). https://doi.org/10.1186/s13023-016-0410-6 Peres, M.; Almeida, M.F.; Pinto, É.J.; Carmona, C.; Rocha, S.; Guimas, A.; Ribeiro, R.; Martins, E.; Bandeira, A.; MacDonald, A.; et al. Implementing a Transition Program from Paediatric to Adult Services in Phenylketonuria: Results after Two Years of Follow-Up with an Adult Team. Nutrients 2021, 13, 799. https://doi.org/10.3390/nu13030799 Giacomo Biasucci, Lucia Brodosi, Ilaria Bettocchi, Davide Noto, Francesca Pochiero, Maria Letizia Urban, Alberto Burlina, The management of transitional care of patients affected by phenylketonuria in Italy: Review and expert opinion, Molecular Genetics and Metabolism, Volume 136, Issue 2, 2022, https://doi.org/10.1016/j.ymgme.2022.04.004 van Wegberg, A.M.J., MacDonald, A., Ahring, K. et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis 12, 162 (2017). https://doi.org/10.1186/s13023-017-0685-2

Building Block 5
Health system financing

This building block focuses on financing. Health systems are challenged with limited resources even as population health needs are exponentially increasing. From an economic standpoint, policymakers have to weigh the trade-offs, and often lean towards the solutions that benefit the greatest number of people. Inevitably, such decisions, though pragmatic, can place those with rare disease, who are seen as a minority group, at a disadvantage. Financing mechanisms need to be addressed to ensure that people living with rare diseases are not denied care due to inability to pay, and that people living with rare diseases have equitable access to health systems.

05

OUR ASPIRATION

Health system financing meets rare disease community needs.

To achieve this

- People living with rare diseases and those caring for them have sufficient financial and non-financial support, as well as reliable information on funding options.
- Health systems would make open, transparent decisions on rare disease coverage in consultation with people living with rare diseases, based on Patient Reported Outcomes, and provide quality care at a sustainable cost by taking the unique characteristics of rare disease treatments into account.
- Governments would allocate funding to tackling inequalities in care access, ensure sufficient investment to effectively implement rare disease plans, and collect data about the socio-economic impacts of life with a rare disease to inform their funding decisions.
- Both public and private sectors should join forces to co-fund and invest in health research for rare diseases.

OUTCOMES AND PROGRESS MEASURES

OUTCOME 1

Financing accounts for and addresses inequalities in access to care

Health services often suffer from a 'postcode lottery', where the care and treatment access is dependent on where a person lives. For people living with rare diseases, this exacerbates the challenges they already face in meeting their medical needs. Additionally, health inequalities should be addressed across the healthcare system, including in rare disease. Governments should invest in ensuring that all people with rare diseases – regardless of where they live – have an equal ability to access care, free from any form of discrimination.

OUTCOME 2

Health system financing decisions on rare disease coverage are open and transparent

An ideal financing system would be reliable, consistent, and understandable for all stakeholders involved, as well as work for both rare and common health conditions. However, it is important to maintain a delicate balance between transparency and confidentiality while supporting access to quality care.

OUTCOME 3

People living with rare diseases have access to reliable information on care funding options

Sometimes, people have to travel to access particular kinds of rare disease care that are unavailable in their locality. They should be provided with reliable information and guidance on how to choose and arrange such treatment from quality providers, as well as with professional support to secure funding from their health system. Ideally, information about out-of-pocket costs should be available upfront.

OUTCOME 4

Innovative rare disease care is affordable to people living with rare diseases

People living with rare diseases should be financially protected and not suffer from catastrophic out-of-pocket payments. Therefore, countries must have pricing and reimbursement systems that are suited to and prepared to fund innovative care. People with rare diseases that lack treatment options should be able to benefit from early access to promising products.

OUTCOME 5

Governments collect data about socioeconomic impacts of living with a rare disease to determine funding allocations

Collection of socioeconomic data – such as by sex, age, and income –can provide meaningful information that can help policymakers take effective action to tackle disparities in access to education, employment, and healthcare. Patient advocacy groups (PAGs) and should be involved in the gathering or development of any data disaggregation approaches as a safeguard to protect the anonymity and privacy of people living with rare diseases.

OUTCOME 6

Service provision and coverage decisions take into account patient-reported outcomes (PROs) and are value-added for people living with rare diseases

PROs provide a way of measuring outcomes that matter to people living with rare diseases, and should be implemented throughout the regulatory process from marketing authorisation to pricing and reimbursement. These should be supplemented by other outcomes that people living with rare diseases see as meaningful, regardless of reporting method. As a result, health system coverage decision-making will operate to the benefit of people living with rare diseases.

OUTCOME 7

Rare disease plans include funding for implementation or signpost to funding sources

Having policies in place is an essential first step to creating enabling access for people living with rare diseases. Implementation of the policies frequently suffers from lack of funding. There are examples of good practice on funding for fulfilment of rare disease plans at EU level, and in both France and Italy.

OUTCOME 8

People living with rare diseases and those caring for them receive adequate financial and non-financial support

People living with rare diseases and their loved ones often have to undertake social care support tasks and shoulder the burden of disease-related costs. Those who care for people living with rare diseases must often reduce their working hours, in turn reducing their earning potential. This risks placing them in financial hardship and puts professional care assistance out of their financial reach. Without any support, people living with rare diseases and their families will not be able to escape this vicious cycle of economic impoverishment and lack of access to care.

OUTCOME 9

Health systems maintain quality of care at a sustainable cost

With health systems under pressure to contain costs impacting the funding for rare diseases. Health systems will need to seek alternative sources of funding models, such as public-private financing partnerships, to ensure that those living with rare diseases are still able to access quality care and treatment.

OUTCOME 10

Public-private models of financing support research in rare disease

Shared public-private investment in health research into rare disease and public-private partnerships (PPPs) funding research networks are both tried-and-tested methods of supplementing state funding with private sector capital in the rare disease space.

> It isn't enough to have systems in place. What matters for people living with rare diseases is how they're implemented in practice.
>
> **Alexander Natz**

MAKING ASPIRATION A REALITY

EXAMPLE	OUTCOME	DETAILS	MORE INFORMATION
Critical Path for Rare Neurodegenerative Diseases (CP-RND)	Public-private models of financing support research in rare disease	Public-private partnership between experts in rare neurodegenerative diseases, biopharma companies, regulators, PAGS to improve understanding of natural history of disease, identify biomarkers and improve clinical trial design to make treatment development more successful and efficient.	Critical Path Institute, 2022. *C-Path Awarded FDA Grant to Establish Public-Private Partnership to Advance Treatments for Rare Neurodegenerative Diseases.* [Online] Available at: https://c-path.org/c-path-awarded-fda-grant-to-establish-public-private-partnership-to-advance-treatments-for-rare-neurodegenerative-diseases/
National Rare Disease Plan 2023-2026 - Italy	Rare disease plans include funding for implementation or signpost to funding sources	Includes allocation of 25 million EUR annually	Ministero della Salute, 2023. *Piano nazionale malattie rare 2023 – 2026.* [Online] Available at: https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2023&codLeg=95257&parte=1%20&serie=null

Building Block 6
Health workforce

This building block emphasises the role of all health and social care professionals in providing high-quality care to people living with rare diseases.

OUR ASPIRATION

Health workforce supports access to high-quality care

To achieve this

- Rare disease topics need to be integrated in medical curricula and continuous professional development, so that people living with rare diseases are well-supported in handling the daily realities of their conditions.
- Professional development courses are informed by and developed with reference to the experiences of people living with rare diseases.
- Social services should also be knowledgeable about rare diseases and how best to support those living with them. Finally, people living with rare diseases should have easy access to specialist care.
- Policies are in place to encourage researchers and HCPs to specialise in genetics and genomics, so that the field has sufficient capacity to support the provision of clinical genetic care.

06

OUTCOMES AND PROGRESS MEASURES

OUTCOME 1

People living with rare diseases provide input into medical workforce training

Rare disease medical expertise should be supplemented by the knowledge people living with rare diseases have about their own needs and experiences. As such, HCPs will benefit from a deeper understanding of what it means to live with a rare disease that cannot be acquired from traditional lectures and textbooks.

OUTCOME 2

Social services professionals are trained and equipped to support people living with rare diseases

Amid increasing calls to improve the integration of health and social care, it is important that those working in the social services sector understand rare diseases, are aware of their impacts and specificities, and are prepared to support people living with them.

OUTCOME 3

Medical education systems prioritise rare disease care

Within the education system, it is important for medical schools to include rare disease content in their courses overall, and within lectures as part of the principle of integrating rare diseases into wider healthcare activities.

OUTCOME 4

Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases

Generalist and specialist HCPs should be aware of rare diseases and how to treat people living with rare diseases as part of their routine practice. In the absence of such awareness, referral and diagnosis may be delayed – which may result in avoidable disease progression.

OUTCOME 5

People living with rare diseases have easy access to specialist care

People living with rare diseases often have to travel to obtain a diagnosis or treatment, and long-distance travel can be complicated or prohibitive for health, financial, and familial reasons. Where serious access difficulties persist, some may even feel obliged to move house.

OUTCOME 6

People living with undiagnosed and rare diseases have access to genetic testing and counselling

Genomics can be a lifeline for people living with rare and undiagnosed diseases, as well as an emotionally challenging process for the person undergoing genetic testing and for their loved ones. Genomic medicine should always involve genetic counselling, but waiting lists can be long and some countries do not officially recognise genetic counselling as a healthcare profession. Disparities in geographical access can be addressed via the provision of telegenetics services.

MAKING ASPIRATION A REALITY

EXAMPLE	OUTCOME	DETAILS	MORE INFORMATION
European Reference Network Exchange Programme	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	European Commission funded exchanges for healthcare professionals to carry out a short secondment in another member centre of European Reference Networks, in order to spread knowledge and fill gaps in expertise. Applies to all disciplines, permits preference for particular topics that could particularly benefit from experience and knowledge sharing across centres. Staff whose centre is involved in a particular ERN (e.g. Rare Neurological Diseases) can also be seconded to a centre involved in a different ERN of relevance (e.g. Rare and Complex Epilepsies).	ECORYS, 2023. *ERN Exchange Programme: Striving for better and fairer healthcare.* [Online] Available at: https://www.ecorys.com/case-studies/ern-exchange-programme-striving-for-better-and-fairer-healthcare/
National Society of Genetic Counsellors	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	Provides online education for genetic counsellors and approves continuing education activities for recertification purposes. Provides practice guidelines based on clinical evidence, and practice resources for topics without such a full clinical evidence base - including certain rare diseases, based on experiences and opinions of the authors.	National Society of Genetic Counselors (NSGC), n.d. *About.* [Online] Available at: https://www.nsgc.org/About/About-NSGC

Annex I
Measuring the Framework

BUILDING BLOCK: LEADERSHIP AND GOVERNANCE
GUARANTEE PUBLIC HEALTH PRIORITISATION OF PEOPLE LIVING WITH RARE DISEASES

OUTCOMES	MEASURES
Effective incentives spur research and innovation in rare disease [OVERLAP INNOVATION]	• Support for orphan medicines: presence/absence of dedicated market exclusivity award for orphan medicines • Support for orphan medicines: total number of orphan drugs receiving research and development support[6] • Non-economic incentives: providing support to developers in navigating the regulatory process (e.g. scientific advice) • Non-economic regulatory incentives: existence of flexibility for authorisation procedures for research and innovation in rare diseases
Value assessment frameworks for rare diseases are aligned and harmonised	• Existence of specific pathways for access to orphan devices [yes/no] • Total number of licensed devices in a particular jurisdiction • Existence of healthcare coverage of medical devices for people living with rare diseases) [yes/no] • Programmes are implemented for HCPs and people living with rare diseases to take part in value assessment • Value assessment processes are ongoing and responsive to new evidence: e.g. early access schemes and other flexible frameworks that allow ongoing evidence generation to determine clinical effectiveness • Value assessment systems are taking characteristics of orphan products into account and provide flexibilities accordingly: Existence of OMP-specific value assessment frameworks

Rare disease is integrated into overall health policy	• Strategies are in place for mainstreaming rare disease into other health plans, and vice versa[7]
	• Healthcare guidelines include people living with rare diseases with other co-morbidities:
	  ○ Existence of guidance for pregnant people living with rare diseases[8]
	  ○ Existence of COVID-19[9] and other health emergency guidance for people living with rare diseases
	• Rare diseases included in hospital national speciality plans/structures:
	  ○ E.g. NAMSE three-tier standards (A/B/C) for centres[10]
	  ○ E.g. NORD Centres of Excellence[11]

Rare disease policies are monitored and adapted based on outcomes achieved	• Addressing unmet needs: Estimated number of medicines authorised in rare diseases:[12]
	  ○ Which previously lacked an authorised treatment
	  ○ Which represent an improvement over existing treatments
	• Wider accessibility: Estimated % of the national population who can now access OMPs due to orphan specific legislation[13]
	• Improving quality of life: Estimated Quality-adjusted life years (QALYs) gained as a result of orphan specific legislation.[14]

Mechanisms exist for people living with rare diseases to contribute to rare disease policy process	• Existence of Rare Disease Advisory Councils: total number of active RDACs[15] • Existence of a National Plan for Rare Diseases that has a Rare Diseases National Committee with patient participation • People living with rare diseases are represented in NBS programme governance bodies • Patient involvement in national health service reimbursement decisions: total number of patients on official pricing and reimbursement committees[16] • Patient involvement in payer decisions: number of patients on coverage boards like Medicaid DUR and private insurance P&T committees

[6](European Commission, 2019)

[7]Ibid.
[8](European Reference Network VASCERN, 2023)
[9](Orphanet, 2020)
[10](Research For Rare, n.d.)
[11](NORD, n.d.)
[12](European Commission, 2019)
[13]Ibid.
[14]Ibid.
[15](NORD, n.d.)
[16](Stabsstelle Patientenbeteiligung des G-BA, n.d.)

OUTCOMES	MEASURES
Actionable rare disease plans are implemented	• Availability of essential medicines for rare disease: Proportion of the 204 IRDiRC recommended essential products[17] available in the country • National Centres of Expertise receive sufficient funding: size of budget allocation for Centres of Expertise • Existence of a rare disease advisory committee or working group that oversees implementation of the plan[18]: ○ Meets regularly (yes/no) ○ Includes all relevant stakeholders – patients, government, industry, HCPs, payers, academia (yes/no) • Number of centres of expertise/excellence or national equivalent per million people[19] • Existence of help lines providing information on rare diseases: directed at patients/directed at professionals/both[20] • Existence of a national policy on registry and data collection for rare disease (yes/no)[21] • Provision for rare disease research at national level:[22] ○ In a dedicated programme ○ As part of the general research funding programme • Public funds specifically allocated for rare disease research actions/ projects per year since the plan started: value in national currency[23] • Publication of monitoring and evaluation reports [yes/no]
Rare disease plans are long-term and are regularly adapted	• Rare disease national plans and strategies: ○ existence of a national plan/strategy[24,25] • actively ongoing without end date/time-limited and ongoing/ expired/not yet adopted[26] ○ regular review of plan/strategy: time since last review ○ Existence of regulations/laws that support establishment and development of a rare disease plan: Yes/in progress/no[27] • People living with rare diseases are represented in all stages of developing, updating, monitoring, and developing the plan[28]: ○ Yes, and they have an official input role ○ Yes, but only as observers ○ Yes, but only for consultation purposes ○ No

[17](Gahl, et al., 2021)
[18](European Union Committee of Experts on Rare Diseases (EUCERD), 2013)
[19]Ibid.
[20]Ibid.
[21]Ibid.
[22]Ibid.
[23]Ibid.
[24](FDA, 2022)
[25](Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen, 2013)
[26](European Commission, 2019)
[27](European Union Committee of Experts on Rare Diseases (EUCERD), 2013)
[28]Ibid.

OUTCOMES	MEASURES
National genomics programmes are implemented for rare disease care and research	• Existence of national genomics programmes in country (e.g. Genomics England, Mayo Clinic Program for Rare and Undiagnosed Diseases)
The public understands what rare disease means	• Educational campaigns/programmes on rare disease for the general public are in place • % of people who have never heard about anyone with a rare disease[29] • % of people who had heard of particular rare diseases[30]: ○ Cystic fibrosis ○ Duchenne muscular dystrophy ○ Haemophilia ○ Huntington's disease ○ Osteogenesis imperfecta ○ Progeria • % of people reporting themselves to be knowledgeable about rare disease[31] • % of people reporting familiarity with their national rare disease patient organisation[32] • % of people reporting they know someone living with a rare disease[33] • % of people who would like to learn more about rare disease[34] • % of people who have heard of Rare Disease Day[35]
National governments collaborate on international disease registries	• Interoperability of national rare disease registries [yes/no] • Availability of cross-registry analysis of interoperable rare disease registries [yes/no]
Regulatory approvals reference international clinical trial data	• Existence of international or mutual recognition regulatory framework that can expedite market authorisation • National implementation of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines[36]

[29](Directorate-General for Communication - European Commission, 2014)
[30]Ibid.
[31]Adapted from (Kobau & Zack, 2021)
[32]Ibid.
[33]Ibid.
[34]Ibid.
[35]Ibid.
[36](International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) , n.d.)

BUILDING BLOCK: **INNOVATIVE IDEAS** BECOME LIFE-CHANGING TECHNOLOGIES AND THERAPIES

OUTCOMES	MEASURES

Effective incentives spur research and innovation in rare disease	• Tax and intellectual property incentives drive innovation to create new treatments: regulatory exclusivity length[37,38,39,40]
	• Tax and intellectual property incentives drive innovation to create new treatments: tax credits for research and development[41,42]
	• Regulatory bodies provide incentives for the development of rare disease therapies:
	  ○ Discounts/waivers on regulatory fees for orphan medicinal products[43,44]
	  ○ Accelerated reviews[45,46]
	  ○ Early engagement opportunities[47,48]
	  ○ Assessor understanding of rare disease[49,50]
	  ○ Regulatory flexibility on data packages[51,52]
	  ○ Conditional authorisation pathways/exceptional circumstances[53,54,55,56]
	• Increase in number of clinicians driving research: % of clinical academics as a proportion of national health service medical consultants[57]
	• Funding levels for rare disease research: Amount of grant funding offered by public bodies/private companies/third sector for rare disease research (total per year, in local currency)
	• Incentives encourage the development of new clinical outcome measures: Regulators work with researchers to develop promising novel measures for evaluating effectiveness of rare disease treatments.[58]

Health data related to rare disease diagnosis and care is accessible for research purposes	• Secondary use for research is permitted: Electronic Health Records are available in pseudonymised form for research[59,60] • Secondary use for research is permitted: industry researchers can access health data[61] • Scope of data available: Data from healthcare context alongside health registries, research context, social systems[62]

[37](Food and Drug Administration (FDA), 2022)
[38](FDA, 2023)
[39](National Organization for Rare Disorders, Inc. (NORD), 2023)
[40](German Federal Institute for Drugs and Medical Devices, n.d.)
[41](OECD, 2022)
[42](OECD, 2022)
[43](EMA, 2020)
[44](FDA, 2019)
[45](EMA, 2022)
[46](FDA, 2018)
[47](EMA, 2023)
[48](FDA, 2018)
[49](EMA, 2024)
[50](FDA, 2023)
[51](FDA, 2023)
[52](Rare Impact, 2020)
[53](FDA, 2018)
[54](FDA, 2018)
[55](EMA, n.d.)
[56](EMA, 2024)
[57](Academy of Medical Sciences, 2020)
[58](FDA, 2024)
[59](Bundesministerium für Gesundheit, 2023)
[60](Office of the Assistant Secretary for Planning and Evaluation, n.d.)
[61](HealthData@EU Pilot, 2023)
[62]Ibid.

OUTCOMES	MEASURES

	• Metadata catalogues: Existence of metadata catalogue[63]
	• Policy promotes secondary data availability: opt-out system for electronic health records[64]
	• Policy promotes secondary data availability: reduced public financial support for hospitals that do not use Electronic Health Records[65]
	• Existing data infrastructures allow access and cross-site analysis of data:
	  ○ Interconnection of individual site databases to create regional/national/international databases[66]
	  ○ Ability of healthcare facilities to send and receive electronic health information to/from other facilities and clinicians[67]
	  ○ Secure IT tools are in place for electronic exchange of health data between authorised healthcare providers for the purpose of diagnosing and treating people with rare diseases.[68]
	• Data access involves an informed consent process.
	  ○ Consent forms[69]:
	  • Provide information about how data would be used[70]
	  • Explain individuals' data protection rights[71]
	  • Permit people to consent to data sharing:
	  • For care[72]
	  • For inclusion in databases/registries[73,74]
	  • To be contacted about research[75]
	  • To connect with family members' health data[76]
	  • Of audiovisual imaging[77]
	  • Allow people to consent to linking-up of their health data across various sources[78]
	• Data Access Committees (DACs) are established to help guide the implementation of data access processing requirements and protect people's data
	  ○ % of rare disease registries that have a data access committee[79]
	  ○ Number of access requests made to DACs – both approved and denied[80]
	  ○ Average time from submission to DAC decision[81]
	  ○ Number of users approved for access to the DAC[82]
	• Country adopts and implements data standards needed for data sharing in all relevant care/research
	  ○ Scoring based on level of implementation – country scores 0 for no adoption of common health data standards, 1 for voluntary[83] implementation, and 2 for mandatory implementation

[63]Ibid.
[64](Bundesministerium für Gesundheit, 2023)
[65](Centers for Medicare & Medicaid Services, 2023)
[66](Office of the National Coordinator for Health Information Technology (ONC) , 2019)
[67](Clinovations Government + Health (CGH), 2016)
[68](European Commission, 2019)
[69](European Commission, n.d.)
[70,71,72,73]Ibid.
[74](Nguyen, et al., 2019)
[75](European Commission, n.d.)
[76](Nguyen, et al., 2019)
[77,78]Ibid.
[79](Ali, et al., 2020)
[80](Global Alliance for Genomics & Health, 2021)
[81,82]Ibid.
[83](Office of the Assistant Secretary for Planning and Evaluation (ASPE), n.d.)

OUTCOMES	MEASURES

Researchers participate in consortia to share knowledge and expertise	• Active consortia: Country has/has access to national reference networks for rare disease[84] adapted to national characteristics
	• Active consortia: Country has a healthcare provider involved in a European Reference Network[85] or in NORD's Rare Disease Centers of Excellence program[86] [EU/US]
	• Active consortia: Country has a member organisation in the International Rare Diseases Research Consortium (IRDiRC)[87]
	• Country has a national rare disease reference network in place
	• Country has a member organisation in Rare Diseases International[88]
	• Country has at least one healthcare provider involved per European Reference Network[89] [Europe only]
	• Researchers of a country share knowledge and data in community-based rare disease research consortia
	  ○ % of regions in a country with rare disease networks[90,91,92,93]
	  ○ % of rare disease registries funded by regional authorities[94]
	  ○ % of rare disease registries reporting they share data with other registries[95]

[84](SE-Atlas, 2023)
[85](Hedley, et al., 2019)
[86](NORD, 2023)
[87](European Commission, 2019)
[88](Rare Diseases International, n.d.)
[89](European Commission, n.d.)
[90](NHS England, n.d.)
[91](Pieroni, et al., 2023)
[92](Asia-Pacific Economic Cooperation, 2018)
[93](Oregon Health & Science University, n.d.)
[94](Taruscio, et al., 2014)
[95]Ibid.

OUTCOMES	MEASURES

Innovative research in rare disease is being advanced	• Clinical trial support incentives: Tax credits offsetting clinical trial costs[96,97,98]
	• Clinical trial support programmes: Regulators provide support, guidance, and flexibility on evidence-generation for rare disease candidate treatments[99]
	• Regulators provide guidance on the types of data they would require to monitor outcomes [yes/no]
	• Benchmarking: The number of genes identified as linked to rare diseases since 2010, the cumulative number of new orphan drugs since 2010[100]
	• Benchmarking: % of orphan drugs with indications for:[101]
	  ○ One rare disease
	  ○ Multiple rare diseases
	  ○ Both rare and common diseases
	• Benchmarking: % of orphan drugs with follow-on approvals[102]:
	  ○ For a new rare disease
	  ○ Expanding its use in the same rare disease
	  ○ In a different therapeutic area than the first one
	  ○ For a rare paediatric indication
	• Levels of government funding provided for rare disease research year-on-year
	  ○ Annual estimates of funding provided to research projects on rare disease[103]
	• Systematic establishment and operation of natural history registries that are modular and interoperable for at least a basic set of core data elements
	  ○ % of rare disease registries with clearly defined core data elements[104]
	  ○ % of rare disease registries aiming to record natural history of the disease[105]
	  ○ % of rare disease registries which use their own coding systems, or have no coding system[106]
	• Benchmarking: rare diseases for which interoperable high quality healthcare data is available for secondary use
	  ○ % of rare disease registries with procedures for checking data quality[107]
	  ○ % of rare disease registries that use quality indicators[108]
	  ○ % of registries linked to external data providers[109]
	  ○ % of approved requests for registry data[110]

[96](NORD, 2022)
[97](118th Congress, 2023)
[98](Prader-Willi Syndrome Association USA, n.d.)
[99](European Medicines Agency (EMA), 2023)
[100](International Rare Diseases Research Consortium (IRDiRC), 2022)
[101](Miller & Lanthier, 2024)
[102]Ibid.
[103](National Institutes of Health (NIH), 2023)
[104](Ali, et al., 2021)
[105](Taruscio, et al., 2014)
[106]Ibid.
[107](Ali, et al., 2021)
[108](Taruscio, et al., 2014)
[109](Pristas, et al., 2015)
[110]Ibid.

OUTCOMES	MEASURES

People living with rare diseases are able to participate in clinical research	• Participation in research:
	  ○ % of people living with rare diseases who have taken part in studies[111]
	  ○ % of rare disease clinical trials that are discontinued due to low participation rates[112]
	• Measures derived from surveys investigating willingness and ability to participate in research, conducted by governmental and patient organisations
	  ○ Self-reported positive/negative experiences of research participation[113]
	  ○ Self-reported motives for taking part in rare disease research[114]
	  ○ Willingness to share health information with a patient-led rare disease database[115]
	  ○ Self-reported motives for sharing health information in a patient-led rare disease database[116]
	  ○ Self-reported concerns about sharing health information in a patient-led rare disease database[117]
	• Peer-to-peer education among people living with rare diseases regarding clinical research and clinical trials
	  ○ Number of patient advocates that have received peer education on participating in medicines research and development[118]
	  ○ % of peer-educated people living with rare diseases who go on to advise developers on research[119]
	• Evidence of diversity in clinical trial participants in research studies
	  ○ % of registries that collect sociodemographic information[120]
	  ○ Disaggregated data on rare disease research participation by:
	  • Gender[121,122]
	  • Age[123]
	  • Race/ethnicity[124]
	  • Level of education completed[125]
	  • Before-tax annual income[126]
	  • Health insurance coverage[127]
	  ○ Patient advocacy organisations offer resources and services designed to ensure diverse representation in clinical research[128]:

[111](EURORDIS, 2018)
[112](Rees, et al., 2019)
[113]Ibid.
[114]Ibid.
[115](RARE-X, 2022)
[116]Ibid.
[117]Ibid.
[118](EURORDIS, n.d.)
[119](Centre for Innovation in Regulatory Science (CIRS), 2021)
[120](Taruscio, et al., 2014)
[121](EURORDIS, 2018)
[122](RARE-X, 2022)
[123]Ibid.
[124]Ibid.
[125]Ibid.
[126]Ibid.
[127]Ibid.
[128](Black Women's Health Imperative (BWHI), Rare Disease Diversity Coalition (RDDC), Upequity, 2022)

OUTCOMES	MEASURES

	• Information in languages other than the majority language of the country
	• Proactive promotion of clinical trials through new outlets to reach diverse populations
	• Awareness raising about diversity in clinical trials on social media
	• Reaching out to community groups to reach people not previously targeted
	• Offering accessible information on clinical trials
	  ○ Regulators recommend that developers provide a plan for increasing research enrolment among historically underrepresented groups [yes/no][129]
	  ○ Regulators provide guidance on increasing research enrolment among historically underrepresented groups (yes/no)[130]
	• Number of rare diseases with:
	  ○ active trials
	  ○ natural history studies in place
	• National authorities permit telehealth participation in clinical trials [yes/no]

Innovative ideas are translated to new technologies and treatments for rare disease	• Medicines developed: Number of authorised OMPs in the locality[131,132,133,134] • Number of OMPs which payers have approved for use in their market • Amount of money invested in innovative medical research: government budget allocations for research and development in health[135] • Number of specific rare disease research programmes per country • Existence of clinical research networks for rare disease • Number of academic projects transitioning to industrial development[136] • Number of investigational medicinal products implemented into clinical research and developed in the country[137]

[129](Food and Drug Administration, 2022)
[130]Ibid.
[131](EMA, 2023)
[132](EMA, 2023)
[133](FDA, 2024)
[134](FDA, 2023)
[135](OECD, 2023)
[136](European Commission, 2022)
[137]Ibid.

OUTCOMES	MEASURES

Researchers are inspired to work on rare disease	• Legislation creates a positive environment for rare disease research: Estimated impact on research and development spending on OMPs due to the legislative framework[138]
	• Funding for rare disease research and infrastructure is awarded by the government or higher education institutions (or both).
	  ○ Annual estimates of funding provided to research projects on rare disease[139]
	  ○ % of rare disease registries funded by national authorities or university/research institutions[140]
	• Time, workload, funding, management decisions and infrastructure allow clinical rare disease researchers to spend sensible levels of time on research: % of clinical rare disease researchers with dedicated research time allocation[141]
	• All Early Career Researchers in funded projects have the possibility to undertake suitable training courses/certification[142]
	• Targeted mobility programmes for rare disease researchers from under-represented countries[143]

Advancements in rare disease research result from collaboration across disciplines	• Public funding for programmes that bring experts from multiple disciplines together to understand, diagnose and treat rare diseases more efficiently and effectively: % of funded studies which are multidisciplinary[144]
	• Public funding for partnerships establishing multidisciplinary doctoral programmes facilitating interdisciplinary innovative research: Public funding is provided for the organisation and delivery of interdisciplinary doctoral programmes[145]
	• Evidence of precompetitive and/or non-competitive research being undertaken across multi-stakeholder collaborations, including industry.
	  ○ Proportion of research funding that is non-competitive[146]
	  ○ Public funding is provided for pre-competitive research networks[147]
	• Public/Private partnerships undertaking research
	  ○ % of national research and development expenditure funded by the private sector[148]
	  ○ % of public research budget allocated to public-private partnerships[149]

[138](European Commission, 2019)
[139](National Institutes of Health (NIH), 2023)
[140](Taruscio, et al., 2014)
[141](Academy of Medical Sciences, 2020)
[142](European Commission, 2022)
[143]Ibid.
[144](Academy of Medical Sciences, 2016)
[145](European Commission, 2022)
[146](Ghent University, 2023)
[147](Bundesministerium für Wirtschaft und Klimaschutz (BMWK), 2024)
[148](Reillon, 2017)
[149]Ibid.

OUTCOMES	MEASURES

Innovative care for rare diseases is advanced throughout the life course	• Diagnostic: Time between age of onset and age of diagnosis[150]
	• Diagnostic: Time between first related contact with healthcare system and diagnosis
	• Diagnostic: Healthcare system allows quick access to genetic high-quality testing
	• Diagnostic: reduction in time taken to diagnose
	• Diagnostic: accuracy and quality of diagnosis (no diagnosis/ misdiagnosis/diagnosis)[151]
	• Prevalence: Prevalence at birth[152]
	• Prevalence: Measurement of age distribution[153]
	• Prevalence: Number of patients[154]
	• Prevalence: Mortality rate[155]
	• Natural history: patient-meaningful outcomes[156]
	• Natural history: Real world data on disease progression and management[157]
	• Intervention/treatment: patient-meaningful endpoints
	  ○ % of trials with patient advocates actively involved in design[158,159]
	  ○ % of public research budget awarded to patient-oriented research projects[160]

Payers engage in open dialogue early in the development process for innovative treatments	• Guidance is in place for communication between payers and developers: Guidance from payers on how developers can engage with them – publicly available/privately shared/does not exist
	• Processes enable systematic early dialogue about innovative treatments
	  ○ Programmes are in place for meetings and feedback provision between regulators and developers of new technologies[161]
	  ○ Processes are in place for requesting input on whether planned research meets the regulator's requirements[162]
	• Payers regularly communicate with developers of orphan medicinal products
	  ○ Number of requests for scientific advice on orphan medicinal products and of responses provided[163]
	  ○ % of orphan product marketing authorisation applications that had received scientific advice[164]
	• Developers are explicitly permitted to exchange product information with payers prior to approval, including factual presentation of results of studies - [yes/no]

[150](Zanello, et al., 2022)
[151]Ibid.
[152]Ibid.
[153]Ibid.
[154]Ibid.
[155]Ibid.
[156]Ibid.
[157]Ibid.
[158](Bundgaard, et al., 2022)
[159](Fergusson, et al., 2018)
[160](Canadian Institutes of Health Research, 2011)
[161](FDA, 2023)
[162](EMA, 2023)
[163](EMA, 2023)
[164]Ibid.

OUTCOMES	MEASURES

People living with rare diseases are able to access available treatments	• Availability of orphan medicine: % of healthcare providers unable to prescribe an existing orphan medicine because it was not available in their country of practice[165]
	• Availability of orphan medicine: Presence/absence of alternative access methods where a product is not available in the country
	  ○ Named patient programmes
	  ○ Cross-border access routes
	• Orphan-specific value assessment systems: % of countries with orphan-specific value assessment systems[166]
	• Time to access: Days between marketing authorisation and date of availability to patients[167]
	• Market access:
	  ○ Estimated impact of EU Orphan Regulation on time-to-market[168]
	  ○ Food and Drug Administration median review time for orphan marketing approvals[169]
	• Approval time for orphan and non-orphan medicinal products (OMPs) (European Medicines Agency and Food and Drug Administration)[170]

[165](European Commission, 2019)
[166]Ibid.
[167](EFPIA & IQVIA, 2023)
[168](European Commission, 2019)
[169](United States Government Accountability Office, 2018)
[170](Centre for Innovation in Regulatory Science (CIRS), 2023)

BUILDING BLOCK: **HEALTH INFORMATION SYSTEMS** ACCELERATE ACCESS TO AND DEVELOPMENT OF NEW WAYS TO CARE FOR RARE DISEASES

OUTCOMES	MEASURES
New technologies are harnessed to reduce complexity of diagnosis for rare diseases	• Telemedicine uptake: Doctors offer telehealth or telemedicine appointments[171] • Big data applications in the context of rare diseases: publicly funded pilot projects of big data for rare disease take place[172] • Implementation of genome sequencing in rare disease diagnosis: genome sequencing is available in the national health system

Health data related to rare disease diagnosis and care is accessible for research purposes	• Implementation of EHR: HIMSS Electronic Medical Record Adoption Model (EMRAM) score (0-7, where 7 is the most advanced EMR system)[173]
	• Sample Retention: Are dried blood spot (DBS) samples retained for scientific purposes?[174]
	• Self-registration system for government-run rare disease data registries:
	  ○ Existence of government-run portals connecting different rare disease registries
	  ○ Presence/absence of a national registry of rare diseases[175,176]
	  • % of regions contributing data to this registry
	  • Number of diseases included in the registry

People living with rare diseases have access to multidisciplinary, interoperable services throughout the patient pathway	• Provision for e-prescriptions[177] • Telemedicine uptake: Doctors offer telehealth or telemedicine appointments[178] • Legislation for system digitalisation: digital law legislation in place[179] • Legislation for system digitalisation: health IT - legislation in place[180] • Specialty prescriptions processed electronically[181] • Existence of individualised multidisciplinary care networks for rare disease patients that are facilitated through the respective e-infrastructure [yes/no]

[171](Myrick, et al., 2022)
[172](Bundesministerium für Gesundheit (BMG), 2021)
[173](Amelung, et al., 2022)
[174](NORD, n.d.)
[175](Federación Española de Enfermedades Raras, 2022)
[176](Sciensano, n.d.)
[177](Gesellschaft für Telematik (gematik), n.d.)
[178](Myrick, et al., 2022)
[179](Bundesministerium für Gesundheit, 2023)
[180](Office of the National Coordinator for Health Information Technology (ONC), n.d.)
[181](Surescripts Network Alliance, 2022)

OUTCOMES	MEASURES
Data is standardised for use across all care settings	• Standardised coding system: Use of an interoperable standard - Alpha-ID/Orphacodes[182,183] • Coding of rare diseases on national level:[184] use of Orphacodes in national health information systems • Digitalisation strategy for healthcare and nursing: strategy in place that is also mentioning rare[185] [yes/no] • Digitalisation strategy for healthcare and nursing: National plan of action for people living with rare diseases[186] [yes/no] • Existence of a national data strategy[187] [yes/no] • Existence of a Public Health Data Strategy[188] [yes/no] • Inclusion of health data in the rare disease strategy[189] [yes/no]
People living with rare diseases contribute to data and evidence on Patient-Reported Outcomes	• Nationwide use of Patient Reported Outcome Measures (PROMs): Common definitions of PROMs in place[190] • Existence of a PROM database[191] • Existence of a PROM information system[192] • Patient organisations involved in interactions with regulatory and HTA institutions for agreement on PCOMs and PROMs[193]
Genomic data on rare diseases is consistently captured in an accessible database	• Establishment of biobanks: National level biobank platform[194,195] • Establishment of genomic databases: Number of sequenced genomes available in biobanks
Rare disease patient registries are integrated into the healthcare system	• Healthcare systems enable secondary use of data which could be of use for patient registries: Secondary use of healthcare data is permitted for purposes of connectivity with registries (yes/no)

[182](Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), n.d.)
[183](National Institutes of Health, n.d.)
[184](Bundesministerium für Gesundheit (BMG), 2021)
[185](Bundesministerium für Gesundheit (BMG), 2023)
[186](Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen, 2013)
[187](Office of Management and Budget, 2020)
[188](Centers for Disease Control, 2023)
[189](FDA, 2022)
[190](ERICA, 2022)
[191](ERICA, 2023)
[192](Northwestern University, 2023)
[193](European Commission, 2022)
[194](German Biobank Node, n.d.)
[195](All of Us Research Program, 2024)

BUILDING BLOCK: **HEALTH SERVICES** WORK FOR PEOPLE WITH RARE DISEASES

OUTCOMES	MEASURES

Early screening and testing lead to early or timely diagnosis	• Timely diagnosis - newborn screening:
	  ○ Number of Recommended Uniform Screening Panel (RUSP) diseases screened for (USA)[196]
	  ○ Whole Genome Sequencing (WGS) coverage[197]
	  ○ Number of newborns screened[198]
	  ○ Routine follow-up on positive NBS tests[199]
	  ○ Number of diseases included in NBS programme[200]
	• Diagnostic support measures for adult patients:
	  ○ % of patients being misdiagnosed at least once prior to being correctly diagnosed[201]
	  ○ Genes tested in country[202]
	• Genetic tests/year[203]
	• Availability/uptake of next generation sequencing[204]
	  ○ NGS centre availability [yes/no]
	  ○ NGS is regularly used in clinical practice [yes/no]
	  ○ Number of patients being tested
	• Routine and regular quality assurance processes for genetic testing are in place[205]
	  ○ Labs/institutions are ISO accredited/certified [yes/no]
	  ○ Clinical standards are regularly updated [yes/no]
	  ○ Internal and external standards are used [yes/no]
	  ○ Processes are subject to external quality assessment [yes/no]

Health services provide the same high quality care to all people living with rare diseases	• Access to clinical advice, diagnosis, treatment and follow up of patients in national and European Reference Networks:
	  ○ number of new patients referred to the healthcare providers participating in the network with the diagnosis of a disease / condition that fall within its the scope[206]
	  ○ Total volume of patients entered into the network's patient management system[207]

[196](NORD, n.d.)
[197](Rady Children's Institute: Genomic Medicine, 2023)
[198](German Society for Neonatal Screening (DGNS), 2020)
[199](Speckmann, et al., 2023)
[200](Gemeinsamen Bundesausschusses, 2023)
[201](EURORDIS, 2009)
[202](Hedley, et al., 2019)
[203](Halbisen & Lu, 2023)
[204](Horgan, et al., 2024)
[205]Ibid.
[206](ERN Continuous Monitoring Working Group of the ERN Coordinators Group & the Board of Member States, 2019)
[207]Ibid.

OUTCOMES	MEASURES

People living with rare diseases have access to multidisciplinary, interoperable services throughout the patient pathway	• Inter-service coordination:
	  ○ % of people living with rare diseases and carers reporting poor communication[208]
	  ○ % of people living with rare diseases and carers declaring they have to visit different health, social and local support services in a short space of time.[209]
	  ○ % of people living with rare diseases and carers feeling these services communicate badly among each other[210]
	• Specific rare disease care diagnosis and care guidelines exist:
	  ○ Emergency care guidance[211]
	  ○ Guideline on diagnosis[212]
	  ○ Existence of centres/programmes for undiagnosed diseases[213,214]
	• Rare disease centres with established follow-up processes: % of rare disease centres with these in place[215]
	• People living with rare diseases are signposted to relevant support by HCPs [yes/no]
	  ○ People living with rare diseases report that HCPs encouraged them to attend groups/classes providing support on their rare disease[216]
	  ○ HCPs have access to a list of relevant resources and services for people living with rare diseases in their local area (yes/no)
	• Rare disease is integrated into the work and day-to-day practice of HCPs
	  ○ Existing health services are deployed in ways that benefit people living with rare diseases[217] e.g.:
	  • Sexual and reproductive healthcare
	  • Antenatal and postnatal care
	  • Newborn Screening (NBS)
	  • Neonatal health services
	  • Paediatric primary care
	  • Community health work
	  • Rehabilitation
	  • Nutrition support
	  ○ Funding is available for pilot projects on rare disease mainstreaming into general healthcare services, and for rolling them out across the health system[218]
	  ○ Strategies are in place for mainstreaming rare disease into other health plans, and vice versa[219]

[208](EURORDIS, 2017)
[209]Ibid.
[210]Ibid.
[211](Orphanet Urgences, 2018)
[212](Wiendl & Meisel, 2022)
[213](Universitätsklinikum Gießen – Marburg, 2022)
[214](National Human Genome Research Institute (NHGRI), 2023)
[215](Schmidt, et al., 2020)
[216](EURORDIS, 2021)
[217](Choudhury & Chaube, 2022)
[218](EURORDIS, 2019)
[219]Ibid.

OUTCOMES	MEASURES

People living with rare diseases can access social care services	• Access to sickness/disability benefits[220]: presence/absence of fast-track routes to access disability benefits[221]
	• Access to sickness/disability benefits: % of people living with rare diseases and carers reporting sufficient access to disability benefits for their needs[222]
	• Access to services beyond standard primary care:
	  ○ % of people living with rare diseases and carers that have to visit multiple health and social support services in a short space of time[223]
	  ○ % of people living with rare diseases and carers with unmet needs for rehabilitation services[224]
	  ○ % of people living with rare diseases and carers with unmet needs for psychological support[225]
	• Rare disease centres have designated staff supporting non-medical daily life of patients[226]

Rare disease pathways are adapted to individual needs	• Healthcare coverage includes treatments and medicines that meet the needs of people living with rare diseases: Healthcare costs not covered by insurance (e.g. experimental, alternative, non-traditional treatment spending, over-the-counter drugs, dental surgeries): per person (2019 $)[227] • Existence of flexible care pathway model(s) mapped against individual patient journeys[228]

[220]Ibid.
[221](Social Security Administration, 2023)
[222](Euregio Meuse-Rhine Rare Diseases (EMRaDi), 2020)
[223](EURORDIS, 2017)
[224]Ibid.
[225]Ibid.
[226](Toledano-Alhadef, et al., 2020)
[227](Yang, et al., 2022)
[228](Ward, et al., 2022)

OUTCOMES	MEASURES

Service provision and coverage decisions take into account patient-reported outcomes and are value-added for people living with rare diseases	• Patient organisations represented in national and European Reference Networks[229]:
	  ○ Percentage of networks with patient associations with voting members on the network board
	  ○ Number of patient associations leading or co-leading specific network project activities
	  ○ Number of patient associations represented on panels involved in producing clinical guidelines
	  ○ Number of patient associations involved in evaluating patient information and other network documents to ensure accessibility for laypeople
	• PROMs are used in practice
	• Requirement for a patient-reported outcome to be recorded in clinical outcome assessments[230]
	  ○ Guidance on using PROMs as an endpoint in a clinical trial[231]
	• Health technology assessments: patients are included in the process: People living with rare diseases have the chance to provide feedback and comments throughout the assessment process
	• Health technology assessments: patients have a formal role in providing input to the HTA process [yes/no]
	• Health technology assessments: authorities engage in discussion with developers and patients in defining appropriate PICOs [yes/no]
	• Disease-specific patient journeys have been developed and implemented:
	  ○ Existence/absence of clinical practice guidance for a specific rare disease[232]
	  ○ Existence/absence of co-created care pathways for a specific rare disease[233]

[229](ERN Continuous Monitoring Working Group of the ERN Coordinators Group & the Board of Member States, 2019)
[230](FDA, 2022)
[231](FDA, 2009)
[232](Pavan, et al., 2017)
[233](European Reference Network Neurological Diseases, n.d.)

OUTCOMES	MEASURES

Clinical standards for rare disease are harmonised across borders	• Cross border care in practice[234]:
	  ○ Patient access to information in their own language
	  ○ Existence of a policy on participation of patient/relatives in care process and decision-making
	  ○ Ability to access reimbursement for treatment outside the country/state of residence (no/uncertain/guaranteed)
	  ○ Availability of online information from national government (yes/no)[235]
	• Access to clinical advice, diagnosis, treatment and follow up of patients in national and European Reference Networks[236]:
	  ○ Number of new in-scope condition referrals to participating healthcare providers
	  ○ Number of patients entered into Clinical Patient Management System (total volume)
	• Reference Network operations[237]:
	  ○ Within a network, the number and percentage of Member States/States with healthcare providers as full members
	  ○ Number of healthcare providers represented in the network
	  ○ Number of clinical trials within the network[238]
	• Procedures are in place for long-term follow-up and health data connection with the jurisdiction of primary residence
	  ○ Jurisdiction of treatment systems can update patient health data in jurisdiction of residence systems with treatment information
	  ○ % of HCPs reporting barriers to follow-up of patients who travelled for treatment
	  ○ Health system has procedures in place on handling patients who return from being treated abroad
	• Rare disease patient ability to travel for healthcare: ease of travel
	  ○ % of people with rare diseases reporting cost-barriers to travel for healthcare
	  ○ Distance-to-treatment from the person's home
	  ○ Availability of financial support for costs associated with healthcare away from home

[234](European Health and Digital Executive Agency (HaDEA)., 2019)
[235](European Commission, 2022)
[236](ERN Continuous Monitoring Working Group of the ERN Coordinators Group & the Board of Member States, 2019)
[237]Ibid.
[238](European Commission, 2022)

OUTCOMES	MEASURES
There are mechanisms to support coordination between the health and social care systems for people living with rare diseases	• Healthcare practices frequently coordinates care with social services or community providers: % of primary care physicians who reported challenges in coordinating patient care with social services and other community providers[239] • Existence of a policy on participation of patient/relatives in care process and decision-making[240]
Caregivers are able to access support services	• Ability of caregivers to access and remain in the workplace: Indirect cost due to productivity loss - Per-person (2019 $) - primary & secondary caregivers[241]
Young people living with rare diseases experience a smooth, quality transition from paediatric to adult services	• Transition coordinators help people living with rare diseases to move from paediatric to adult care: proportion of young people living with rare diseases who have such a transition coordinator[242,243] • People living with rare diseases have the chance to have a joint meeting with their paediatric healthcare team and the adult healthcare team: proportion of young people living with rare diseases who have had a meeting in the previous 12 months to review transition planning[244,245] • The paediatric and adult healthcare teams meet regularly throughout the process of transition for each young person living with a rare disease: meetings take place (yes/no)[246] • The transition process, including the speed of transfer of care, is flexible and based on the person's needs and preferences: reported satisfaction of young people with the process[247,248] • Young people living with rare diseases have a contact person or access to a navigator to get guidance and raise concerns about the transition process and their health in general: proportion of young people with rare diseases who have such a contact person[249] • Young people living with rare diseases are aware of their rights within the healthcare system and beyond: self-reported awareness levels[250] • Guidelines or benchmarks are in place for measuring service performance in the transition process [yes/no][251] • Proportion of young people living with rare diseases who continue to participate in adult care services a year after transition[252] • Proportion of young people living with rare diseases who moved from children's to adults' services who met a practitioner from each adults' service they moved to before they transferred[253] • Follow-up arrangements are in place to contact young people with rare diseases who do not attend their first adult care service appointments [yes/no] • Proportion of young people living with rare diseases who have moved from children's to adults' services but did not attend their initial meetings or appointments who were contacted by adults' services and given further opportunities to engage.[254]

[239](Doty, et al., 2019)
[240](ERN Continuous Monitoring Working Group of the ERN Coordinators Group & the Board of Member States, 2019)
[241](Yang, et al., 2022)
[242](Costello Medical, Cambridge Rare Disease Network and Beacon, 2022)
[243](National Institute for Health and Care Excellence (NICE), 2023)
[244](Costello Medical, Cambridge Rare Disease Network and Beacon, 2022)
[245](National Institute for Health and Care Excellence (NICE), 2023)
[246](Costello Medical, Cambridge Rare Disease Network and Beacon, 2022)
[247]Ibid.
[248](National Institute for Health and Care Excellence (NICE), 2023)
[249](Costello Medical, Cambridge Rare Disease Network and Beacon, 2022)
[250,251]Ibid.
[252](National Institute for Health and Care Excellence (NICE), 2023)
[253,254]Ibid.

BUILDING BLOCK: **HEALTH SYSTEM FINANCING** MEETS RARE DISEASE COMMUNITY NEEDS

OUTCOMES	MEASURES

Financing accounts for and addresses inequalities in access to care	• Funds are available for people living with rare diseases
	  ○ Amount of public funds available to help people living with rare diseases pay for healthcare
	  ○ Third sector organisations offer funding for access to rare disease care
	• Financial resources to improve health equity across a nation: Public investment levels to reduce geographic health disparities within a country
	• Funding for rare disease care-oriented networks of healthcare providers that implement activities that reduce inequalities in access to care (such as the European Reference Networks) – amount of health budget funding supplied to such networks
	• People living with rare diseases benefit from evidence-based decisions on treatment reimbursement: health insurers seek the advice of expert clinicians when deciding whether to pay for orphan medicines
	• People enrolled in government-sponsored medical insurance programmes have comprehensive, consistent, and affordable access to rare disease treatment and care:
	  ○ Frequency of coverage denials for people living with rare diseases
	  ○ Amount of cost-sharing payments incurred by people living with rare diseases

Health system financing decisions on rare disease coverage are open and transparent	• Budget transparency: public healthcare bodies publish annual budget spending report [yes/no] • Consultation of people living with rare diseases in decision-making: Legislation requiring commissioning bodies to include service users in their decision-making on the provision of health services[255] • Consultation of people living with rare diseases in decision-making: patient/caregiver included on Medicaid Drug Utilization Review (DUR) boards • Formal cost-effectiveness assessment measures, where used have been adapted to take into account rare disease specificities[256,257,258] • Public eligibility criteria for coverage/reimbursement of rare and innovative treatments: coverage/reimbursement decision-making bodies provide a public list of the criteria that factor into their decisions (yes/no) • Effective integration of patient input into HTA discussions and assessments: Patient organisation contribution to HTAs across all countries and by therapy area[259]

[255](NHS England, 2023)
[256](Institute for Clinical and Economic Review (ICER), 2017)
[257](Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V., 2022)
[258](Canadian Agency for Drugs and Technologies in Health, 2018)
[259](IQVIA Institute for Human Data Science, 2023)

OUTCOMES	MEASURES
People living with rare diseases have access to reliable information on care funding options	• Guidance provided at point of choosing and booking care: satisfaction with advice received[260] • Guidance provided at point of choosing and booking care: unwillingness/inability to travel for care due to insufficient information on quality and availability of treatment[261] • Number of patient navigators/healthcare system navigators that assist in finding appropriate care, secure funding and communicate between different involved healthcare providers • Publicly consultable databases of specialised resources in the rare disease field (exist/do not exist) • Legislation requires information on the out-of-pocket costs to be available prior to receiving rare disease treatment [yes/no]

Innovative rare disease care is affordable to people living with rare diseases	• Reimbursement: country has an orphan-specific reimbursement system[262]
	• Reimbursement: country funds Orphan Medicinal Product treatment in its national health system[263]
	• Reimbursement: out-of-pocket payments for Orphan Medicinal Product treatment[264]
	• Yearly medical costs:
	  ○ Annualised per patient medical costs relative to timing of diagnosis of a rare disease[265]
	  ○ Annual excess medical cost of life with a rare disease[266]
	• Country has an early access programme for innovative medicines that have not yet received marketing authorisation and/or a reimbursement decision [yes/no]

Governments collect data about socioeconomic impacts of living with a rare disease to determine funding allocations	• Financial impact[267]:
	  ○ Avoidable costs attributable to delayed diagnosis and treatment, as well as care costs caused by wrong diagnosis
	  ○ Productivity loss e.g. Productivity loss e.g. wages lost/year and days of work missed/year
	• Education/employment status:
	  ○ Days missed work per year[268]
	  ○ Access to mainstream education – costs of home-schooling/ missed school/special education[269]
	• Data is available about people living with rare diseases from under-served groups such as women, ethnic minorities, LGBTQ+ people, people with disabilities etc.[270,271,272]
	• Patient advocacy organisations collect socioeconomic data of their members [yes/no]

[260](European Commission, 2022)
[261](EURORDIS-Rare Diseases Europe, 2021)
[262](European Commission, 2019)
[263]Ibid.
[264]Ibid.
[265](EveryLife Foundation for Rare Diseases, 2023)
[266](Yang, et al., 2022)
[267](EveryLife Foundation for Rare Diseases, 2023)
[268](EveryLife Foundation for Rare Diseases, 2023)
[269](Yang, et al., 2022)
[270](Patel, et al., 2023)
[271](EveryLife Foundation for Rare Diseases, n.d.)
[272](Patel, et al., 2023)

OUTCOMES	MEASURES

Service provision and coverage decisions take into account patient-reported outcomes (PROs) and are value-added for people living with rare diseases	• Use of PROs and patient-meaningful outcomes:
	  ○ In research: % of clinical trials using Patient-Reported Outcome Measures[273] and/or patient-meaningful outcomes
	  ○ In regulatory approval processes: authorising bodies accept patient-reported outcome evidence in authorisation applications
	  ○ In treatment: % of approved orphan drugs containing PROs language in their summary of characteristics[274]
	  ○ In pricing and reimbursement decisions: payers accept patient-reported outcomes as relevant criteria in reimbursement decision-making

Rare disease plans include funding for implementation or signpost to funding sources	• Rare disease budgets: Funding for ERNs from EU budget[275] • Country has a national rare disease plan with allocated funding for implementation (no funding/repurposing existing funding/additional funding) Amount of public funds allocated to the rare disease plan/ strategy[276] • Existence of a policy/decision to ensure long-term funding and/or sustainability of the measures in the RD plan/strategy[277]
People living with rare diseases and those caring for them receive adequate financial and non-financial support	• Financial barriers to care access: % of people living with rare diseases/ parents or caregivers of children with rare diseases that cited finances as a barrier to accessing care.[278] • Financial barriers to care access: % of people reporting unmet needs for healthcare-related services due to financial reasons[279] • Social care support: Time spent by patients/carers/both on care-related tasks[280] • Cost related to the disease: % of people living with rare diseases and/ or carers declaring cost related to the disease is high[281]
Health systems maintain quality of care at a sustainable cost	• Existence of alternative funding sources to support sustainable financing of rare disease care ○ Public-private funding for rare diseases • Sustainable increase in healthcare spending on rare disease that reflects the needs of people living with rare diseases • Levels of public funding for Centres of Excellence that create, share, and coordinate access to diagnosis, care, and treatment expertise
Public-private models of financing support research in rare disease	• Public-private shared expense schemes: Public and private sectors cooperate on investing in health research[282,283,284] • Rare disease research institutions or networks funded through public-private partnerships: amount of investment in local currency

[273](Maruszcyk, et al., 2022)
[274](Jarosławski, et al., 2018)
[275](European Commission, 2023)
[276](European Union Committee of Experts on Rare Diseases (EUCERD), 2013)
[277]Ibid.
[278](Bogart, et al., 2022)
[279](Eurostat, 2023)
[280](EURORDIS, 2017)
[281]Ibid.
[282](Innovative Health Initiative, 2024)
[283](National Institutes of Health (NIH), 2021)
[284](Critical Path Institute, 2022)

BUILDING BLOCK: **HEALTH WORKFORCE** SUPPORTS ACCESS TO HIGH-QUALITY CARE

OUTCOMES	MEASURES
People living with rare diseases provide input into medical workforce training	• Mechanisms are in place for patient organisations to give input into medical workforce rare disease education
Social services professionals are trained and equipped to support people living with rare diseases	• Social services' knowledge of people living with rare diseases: % of people living with rare diseases and carers reporting that social services' knowledge of rare diseases is lacking[285] • Social services preparedness for people living with rare diseases: % of people living with rare diseases and carers reporting that social services are underprepared to support people with rare diseases[286]
Medical education systems prioritise rare disease care	• Rare disease content in curricula for medical degrees: rare disease is integrated into lectures/courses[287] • Postgraduate curricula are established and implemented by European Reference Networks • Rare disease education is part of Rare Disease Centre certification • Development of rare disease education hubs • Existence of community-based education and training centres delivering rare disease-related courses e.g. The Rare Hub in Washington DC

Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	• Number of rare disease centres involved in training:
	  ○ Number of centres organising training on rare diseases at their centre[288]
	  ○ Number of centres organising training on rare diseases outside their centre[289]
	  ○ Number of centres offering academic training on treating rare diseases[290]
	• GP recognition of rare disease: total number of cases where GPs recognise symptoms potentially related to rare disease and correctly referred to a specialist[291]
	• Existence of accompanying psychological support during announcement of the diagnosis: % of people living with rare diseases and carers reporting the announcement of the diagnosis without accompanying psychological support[292]
	• Healthcare workforce knowledge on rare diseases: awareness and knowledge of rare diseases among HCPs that do not specialise in rare disease[293]
	• Development of rare disease education hubs
	  ○ Existence of community-based education and training centres delivering rare disease-related courses e.g. The Rare Hub in Washington DC

[285](EURORDIS, 2017)
[286]Ibid.
[287](Euregio Meuse-Rhine Rare Diseases (EMRaDi), 2020)
[288](Schmidt, et al., 2020)
[289]Ibid.
[290]Ibid.
[291](European Brain Council (EBC), 2022)
[292](EURORDIS, 2009)
[293](Benz, et al., 2022)

OUTCOMES	MEASURES
People living with rare diseases have easy access to specialist care	• Patient access to specialist centres people living with rare diseases attending specialist clinics for their condition[294] • Treatment access: paediatric and relevant specialist departments reporting that they treat people with a rare disease[295] • Distance from a treatment centre/provider: Time travelled to access healthcare • Number of rare disease centres of expertise in country[296,297] • Easy access to diagnosis centre: % of people living with rare diseases and carers reporting travelling to another region to obtain diagnoses[298] • % having to travel for medical care related to a rare disease[299] • % considering or having already relocated permanently for medical care related to a rare disease[300]
People living with undiagnosed and rare diseases have access to genetic testing and counselling	• Recognition of genetic counselling as a healthcare profession:[301] there are officially recognised professional titles and career paths for genomic medicine[302] • % of people waiting over 12 months for a clinical genetics outpatient appointment[303] • % reporting satisfaction with their genetic testing experience[304] • % who had not been referred to clinical genetics but wished to be[305] • % of counties with at least one certified genetic counsellor[306] • % of genetic counsellors offering telegenetics services[307] • % of cases solved through genomic medicine as a % of referrals[308] • Number of people registered as having a genomically-confirmed rare disease, following genomic testing for a suspected rare genetic disease[309] • Individuals/families with a definite molecular diagnosis (diagnostic yield) following inclusion in an undiagnosed diseases programme[310] • Number of geneticists and genetic counsellors trained in the country • % of medical schools with genetics programmes • Availability of genetics fellowships [yes/no]

[294]Adapted from (European Brain Council (EBC), 2022)
[295]Adapted from (Reimer, et al., 2018)
[296](NORD, n.d.)
[297](Research For Rare, n.d.)
[298](EURORDIS, 2009)
[299](NORD, 2020)
[300]Ibid.
[301](Álvaro-Sánchez, et al., 2021)
[302](Beyond 1 Million Genomes (B1MG), n.d.)
[303](Ward, et al., 2023)
[304]Ibid.
[305]Ibid.
[306](Triebold, et al., 2021)
[307](National Society of Genetic Counselors, 2023)
[308](Genomics England, 2023)
[309](Office for Life Sciences (OLS) , 2022)
[310](Curic, et al., 2023)

Annex II
Good Practice Examples

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Leadership and governance guarantee public health prioritisation of people living with rare diseases	**Modulate market exclusivity based on**	Effective incentives spur research and innovation in rare disease	Extending market exclusivity to incentivise particular behaviours among rare disease researchers/treatment developers e.g.: • Addressing ultra-rare disease • Addressing diseases from a priority framework • Generating and sharing data	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2021. *ORPHAN MEDICINE INCENTIVES: How to address the unmet needs of rare disease patients by transforming the European OMP landscape.* [Online] Available at: https://od-expertgroup.eu/wp-content/uploads/2021/06/european-expert-group-on-orphan-drug-incentives-report.pdf
	Transferable reward voucher	Effective incentives spur research and innovation in rare disease	A developer who produces a new medicine for a priority disease and brings it to market would receive a voucher for regulatory rewards. They could use this for one of their future products or sell it to another company.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2021. *ORPHAN MEDICINE INCENTIVES: How to address the unmet needs of rare disease patients by transforming the European OMP landscape.* [Online] Available at: https://od-expertgroup.eu/wp-content/uploads/2021/06/european-expert-group-on-orphan-drug-incentives-report.pdf
	Fiscal incentives for developing medicines – e.g. US Orphan Drug Tax Credit	Effective incentives spur research and innovation in rare disease	Tax credits can help offset the costs of running clinical trials, and therefore support the transition from basic research to clinical development. The US Orphan Drug Tax Credit is an example, which provides a 50% tax credit of clinical trial costs for rare disease medicines.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2021. *ORPHAN MEDICINE INCENTIVES: How to address the unmet needs of rare disease patients by transforming the European OMP landscape.* [Online] Available at: https://od-expertgroup.eu/wp-content/uploads/2021/06/european-expert-group-on-orphan-drug-incentives-report.pdf
	Common value assessment for OMPs	Value-assessment frameworks for rare diseases are aligned and harmonised	A common value assessment would provide clarity for developers on evidence requirements and value determination processes, and would also be designed to accommodate rare diseases. Currently, standard cost-effectiveness assessments do not effectively reflect the value of OMPs because they do not take into account the prevalence of the condition in question.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2021. *ORPHAN MEDICINE INCENTIVES: How to address the unmet needs of rare disease patients by transforming the European OMP landscape.* [Online] Available at: https://od-expertgroup.eu/wp-content/uploads/2021/06/european-expert-group-on-orphan-drug-incentives-report.pdf
	European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL)	Value-assessment frameworks for rare diseases are aligned and harmonised	European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL) - involving experts, patient representatives, academics, HTA professionals, politicians, industry. Its principles cover decision criteria and process, sustainable funding, and European coordination - aiming to support a more consistent way of making OMP pricing and reimbursement decisions among European countries.	Annemans, L. et al., 2017. Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL). *Orphanet Journal of Rare Diseases*, 12(50).

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Leadership and governance guarantee public health prioritisation of people living with rare diseases	**Policy framework for use of real-world evidence**	Value-assessment frameworks for rare disease are aligned and harmonised	Rare disease medicines can particularly benefit from real world evidence (RWE) in value assessment, due to the challenges involved in using standard clinical trials to collect evidence about orphan medicinal products. Consistent, harmonised guidance would facilitate its use in regulatory approval and pricing & reimbursement processes by setting standards for RWE. In turn, this would increase trust in RWE's use during the regulatory process.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2021. *ORPHAN MEDICINE INCENTIVES: How to address the unmet needs of rare disease patients by transforming the European OMP landscape.* [Online] Available at: https://od-expertgroup.eu/wp-content/uploads/2021/06/european-expert-group-on-orphan-drug-incentives-report.pdf
	German Centres for Rare Diseases included in hospital planning in many Federal states	Rare disease is integrated into overall health policy	Centres for Rare Diseases (ZSE, Zentren für Seltene Erkrankungen) established under the National Action Plan for Rare Diseases - more than 30 as of December 2023	Fehr, A. & Prütz, F., 2023. Rare diseases: a challenge for medicine and public health. *Journal of Health Monitoring,* 8(4).
	Rare Disease Advisory Councils (RDACs)	Mechanisms exist for people living with rare diseases to contribute to rare disease policy process	26 US states have passed laws setting up RDACs – 11 state governors have signed RDAC legislation since 2020 RDACs allow stakeholders to make formal recommendations to state leaders on rare disease policy issues e.g. Medicaid benefits, health insurance regulation	NORD – National Organization for Rare Disorders, 2023. *Rare Disease Advisory Councils (RDACs).* [Online] Available at: https://rarediseases.org/wp-content/uploads/2023/07/NRD-2301-RDAC-Sell-Sheet_FNL-1.pdf
	Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen (NAMSE)	Mechanisms exist for people living with rare diseases to contribute to rare disease policy process	National Action League for People with Rare Diseases – founded in 2010 by the German Federal Ministry of Health, German Federal Ministry of Education and Research, and the Alliance for Chronic Rare Diseases Brings together 29 partners to take action on improving the health and quality of life of People living with rare diseases in Germany. These include government ministries and agencies, payers, medical societies, and trade associations.	Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen (NAMSE), n.d. *Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen (NAMSE).* [Online] Available at: https://www.namse.de/english
	German Social Code	Mechanisms exist for people living with rare diseases to contribute to rare disease policy process	The German Social Code permits patient organisations to take part in discussions and submit petitions to the Federal Joint Committee (G-BA), including the Allianz Chronister Seltener Erkrankungen e. V. - ACHSE	Gemeinsamen Bundesausschuss, 2023. *Die Patientenbeteiligung im Gemeinsamen Bundesausschuss.* [Online] Available at: https://patientenvertretung.g-ba.de/
	European Patient Advocacy Groups (ePAGs)	Mechanisms exist for people living with rare diseases to contribute to rare disease policy process	Bringing together 300+ patient representatives from 28 European countries, the European Patient Advocacy Groups (ePAGs) represent the patient voice in the European Reference Networks (ERNs). Each of the 24 ePAGs, one per ERN, brings together rare disease patient organisations and advocates who are actively involved in the ERNs, working in partnership with clinicians and researchers.	EURORDIS, n.d. *European Patient Advocacy Groups (ePAGs).* [Online] Available at: https://www.eurordis.org/our-priorities/european-reference-networks/epag/
	French National Rare Diseases Plan	Rare disease plans are long-term and are regularly adapted	This third Rare Disease plan was designed together with patients and all relevant stakeholders, and has set actions, costs, time frames and allocated leader organisations for each focus area	Le ministère des Solidarités et de la Santé et le ministère de l'Enseignement supérieur de la Recherche et de l'Innovation, 2018. *Plan national maladies rares 2018-2022*. [Online] Available at: https://sante.gouv.fr/IMG/pdf/pnmr_3_v25-09pdf.pdf

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Leadership and governance guarantee public health prioritisation of people living with rare diseases	**1+ Million Genomes (1+MG) Initiative**	National genomics programmes are implemented for rare disease care and research	The EU level '1+ Million Genomes' (1+MG) initiative aims to implement cross-border genomic data access via interoperable national databases. GenomDE is the German initiative for medical genome sequencing, funded by the Federal Ministry of Health and resulting in both clinical use and the development of data architecture to facilitate care and research.	European Commission, 2023. *European '1+ Million Genomes' Initiative*. [Online] Available at: https://digital-strategy.ec.europa.eu/en/policies/1-million-genomes
	Genetic Counselling as part of genomics programmes – Italian rare disease action plan	National genomics programmes are implemented for rare disease care and research	Genetic counselling, genetic testing and pre-conception pathways covered on the National Health Service.	Ministero della Salute, 2023. *Piano nazionale malattie rare 2023 – 2026*. [Online] Available at: https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2023&codLeg=95257&parte=1%20&serie=null
	NHS Genomic Medicine Service	National genomics programmes are implemented for rare disease care and research	Implementation of the commitment to be the first national healthcare system to offer WGS as part of routine care - includes seven laboratory hubs across England and Wales, supported by regional service alliances.	NHS England, n.d. *NHS Genomic Medicine Service*. [Online] Available at: https://www.england.nhs.uk/genomics/nhs-genomic-med-service/
	genomDE - German strategy for genomic medicine	National genomics programmes are implemented for rare disease care and research	Germany launched this initiative in October 2021, working to include patients, set up the data infrastructure needed, and establish a legal basis for genome sequencing for rare diseases and cancer. A pilot project will run from January 2024 for at least five years, integrating genomic medicine into the German health system. GenomeDE also includes the national platform for medical genome sequencing to be used by the pilot project.	TMF – Technologie- und Methodenplattform für die vernetzte medizinische Forschung e. V., 2024. *genomDE*. [Online] Available at: https://www.genom.de/
	Plan France Médecine Génomique 2025	National genomics programmes are implemented for rare disease care and research	The Plan France Médecine Génomique 2025 (PFMG 2025) contains three aims - prepare for genomic medicine's integration into routine care pathways - guaranteeing access to genomic medicine for patients who need it. Initially, this will be cancer and rare disease only, and will later cover common diseases. The second aim is to establish a national genomic medicine sector and the third to position France as a leader in personalised medicine.	Alliance nationale des sciences de la vie et de la santé, 2024. *Plan France médecine génomique 2025*. [Online] Available at: https://pfmg2025.aviesan.fr/
	100,000 Genomes Project	National genomics programmes are implemented for rare disease care and research	UK genomic sequencing project - which sequenced its 100,000th genome in 2018 - to find diagnoses for cancer and rare diseases, where whole genomic sequencing led to a new diagnosis for 25% of participants and researchers are using data to develop treatments and medical products.	Genomics England, 2024. *100,000 Genomes Project*. [Online] Available at: https://www.genomicsengland.co.uk/initiatives/100000-genomes-project
	Ending prior authorisation requirements for reimbursement of genomic tests	National genomics programmes are implemented for rare disease care and research	Following German authorities' 2020 decision to lift requirements for prior authorisation for reimbursement of comprehensive genomic profiling (CGP), whole-genome sequencing (WGS) and whole-exome sequencing (WES), some German health insurers began to cover WGS and WES.	EUCOPE Genomics Working Group and Charles River Associates, 2021. *Developing an advanced diagnostics ecosystem in Europe: A proposal for change*. [Online] Available at: https://www.eucope.org/wp-content/uploads/2021/03/eucope-advanced-diagnostics-white-paper.pdf

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Leadership and governance guarantee public health prioritisation of people living with rare diseases	**MoIDX framework**	National genomics programmes are implemented for rare disease care and research	Private company Palmetto GBA was commissioned by a group of Medicare providers to develop a framework assessing the clinical utility of genomic tests. The MoIDX framework includes conducting technical assessments and setting up reimbursement of new molecular diagnostics and has been put into use by multiple Medicare jurisdictions. It alleviates the need to do an RCT for each product and indication, speeding up access to these new diagnostics.	EUCOPE Genomics Working Group and Charles River Associates, 2021. *Developing an advanced diagnostics ecosystem in Europe: A proposal for change*. [Online] Available at: https://www.eucope.org/wp-content/uploads/2021/03/eucope-advanced-diagnostics-white-paper.pdf
	Rare Disease Day	The public understands what rare disease means	Rare Disease Day, 29 February, is a global awareness-raising day on which the rare disease community organises events and activities to increase the profile of rare diseases and call for action to secure equity for people living with rare diseases.	EURORDIS, 2024. *Rare Disease Day*. [Online] Available at: https://www.rarediseaseday.org/
	European Rare Disease Registry Infrastructure (ERDRI)	National governments collaborate on international disease registries	The European Rare Disease Registry Infrastructure (ERDRI) makes registry data searchable and findable, by facilitating interoperability between participating registries.	European Commission, n.d. European Rare Disease Registry Infrastructure (ERDRI). [Online] Available at: https://eu-rd-platform.jrc.ec.europa.eu/erdri-description_en
Innovative ideas become life-changing technologies and therapies	**Collaboration on Rare Diseases (CORD-MI)**	Health data related to rare disease diagnosis and care is accessible for research purposes	Connection between German university hospitals to collect sufficient harmonized Electronic Health Record data to support clinical research on rare disease Adding ORPHACODES became mandatory for all rare disease documentation in Hospital Remuneration Act data in Germany as of 1 April 2023.	Tahar, Kais et al. "Local Data Quality Assessments on EHR-Based Real-World Data for Rare Diseases." Studies in health technology and informatics vol. 302 (2023): 292-296. doi:10.3233/SHTI230121
	EBC Value of Treatment research project on rare diseases: patient surveys in the area of ataxia and phenylketonuria	Health data related to rare disease diagnosis and care is accessible for research purposes	Value of Treatment for Brain Disorders (VOT) is a health economics and outcomes research project coordinated by EBC. Its second round includes a focus on early diagnosis and coordinated care in RDs (Ataxia, Dystonia and Phenylketonuria).	European Brain Council (EBC), 2020. *The Value of Early Coordinated Care for Patients Affected by Rare Neurological Diseases Study.* [Online] Available at: https://www.braincouncil.eu/wp-content/uploads/2020/05/VoT2_20.05.2020_Value-Proposition_V9pp.pdf
	EBC survey of patients and patient associations on where and how digital tools can support PKU diagnosis, treatment, and follow-up	Health data related to rare disease diagnosis and care is accessible for research purposes	Study of patients and caregivers to understand what people living with PKU would find relevant and useful, what kind of IT tools could help them, and designing policy and communication strategy recommendations.	Canizzo, S. et al., 2023. The role of patient representatives in the optimization of Patient Care Pathways at European level: the Phenylketonuria experience. [Online] Available at: https://www.braincouncil.eu/wp-content/uploads/2023/08/PKU-Poster.pdf

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Innovative ideas become life-changing technologies and therapies	**UK Medical Research Council (MRC) clinical and translational research funding schemes**	Innovative ideas are translated to new technologies and treatments for rare disease	• Supporting research that brings academic researchers together with funders and industry to turn discoveries into clinical development. • Experimental medicine funding for studies into how the human body works in order to find new therapeutic/diagnostic approaches. • Funding for short-term translational projects on the viability of an approach and to de-risk projects so they can seek further funding. • Funding for projects to move development of treatments/ interventions/products forward, all the way up to phase IIa clinical trials. • Funding for clinical evaluation of efficacy and mechanism post proof-of-concept attainment.	UK Research and Innovation, 2023. *Clinical and translational research.* [Online] Available at: https://www.ukri.org/what-we-do/our-main-funds-and-areas-of-support/browse-our-areas-of-investment-and-support/clinical-and-translational-research/
	Rare Disease PPP fund for basic research and early development	Innovative ideas are translated to new technologies and treatments for rare disease	Public and private sectors would share the responsibility of funding basic research. This would increase the availability of funding by involving additional actors and cooperating with venture capital firms in life sciences. A governing board (involving government officials, regulators, research institutes, academics, patient organisations, and industry representatives) would direct funding to address unmet medical needs and make its funding conditional on producing development-ready research and sharing data with other OMP researchers.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2021. *ORPHAN MEDICINE INCENTIVES: How to address the unmet needs of rare disease patients by transforming the European OMP landscape.* [Online] Available at: https://od-expertgroup.eu/wp-content/uploads/2021/06/european-expert-group-on-orphan-drug-incentives-report.pdf
	Establishment of national Undiagnosed Disease Programs such as in Germany	Innovative care for rare diseases is advanced throughout the life course	Type A reference centres for rare disease address the needs of all who need them, and funding for setting up structures and processes for people without a diagnosis/with a suspected rare disease, integrating physical and mental health services	Schlangen, M. & Heuing, K., 2023. Rare diseases in Germany – Developments in the status of medical care. *Journal of Health Monitoring*, 8(4).
	Sciensano disease-specific registries	Researchers participate in consortia to share knowledge and expertise	Belgian Neuromuscular Diseases Registry (BNMDR) - in cooperation with the 7 Neuromuscular Disease Reference Centres (CRNM [FR]) and collecting data for international "TREAT-NMD" network (Duchenne and Becker muscular dystrophies, and spinal muscular atrophies) Belgian Cystic Fibrosis Registry - in cooperation with the 7 CF reference centres. Sciensano carries out benchmarking for each reference centre to its peers via a report comparing their results to those of the others, and they can share their experiences to improve care. Connected to European Cystic Fibrosis Patient Registry to allow comparison to other European countries. Belgian Rare Bleeding Disorders Registry - similar to the above with the quality-of-care benchmarking and connection to EU/international databases to allow research and comparison.	Sciensano - Belgian Institute for Health, 2024. *Rare diseases.* [Online] Available at: https://www.sciensano.be/en/health-topics/rare-diseases
	NCATS Rare Disease Clinical Research Network	Researchers participate in consortia to share knowledge and expertise	The RDCRN is a network of consortia that brings together researchers and patient advocacy groups around the world to study rare diseases and support regional clinical trial readiness. The aim is to support clinical research, understanding of rare disease, and treatment development.	National Center for Advancing Translational Sciences (NCATS), 2024. *Rare Diseases Clinical Research Network (RDCRN).* [Online] Available at: https://ncats.nih.gov/research/research-activities/RDCRN

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Innovative ideas become life-changing technologies and therapies	**Undiagnosed Disease Network**	Innovative care for rare diseases is advanced throughout the life course	A study funded by the US National Institutes of Health involving twelve clinical sites across the USA that aim to improve diagnosis and care for people with undiagnosed diseases. The clinical sites offer a medical and research evaluation by multiple specialists, which often includes genetic testing of the study participant and potentially family members. Following the evaluation, the participant's usual healthcare provider gets the evaluation information and can use it to inform treatment decisions and long-term care. The study also shares the stories of participants who consent to have this information posted online, in the hope of finding others who have similar symptoms or genetic changes.	Undiagnosed Diseases Network, 2024. *Finding Answers through Sharing.* [Online] Available at: https://undiagnosed.hms.harvard.edu/participants/ Undiagnosed Diseases Network, n.d. *Frequently Asked Questions.* [Online] Available at: https://undiagnosed.hms.harvard.edu/about-us/faqs/
	FDA's Orphan Products Grant Program	Researchers are inspired to work on rare disease	Grants for clinical trials and natural history studies advancing treatment development for rare diseases and conditions	FDA, 2023. *Orphan Products Grants Program.* [Online] Available at: https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/orphan-products-grants-program
	Advanced Research Projects Agency for Health (ARPA-H)	Researchers are inspired to work on rare disease	A publicly funded agency to invest in biomedical and health projects that would not usually be carried out as part of traditional research or commercial activity.	ARPA-H, 2024. About ARPA-H. [Online] Available at: https://arpa-h.gov/about/faqs
	Patient Listening Session	Payers engage in open dialogue early in the development process for innovative treatments, Mechanisms exist for people living with rare diseases to contribute to rare disease policy process	The US Food and Drug Administration (FDA) arranges sessions to allow them to talk directly with people affected by a particular disease, to learn more about their needs and priorities which then help the FDA to inform its regulatory thinking. These can be FDA-requested or patient-led.	FDA, 2024. *FDA Patient Listening Sessions.* [Online] Available at: https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-listening-sessions
	Mechanism of Coordinated Access (MoCA) to OMPs	Payers engage in open dialogue early in the development process for innovative treatments	EU level cooperation between relevant stakeholders and OMP developers to exchange information based on a Transparent Value Framework setting out criteria of use to payers.	Cavaller-Bellaubi, M. et al., 2023. Patients, payers and developers of Orphan Medicinal Products: lessons learned from 10 years' multi-stakeholder dialogue on improving access in Europe via MoCA. *Orphanet Journal of Rare Diseases,* 18(144).
	HTA approaches to OMPs - Germany	People living with rare diseases are able to access available treatments	Lower levels of statistical significance are acceptable in HTA processes for designated OMPs and validated surrogate endpoints are considered acceptable to assess clinical effectiveness. Additional benefit is assumed to be proven at marketing authorisation as long as the budget impact is less than 30 million EUR/year for a particular indication, with an assessment only made if the revenue threshold for the product exceeds 50 million EUR/year, and OMPs are automatically classed as having a higher therapeutic benefit for HTA purposes. Patient preferences and ethical issues may be included in the final recommendation, which could lead to a grade of recommendation different from the one expected based on the evidence classification framework.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2023. *AN EU HTA FIT FOR RARE DISEASES – Part 1: Clinical evidence in joint clinical assessments.* [Online] Available at: https://od-expertgroup.eu/277-2/

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Innovative ideas become life-changing technologies and therapies	**The FDA Center for Devices and Radiological Health (CDRH) Early Payor Feedback Program (EPFP)**	Payers engage in open dialogue early in the development process for innovative treatments	EPFP is a voluntary programme for medical device manufacturers to seek payer input on their clinical trial designs or other plans to collect evidence in support of coverage decisions, with several public and private payer organisations choosing to take part. The FDA facilitates contact and meetings between the manufacturers and payers.	FDA, 2023. *Medical Device Coverage Initiatives: Connecting with Payors via the Payor Communication Task Force.* [Online] Available at: https://www.fda.gov/about-fda/cdrh-innovation/medical-device-coverage-initiatives-connecting-payors-payor-communication-task-force
	HTA approaches to OMPs - France	People living with rare diseases are able to access available treatments	Additional benefit is assumed to be proven at marketing authorisation as long as the budget impact is less than 30 million EUR/year for a particular indication and validated surrogate endpoints are considered acceptable to assess clinical effectiveness. All innovative medicines - not just those for rare diseases - can access an accelerated HTA procedure, and the authorities can issue temporary use authorisations for medicinal products in life-threatening situations or where there is no therapeutic alternative. Historical controls can be used as a comparator if there is no current treatment alternative, and early access measures can support real world evidence generation.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2023. *AN EU HTA FIT FOR RARE DISEASES – Part 1: Clinical evidence in joint clinical assessments.* [Online] Available at: https://od-expertgroup.eu/277-2/
	HTA approaches to OMPs - Scotland	People living with rare diseases are able to access available treatments	The authorities accept alternative kinds of evidence in clinical trials and economic assessment, and may require additional data like surrogate markers and quality of life data. There is a conditional market authorisation pathway for ultra-rare disease treatments to gather evidence of effectiveness in use.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2023. *AN EU HTA FIT FOR RARE DISEASES – Part 1: Clinical evidence in joint clinical assessments.* [Online] Available at: https://od-expertgroup.eu/277-2/
	HTA approaches to OMPs - Sweden	People living with rare diseases are able to access available treatments	Validated surrogate endpoints are considered acceptable to assess clinical effectiveness, and historical controls can be used as a comparator if there is no current treatment alternative. Budget impact analysis is not required for OMPs, and cost-effectiveness thresholds are more lenient for products addressing high needs. Disease severity is factored into decisions.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2023. *AN EU HTA FIT FOR RARE DISEASES – Part 1: Clinical evidence in joint clinical assessments.* [Online] Available at: https://od-expertgroup.eu/277-2/
	HTA approaches to OMPs - Lithuania	People living with rare diseases are able to access available treatments	OMPs can be reimbursed without proving their cost-effectiveness.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2023. *AN EU HTA FIT FOR RARE DISEASES – Part 1: Clinical evidence in joint clinical assessments.* [Online] Available at: https://od-expertgroup.eu/277-2/
	HTA approaches to OMPs - Netherlands	People living with rare diseases are able to access available treatments	Additional benefit is assumed to be proven at marketing authorisation as long as the budget impact is less than 2.5 million EUR/year for a particular indication. There is a pathway for conditional inclusion in the basic health care system for products that address unmet medical need - either before an HTA process or after a negative decision on the grounds of insufficient evidence. This permits up to 7 years of evidence collection with use at a mutually agreed market price between payer and manufacturer - or up to 14 years in special circumstances - before the product is reviewed again. Disease severity is factored into decisions.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2023. *AN EU HTA FIT FOR RARE DISEASES – Part 1: Clinical evidence in joint clinical assessments.* [Online] Available at: https://od-expertgroup.eu/277-2/

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Innovative ideas become life-changing technologies and therapies	**HTA approaches to OMPs - England**	People living with rare diseases are able to access available treatments	A Highly Specialised Technology programme applies to ultra-rare disease treatments, although most OMPs undergo standard cost-benefit assessments based on QALYs as part of cost-benefit thresholds setting out how much the authorities are willing to pay per QALY (ICERs). This is about 20-30,000 GBP/QALY for standard assessments and 100,000 GBP/QALY for HSTs, although the share of OMPs approved through the standard processes is the same as the share of non-OMPs - implying there is some flexibility in evidence thresholds for OMPs in practice.	European Expert Group on Orphan Drug Incentives (OD Expert Group), 2023. *AN EU HTA FIT FOR RARE DISEASES – Part 1: Clinical evidence in joint clinical assessments*. [Online] Available at: https://od-expertgroup.eu/277-2/
Health information systems accelerate access to and development of new ways to care for rare diseases	**European Reference Networks (ERNs)**	New technologies are harnessed to reduce complexity of diagnosis for rare diseases	Virtual networks of multidisciplinary health care providers across Europe come together in advisory panels to discuss cases of rare diseases using the Clinical Patient Management System – an online software application. They also cooperate on developing guidelines, sharing knowledge, facilitating studies, and gathering patient data to inform new care models, eHealth solutions, and new medicines and medical devices. References: https://health.ec.europa.eu/european-reference-networks/overview_en https://health.ec.europa.eu/european-reference-networks/work-erns_en	European Commission, 2023. European Reference Networks Overview. [Online] Available at: https://health.ec.europa.eu/european-reference-networks/overview_en European Commission, 2023. Work of the ERNs. [Online] Available at: https://health.ec.europa.eu/european-reference-networks/work-erns_en
	National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)	Health data related to rare disease diagnosis and care is accessible for research purposes	England's National Disease Registration Service (NDRS) includes two disease registration services - one for cancer (National Cancer Registration and Analysis Service (NCRAS)), and one for congenital anomalies and rare diseases (National Congenital Anomaly and Rare Diseases Registration Service (NCARDRS)). It brings together data on congenital differences, structural, genetic, chromosomal, and metabolic/biochemical conditions for all pregnancy outcomes. It has published data estimating the prevalence and infant mortality rate of spinal muscular atrophy type 1 in England.	National Disease Registration Service (NDRS), 2023. Congenital anomalies and rare diseases. [Online] Available at: https://digital.nhs.uk/ndrs/about/ncardrs
	ParkinsonNet in the Netherlands	People living with rare diseases have access to multidisciplinary, interoperable services throughout the patient pathway	A network of therapists for Parkinson's Disease, with 70+ regional networks covering the whole country. It has been found to reduce hip fractures and hospital admissions, to save the health system money, and to provide more people with access to specialist health care professionals. It is a method of delivering high-quality, specialist care while keeping costs manageable, and has been transferred to other countries for replication.	Organisation for Economic Cooperation and Development (OECD), 2023. Integrating Care to Prevent and Manage Chronic Diseases: Best Practices in Public Health: ParkinsonNet, the Netherlands. [Online] Available at: https://www.oecd-ilibrary.org/social-issues-migration-health/integrating-care-to-prevent-and-manage-chronic-diseases_6dd7b702-en
	Codification for Rare Diseases [RDCODE]	Data is standardised for use across all care settings	Standardisation of rare disease coding in EU member states using Orphacodes means that all known rare diseases are identifiable in the national health information system, permits interoperability of data between hospitals, regions, and countries, and facilitates research through interoperability with registries and other research information systems.	European Commission, 2022. Codification for Rare Diseases [RDCODE] [826607] - Project. [Online] Available at: https://webgate.ec.europa.eu/chafea_pdb/health/projects/826607/summary Orphanet Data For Rare Diseases, n.d. Orphanet Data For Rare Diseases. [Online] Available at: https://od4rd.eu/

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health information systems accelerate access to and development of new ways to care for rare diseases	**Set of common data elements for Rare Diseases Registration**	Data is standardised for use across all care settings	This set of data elements was developed to ensure that data registers on rare diseases across the EU are interoperable and can be compared with each other, and includes requirements on how to record primary clinical data. Therefore, it creates a consistent collection of primary and secondary health data based on the same standards - facilitating EU-wide studies.	European Commission, n.d. Set of Common Data Elements. [Online] Available at: https://eu-rd-platform.jrc.ec.europa.eu/set-of-common-data-elements_en
	National DIMDI project "Kodierung von Seltenen Erkrankungen" (Rare diseases coding)	Data is standardised for use across all care settings	The German Federal Ministry of Health funded a project which checked whether every rare disease in the Orphanet database was included in its ICD-10 framework. If they were not, they got added and assigned to a category there. The project also cross-checked all German ICD-10 codes that were already mapped to rare diseases with Orphanet's coding. Each rare disease entry has both a connected Orphacode and ICD-10-GM code, allowing compatibility with rare disease codes in other parts of Europe, and its own unique Alpha-ID Code. For example: Fibrodysplasia Ossificans Progressiva has the ICD-10-GM code of M61.19 and Orpha number 337, with a unique identifier of I32050.	Federal Institute for Drugs and Medical Devices, n.d. National DIMDI project "Kodierung von Seltenen Erkrankungen" (Rare diseases coding). [Online] Available at: https://www.bfarm.de/EN/Code-systems/Terminologies/Alpha-ID-SE/national-dimdi-project/_node.html
	ERICA Patient Reported Outcome Measures (PROMs) Repository	People living with rare diseases contribute to data and evidence on Patient-Reported Outcomes	The European Rare Disease Research Coordination and Support Action consortium (ERICA) has created a centralised database of patient-centred, patient-reported, observer reported, and clinician reported outcome measures for rare diseases, including links to the questionnaires.	European Rare Disease Research Coordination and Support Action consortium (ERICA), 2023. PROMs Repository. [Online] Available at: https://erica-rd.eu/work-packages/patient-centred-research/proms-repository/
	The Duchenne Registry Established 2007 by Parent Project Muscular Dystrophy (PPMD)	Patient registries are integrated into the healthcare system	Organisers from US government agencies, IT development industry and academic institutions Funded by PPMD, which oversees the Registry Patient-led and managed Registries support advocacy on what matters most to the community – and facilitate trust in the context of decision-making on whether to share highly sensitive and personal data.	Parent Project Muscular Dystrophy, 2024. The Duchenne Registry. [Online] Available at: https://www.duchenneregistry.org/
	Center for Genomics and Data Science Research	Genomic data on rare diseases is consistently captured in an accessible database	The US Center for Genomics and Data Science Research was founded in 2023 as a reconfiguration of the National Human Genome Research Institute (NHGRI)'s computational genomics department. It aims to analyse large-scale genetic and genomic data to discover more about the role of genetic variants in human disease, and also provides genotyping services to other research institutions worldwide.	National Human Genome Research Institute, 2024. Center for Genomics and Data Science Research. [Online] Available at: https://www.genome.gov/about-nhgri/Division-of-Intramural-Research/Center-for-Genomics-and-Data-Science-Research
	Rare Diseases BioResource	Genomic data on rare diseases is consistently captured in an accessible database, Health data related to rare disease diagnosis and care is accessible for research purposes.	Maintains data and samples donated by 200k+ volunteers in 18 centres across the UK, both children and adults, in three cohorts – rare diseases, common diseases, and the healthy population. Later added a COVID-19 cohort. Involves universities, NHS, and commercial researchers. References: https://bioresource.nihr.ac.uk/centres-programmes/rare-diseases-bioresource/	National Institute for Health and Care Research, 2024. Rare Diseases BioResource. [Online] Available at: https://bioresource.nihr.ac.uk/centres-programmes/rare-diseases-bioresource/

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health information systems accelerate access to and development of new ways to care for rare diseases	**American Heart Association: Get With The Guidelines**	Rare disease patient registries are integrated into the healthcare system	A registry for stroke, heart failure and resuscitation that is linked to the healthcare system	Patient-Centered Outcomes Research Institute, 2012. Patient Registries. [Online] Available at: https://www.pcori.org/assets/11-Gliklich-Slides-Registries.pdf
	American College of Surgeons: National Surgical Quality Improvement Program	Rare disease patient registries are integrated into the healthcare system	A registry monitoring surgical outcomes and complications that is linked to the healthcare system	American College of Surgeons, 2024. About ACS NSQIP. [Online] Available at: https://www.facs.org/quality-programs/data-and-registries/acs-nsqip/about-acs-nsqip/
	Cystic Fibrosis Foundation Registry	Rare disease patient registries are integrated into the healthcare system	A registry monitoring the health status of people with cystic fibrosis (a rare disease) that is linked to the healthcare system	Patient-Centered Outcomes Research Institute, 2012. Patient Registries. [Online] Available at: https://www.pcori.org/assets/11-Gliklich-Slides-Registries.pdf
	The Human Genome Project	Genomic data on rare diseases is consistently captured in an accessible database	An international project that sequenced the first human genome, as well as the genomes of other non-human organisms. It also established principles on sharing and release of genomic sequencing data for biomedical research.	National Human Genome Research Institute, n.d. Fact Sheet: Human Genome Project. [Online] Available at: https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genome-project
Health services work for people with rare diseases	**Wales Infants' and ChildreN's Genome Service (WINGS)**	Early screening and testing lead to early or timely diagnosis	A rapid whole genome sequencing service (WGS) for acutely unwell inpatient children whose condition is likely genetic, which can return a genetic diagnosis within 2-3 weeks. Rationale: WGS can potentially identify a cause for the health problems a child is experiencing, cutting the diagnostic odyssey short and enabling earlier access to treatment. Certain rare diseases can be cured or made less severe with timely intervention for infants – e.g. dietary changes, pharmaceutical treatments, cell and gene therapy. References: https://medicalgenomicswales.co.uk/index.php/health-professional-information/wings	All Wales Medical Genomics Service, 2019. Wales Infants' and ChildreN's Genome Service (WINGS). [Online] Available at: https://medicalgenomicswales.co.uk/index.php/health-professional-information/wings
	The UK National Screening Committee and its Bloodspot Task Group	Early screening and testing lead to early or timely diagnosis	The UK National Screening Committee (NSC) addresses population and targeted screening, as well as advising researchers on evidence development. The Bloodspot Task Group is comparing UK NBS principles to those of EURORDIS in order to build its evidence base, and the NSC is exploring the feasibility of WGS as a screening method for particular genetic conditions in newborns.	Department for Health and Social Care, 2023. England Rare Diseases Action Plan 2023: main report. [Online] Available at: https://www.gov.uk/government/publications/england-rare-diseases-action-plan-2023/england-rare-diseases-action-plan-2023-main-report

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health services work for people with rare diseases	**NHS England Highly Specialised Services report**	Health services provide the same quality care to all people living with rare diseases	Highly specialised services are defined as those which are delivered in usually no more than three expert centres, have no more than 500 patients, are clinically distinct and nationally coordinated. Annual reporting provides a description of each service, the centres delivering it, NHS England expenditure on each service, activities carried out, clinical outcomes, and geographical equity of access. This permits the Highly Specialised Commissioning Team (HSCT) to assess centres against their previous performance and each other, as well as studying any discrepancies between expected levels of access per region and the actual number of people attending per region to establish the underlying causes and whether action needs to be taken.	NHS England, 2023. Highly specialised services. [Online] Available at: https://www.england.nhs.uk/commissioning/spec-services/highly-spec-services/ NHS England, 2023. Highly specialised services 2020/21. [Online] Available at: https://www.england.nhs.uk/publication/highly-specialised-services-2020-21/
	Project ECHO	Health services provide the same quality care to all people living with rare diseases	This project has a long track record of facilitating expertise sharing and consultations between rural and academic medical centres. It connects rural healthcare providers with specialised knowledge through virtual communities offering free mentoring and learning opportunities. It was founded in the USA, and has been replicated around the world, including in low- and middle-income countries. The rare disease community in various countries has used the Project ECHO model on multiple occasions to connect HCPs with rare disease subject matter experts.	Project ECHO, 2023. Project ECHO: Moving Knowledge, Not People. [Online] Available at: https://projectechoannualreport.unm.edu/wp-content/uploads/2023/04/ECHO_Explainer_Updated3.31.23.pdf Rare Voices Australia, 2023. Rare Disease Project ECHO® [Online] Available at: https://rarevoices.org.au/rare-disease-project-echo/ Rujeedawa, T., McNairney, N., Cordner, S. et al. Reducing global health inequalities for a rare disorder: evaluating the international Prader–Willi Syndrome Organisation's Echo® programme. Orphanet J Rare Dis 17, 380 (2022). https://doi.org/10.1186/s13023-022-02504-5 Tosi, L. L., Rajah, E. N., Stewart, M. H., Gillies, A. P., Hart, T. S., & Lewiecki, E. M. The Rare Bone Disease TeleECHO Program: Leveraging Telehealth to Improve Rare Bone Disease Care. Current osteoporosis reports, 18(4), 344–349 (2020). https://doi.org/10.1007/s11914-020-00595-2
	Undiagnosed Disease Network International	People living with rare diseases have access to multidisciplinary, interoperable services throughout the patient pathway	The UDNI is an international network of clinical investigators supporting people living with undiagnosed diseases, established to evaluate cases at no cost to the person affected, who will share their data with the investigators in the UDNI (including -omics data where such analysis is performed). The researchers carry out studies to substantiate potential causal relationships between genes and phenotypes, and to address novel therapies. It will shortly publish a report on Rare Disease Centres with established follow-up procedures. The UDNI is set up in a way that provides a consistent patient experience through a single application portal, common set of acceptance criteria and of clinical evaluation methods - as well as an agreement to freely share and use data within the network.	UDNI - Undiagnosed Diseases Network International, 2024. UDNI - Undiagnosed Diseases Network International. [Online] Available at: https://www.udninternational.org/

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health services work for people with rare diseases	**SWAN Clinics**	People living with rare diseases have access to multidisciplinary, interoperable services throughout the patient pathway	There is a specific clinic in the UK - funded by the Welsh Government as a pilot programme - for Syndromes Without a Name (SWAN). It accepts referrals for children and adults, with the referring Consultant remaining responsible for the person's clinical care. The SWAN Clinic brings together a multi-disciplinary team including specialists in genetics, immunology, and paediatrics, clinical nurse specialists and genetic counsellors, and aims to shorten the Diagnostic Odyssey using new testing - including genetic testing - developments.	Cardiff & Vale University Health Board, 2023. SWAN (Syndrome Without A Name) Clinic. [Online] Available at: https://cavuhb.nhs.wales/our-services/swan-clinic/
	Implementation of a coordinated transition process from paediatric to specialised adult care for people with Phenylketonuria (PKU)	Rare disease pathways are adapted to individual needs	Supporting successful follow-up, positive social outcomes, therapeutic adherence, and good, stable metabolic control with multidisciplinary teams	Mütze, U., Thiele, A.G., Baerwald, C. et al. Ten years of specialized adult care for phenylketonuria – a single-centre experience. Orphanet J Rare Dis 11, 27 (2016). https://doi.org/10.1186/s13023-016-0410-6 Peres, M.; Almeida, M.F.; Pinto, É.J.; Carmona, C.; Rocha, S.; Guimas, A.; Ribeiro, R.; Martins, E.; Bandeira, A.; MacDonald, A.; et al. Implementing a Transition Program from Paediatric to Adult Services in Phenylketonuria: Results after Two Years of Follow-Up with an Adult Team. Nutrients 2021, 13, 799. https://doi.org/10.3390/nu13030799 Giacomo Biasucci, Lucia Brodosi, Ilaria Bettocchi, Davide Noto, Francesca Pochiero, Maria Letizia Urban, Alberto Burlina, The management of transitional care of patients affected by phenylketonuria in Italy: Review and expert opinion, Molecular Genetics and Metabolism, Volume 136, Issue 2, 2022, https://doi.org/10.1016/j.ymgme.2022.04.004 van Wegberg, A.M.J., MacDonald, A., Ahring, K. et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis 12, 162 (2017). https://doi.org/10.1186/s13023-017-0685-2
	Development of a patient journey map for people living with cervical dystonia and the patient journey as being produced by ERNs	Rare disease pathways are adapted to individual needs	Patient journey map developed with a survey of patients and an expert-patient focus group, through five stages (symptom onset, diagnosis/HCP relationship, start of care, start of treatment, living with CD). CD is a neurological condition in which botulinum toxin is used to block the signals causing involuntary contractions of the neck muscles.	Benson, Monika et al. Development of a patient journey map for people living with cervical dystonia. Orphanet J Rare Dis 17,1, 130. (2022), https://doi.org/10.1186/s13023-022-02270-4
	Patient pathways for rare diseases in Europe: ataxia as an example	Rare disease pathways are adapted to individual needs	Survey of patients in the UK, Germany and Italy comparing specialist ataxia centres with non-specialist care. Ataxias are a group of chronic progressive neurological disorders. Most of them do not have a disease-modifying treatment but symptoms can be addressed. The study showed that respondents were more positive about attending SACs than they were about non-ataxia-specialised services, and it recommended including referrals to SAC in national care pathways alongside telemedicine to assist those having difficulty with transport.	Vallortigara, Julie et al. Patient pathways for rare diseases in Europe: ataxia as an example. Orphanet J Rare Dis 18,1,328. (2023), https://doi.org/10.1186/s13023-023-0

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health services work for people with rare diseases	**Influencing Factors of Health Technology Assessment (HTA) to Orphan Drugs: Empirical Evidence in England, Scotland, Canada, and Australia**	Service provision and coverage decisions take into account PROs and are value-added for people living with rare diseases	The study looked at the four countries mentioned to understand the reasons behind their differing decisions on coverage recommendation for orphan drugs. They all had different preferences in HTA in relation to clinical evidence and economic modelling, and their decisions were not consistent with each other. Looking at the case study of an orphan monoclonal antibody for certain rare cancers, Scotland had a novel consultation process involving HCPs and people who used the medicine as part of the value consideration process.	Zhou, N. et al., 2022. Influencing Factors of Health Technology Assessment to Orphan Drugs: Empirical Evidence in England, Scotland, Canada, and Australia. Frontiers in Public Health, Volume 10.
	Innovation and Value Initiative and the EveryLife Foundation for Rare Disease - Rare Disease Initiative partnership	Service provision and coverage decisions take into account PROs and are value-added for people living with rare diseases	A partnership between the Innovation and Value Initiative and the EveryLife Foundation for Rare Diseases to develop new approaches to patient-centred outcomes research (PCOR), comparative effectiveness research (CER) and HTA via roundtables and a final report with recommendations.	Innovation and Value Initiative, 2023. Partnering with Rare Disease Patients to Identify Meaningful Approaches to Health Technology Assessment. [Online] Available at: https://thevalueinitiative.org/rare-disease-initiative/
	Ready Steady Go	Young people living with rare diseases experience a smooth, quality transition from paediatric to adult services	Colchester Hospital uses a transition programme, Ready Steady Go, to prompt staff to start conversations early on about transition to adult care with young people, and then to remind them to keep having conversations at specific milestones. Each young person gets a transition plan which is sent to them and to the professionals involved in their care. They also receive support from youth workers so that the transition process focuses on the young person's life as a whole, not just healthcare.	Costello Medical, Cambridge Rare Disease Network and Beacon, 2022. Improving transitions to adult care for young people living with a rare disease. [Online] Available at: https://drive.google.com/file/d/164pML7Jrf4t4Wpz_mb9TjR8r84dNbidD/view
	Teenage and Young Adult (TYA) Ward	Young people living with rare diseases experience a smooth, quality transition from paediatric to adult services	Addenbrooke's Hospital has a special ward for 14-24 year olds, with young people directly involved in the design process. It serves as a less stressful stepping-stone from paediatric to adult wards, and includes areas for socializing and private spaces. It has a homely atmosphere and hosts a multidisciplinary team of clinicians, youth workers, social workers and mental health support staff which engages with young people about their future plans overall, not just their illness.	Costello Medical, Cambridge Rare Disease Network and Beacon, 2022. Improving transitions to adult care for young people living with a rare disease. [Online] Available at: https://drive.google.com/file/d/164pML7Jrf4t4Wpz_mb9TjR8r84dNbidD/view
Health system financing meets rare disease community needs	**EU funding call: Ensuring access to innovative, sustainable and high-quality health care (Two stage - 2024) (HORIZON-HLTH-2024-CARE-04-two-stage)**	Financing accounts for and addresses inequalities in access to care	Research and innovation funding for equal access to health and care services, taking into account that certain groups are at greater risk of unmet medical needs depending on socio-economic and legal status, age, sex and gender identity, disability, ethnicity, and geographical location. Aims to address barriers to care, access across the healthcare system, ways to resolve inequalities in access, and measure the scale and cost of the problem.	European Commission, 2023. Access to health and care services for people in vulnerable situations. [Online] Available at: https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-hlth-2024-care-04-04-two-stage;callCode=null;freeTextSearchKeyword=;matchWholeText=true;typeCodes=1,0;statusCodes=31094501,31094502;programmePeriod=2

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health system financing meets rare disease community needs	**Innovative Medicines Fund NHS England**	Financing accounts for and addresses inequalities in access to care	The Innovative Medicines Fund is a ringfenced sum of 340 million GBP for managed access to non-cancer treatments, including promising products for rare diseases that have limited data availability (impeding market authorisation) and accelerating access to approved medicine products for rare diseases. When a promising product is available through the Fund, real-world data is collected to address remaining uncertainties in the evidence base and facilitate a final decision on whether to make the product available through the National Health Service. If the decision is negative, the patient will still have access to the product at the company's cost. Spending exceeding 340 million GBP will be split between all companies that got money from the Fund and they will have to pay the excess back.	NHS England, 2022. Innovative Medicines Fund. [Online] Available at: https://www.england.nhs.uk/medicines-2/innovative-medicines-fund/
	Belgian Special Solidarity Fund	Financing accounts for and addresses inequalities in access to care, Health system financing decisions on rare disease coverage are open and transparent	Provides reimbursement for rare indications, rare diseases (if they need continuous and complex treatment/specific physiopathological treatment) in the event that the intervention is expensive, the disorder threatens vital functions, the treatment is proven effective and with scientific value, there is no alternative in the compulsory health system, and it was prescribed by a specialist medical doctor in the disease, and the treatment is not eligible for reimbursement by other (private) insurances or reimbursement systems. Usually reimburses 60 or 75% of the costs.	Guillaume P, Moldenaers I, Bulté S, Debruyne H, Devriese S, Kohn L, Pierart J, Vinck I. Optimisation of the operational processes of the Special Solidarity Fund. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE). 2010. KCE Reports 133C. D/2010/10.273/46.
	France: fast-track assessment for orphan medicines	Health system financing decisions on rare disease coverage are open and transparent	In France, assessment timelines for OMPs are 15 days and health economic assessments are not required for products with less than 20 million EUR impact/year on the budget.	Dabbous, O. et al., 2023. Valuation of Treatments for Rare Diseases: A Systematic Literature Review of Societal Preference Studies. Advances in Therapy, 40(2), pp. 393-424.
	Germany: proven benefit	Health system financing decisions on rare disease coverage are open and transparent	In Germany, proven benefit of OMPs authorised by the EMA is recognised automatically. Prices are set freely for a provisional period before negotiated price sets in based on HTA assessment	Dabbous, O. et al., 2023. Valuation of Treatments for Rare Diseases: A Systematic Literature Review of Societal Preference Studies. Advances in Therapy, 40(2), pp. 393-424.
	UK: increased ICER threshold for rare diseases	Health system financing decisions on rare disease coverage are open and transparent	The UK's National Institute for Health and Care Excellence normally uses a cost-effectiveness threshold of 20-30,000 GBP per QALY, rising to 100,000 GBP/QALY for highly specialised medical products.	Dabbous, O. et al., 2023. Valuation of Treatments for Rare Diseases: A Systematic Literature Review of Societal Preference Studies. Advances in Therapy, 40(2), pp. 393-424.
	The Netherlands: Increased ICER thresholds based on illness severity	Health system financing decisions on rare disease coverage are open and transparent	The Zorginstituut Nederland varies its cost-effectiveness threshold based on disease severity, from up to 20,000 EUR/QALY for the least severe to up to 80,000 EUR/QALY for the most severe.	Dabbous, O. et al., 2023. Valuation of Treatments for Rare Diseases: A Systematic Literature Review of Societal Preference Studies. Advances in Therapy, 40(2), pp. 393-424.
	Outcome-based payment models	Rare disease care is affordable to people living with rare diseases	Reimbursement for ATMPs is based on whether the patient experiences certain clinical outcomes within a fixed time period - if they do not, the manufacturer may have to pay back previous payments or forfeit future ones. E.g. Spain: Kymriah and Yescarta reimbursed on the basis of part payment on infusion and a later payment depending on outcome per patient.	EUCOPE Working Group on Gene & Cell Therapies, 2021. Advanced Therapies Medicinal Products: new payment and funding approaches. [Online] Available at: https://www.eucope.org/wp-content/uploads/2022/03/eucope-ipm-paper-2021.pdf

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health system financing meets rare disease community needs	**Annuity payments**	Rare disease care is affordable to people living with rare diseases	Denmark: regions will pay for Luxturna in instalments, outcomes are checked at set times, and if the medicine does not have the effect sought the rest of the payments will not be sent	EUCOPE Working Group on Gene & Cell Therapies, 2021. Advanced Therapies Medicinal Products: new payment and funding approaches. [Online] Available at: https://www.eucope.org/wp-content/uploads/2022/03/eucope-ipm-paper-2021.pdf
	Innovative payment models	Rare disease care is affordable to people living with rare diseases	Italy - 500,000 EUR/year for oncology and 500,000 EUR/year for non-oncology expensive innovative medicines, covered Yescarta and Kymriah under an outcomes-based model.	EUCOPE Working Group on Gene & Cell Therapies, 2021. Advanced Therapies Medicinal Products: new payment and funding approaches. [Online] Available at: https://www.eucope.org/wp-content/uploads/2022/03/eucope-ipm-paper-2021.pdf
	Innovative payment models	Rare disease care is affordable to people living with rare diseases	Germany - partially pooling spending on patients with a yearly cost of care over 100,000 EUR among all sick funds.	EUCOPE Working Group on Gene & Cell Therapies, 2021. Advanced Therapies Medicinal Products: new payment and funding approaches. [Online] Available at: https://www.eucope.org/wp-content/uploads/2022/03/eucope-ipm-paper-2021.pdf
	Early Access Authorisation Procedure (AAP) - France	Innovative rare disease care is affordable to people living with rare diseases	France's AAP (early access) programme for medicines not yet authorised or reimbursed, which allows early access to innovative products classified as safe and effective for addressing unmet needs of people living with serious, rare, or disabling illnesses who cannot wait for treatment. In the two years from 2021, over 250 applications were made, and the time-to-decision remained shorter than the 90 days allocated to standard approvals - at 78 days. 78% of the 125 decisions made as of 1 July 2023 were positive. On average, AAP has allowed treatment to take place 9 months before the product is entered onto the reimbursement lists.	Haute Autorité de Santé, 2023. Autorisation d'accès précoce aux médicaments : un bilan à deux ans positif. [Online] Available at: https://www.has-sante.fr/jcms/p_3470145/fr/autorisation-d-acces-precoce-aux-medicaments-un-bilan-a-deux-ans-positif
	The Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study	Governments collect data about socioeconomic impacts of living with a rare disease to determine funding allocations	An EveryLife Foundation study collecting data on the avoidable costs associated with living with a rare disease - including direct medical costs, indirect costs of productivity loss, and non-medical healthcare costs - for seven rare diseases.	EveryLife Foundation for Rare Diseases, 2023. The Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study. [Online] Available at: https://everylifefoundation.org/delayed-diagnosis-study/
	Highly Specialised Services (NHS England)	Service provision and coverage decisions take into account PROs and are value-added for people living with rare diseases	Annual audit processes which benchmark providers against a set of outcomes they have been commissioned to deliver, and against each other's performance where there are multiple centres providing a particular HHS – collecting clinical outcome information, flagging up gaps, and providing examples of good practice.	NHS England, 2023. Highly specialised services. [Online] Available at: https://www.england.nhs.uk/commissioning/spec-services/highly-spec-services/ NHS England, 2023. Highly specialised services 2020/21. [Online] Available at: https://www.england.nhs.uk/publication/highly-specialised-services-2020-21/

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health system financing meets rare disease community needs	**James Lind Alliance Priority Setting Partnerships (PSPs)**	Service provision and coverage decisions take into account PROs and are value-added for people living with rare diseases	Cooperation between patients, clinicians, and researchers to identify areas of research that they collectively wish to prioritise – culminating in a top ten list of priorities.	James Lind Alliance Priority Setting Partnership Steering Group, JLA, FDSSUK, XLHUK, XLH Network, Genetic Alliance UK, and Oxford BRC, 2018. Rare Musculoskeletal Diseases in Adulthood PSP Report. [Online] Available at: https://www.jla.nihr.ac.uk/priority-setting-partnerships/rare-musculoskeletal-diseases-in-adulthood/Downloads/MSK-PSP-Report-FINAL.pdf James Lind Alliance, 2018. Rare Musculoskeletal Diseases in Adulthood Top 10. [Online] Available at: https://www.jla.nihr.ac.uk/priority-setting-partnerships/rare-musculoskeletal-diseases-in-adulthood/top-10-priorities.htm James Lind Alliance, 2024. About Priority Setting Partnerships. [Online] Available at: https://www.jla.nihr.ac.uk/about-the-james-lind-alliance/about-psps.htm
	National Rare Disease Plan 2023-2026 - Italy	Rare disease plans include funding for implementation	Includes allocation of 25 million EUR annually	Ministero della Salute, 2023. Piano nazionale malattie rare 2023 – 2026. [Online] Available at: https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2023&codLeg=95257&parte=1%20&serie=null
	Joint Action on integration of ERNs into national healthcare systems (JARDIN)	Rare disease plans include funding for implementation	Direct EU grant to Member States to help them integrate ERNs into their healthcare system - 11.2 million EUR in total. The project has total funding of 18.75 million EUR (15 million from the EU and 3.75 million from the Member States) over three years.	European Commission, 2022. Annex I to the Commission Implementing Decision of 14.1.2022 on the financing of the Programme for the Union's action in the field of health ('EU4Health Programme') and the adoption of the work programme for 2022. [Online] Available at: https://ec.europa.eu/assets/sante/health/funding/wp2022_en.pdf European Economic and Social Committee, 2024. Rare Diseases in the EU: Joint Action shaping the future of ERNs - JARDIN kick-off meeting. [Online] Available at: https://www.eesc.europa.eu/en/agenda/our-events/events/rare-diseases-eu-joint-action-shaping-future-ern
	Rare Resource Centres	People living with rare diseases and those caring for them receive adequate financial and non-financial support.	Resource centres act as a one-stop-shop style service for people living with rare diseases and their families to get in touch with all the relevant medical, social, and educational services, as well as help with applying for benefits and management of complex cases.	EURORDIS, 2013. Resource Centres for Rare Diseases. [Online] Available at: https://www.eurordis.org/publications/resource-centres-for-rare-diseases/
	UN Resolution on Addressing the Challenges of Persons Living with a Rare Disease and their Families	People living with rare diseases and those caring for them receive adequate financial and non-financial support.	Approval by consensus of all UN Member States, and binding on the UN Secretariat, budget, and programmes. Urges Member States to implement policies assisting people living with a rare disease to get equal access to education, employment, and health without discrimination, eliminating barriers to work and to financial inclusion for people living with rare diseases and their families. Also calls for programmes for well-being of people living with rare diseases and their families and caregivers, alongside provision of affordable care facilities and measures to reduce the disproportionate share of care and domestic responsibilities placed on women and girls related to a person living with a rare disease.	Rare Diseases International (RDI), 2021. UN Resolution on Persons Living with a Rare Disease. [Online] Available at: https://www.rarediseasesinternational.org/un-resolution/

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health system financing meets rare disease community needs	**Bespoke GT**	Public-private models of financing support research in rare disease	Public-private partnership between NIH, FDA, and various public and private organisations - 76 million USD over 5y to support research into creating a standardised gene therapy development model, building on the PaVE-GT project.	National Center for Advancing Translational Sciences, 2021. NIH, FDA and 15 Private Organizations Join Forces to Increase Effective Gene Therapies for Rare Diseases. [Online] Available at: https://ncats.nih.gov/news-events/news/2021/nih-fda-and-15-private-organizations-join-forces-to-increase-effective-gene-therapies-for-rare-diseases
	PaVE-GT	Public-private models of financing support research in rare disease	Development of four gene therapies using a standardised process, bringing researchers together across disciplines.	National Center for Advancing Translational Sciences, n.d. PaVe-GT > Frequently Asked Questions. [Online] Available at: https://pave-gt.ncats.nih.gov/frequently-asked-questions/
	Critical Path for Rare Neurodegenerative Diseases (CP-RND)	Public-private models of financing support research in rare disease	PPP between experts in rare neurodegenerative diseases, biopharma companies, regulators, PAGS to improve understanding of natural history of disease, identify biomarkers and improve clinical trial design to make treatment development more successful and efficient.	Critical Path Institute, 2022. C-Path Awarded FDA Grant to Establish Public-Private Partnership to Advance Treatments for Rare Neurodegenerative Diseases. [Online] Available at: https://c-path.org/c-path-awarded-fda-grant-to-establish-public-private-partnership-to-advance-treatments-for-rare-neurodegenerative-diseases/
	Rare Disease Moonshot	Public-private models of financing support research in rare disease	Cooperation between C-Path, EUCOPE, the European Clinical Research Infrastructure Network (ECRIN), EuropaBio, EURORDIS-Rare Diseases Europe, the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Infrastructure for Translational Medicine (EATRIS) - to accelerate basic science and translation research in areas which are not currently being studied - with the aim of adding new therapies to research pipelines.	Critical Path Institute, 2022. 'Rare Disease Moonshot' – Scaling-up public-private partnerships to accelerate research into world's rarest diseases. [Online] Available at: https://c-path.org/rare-disease-moonshot-scaling-up-public-private-partnerships-to-accelerate-research-into-worlds-rarest-diseases/
	Alliance4Rare research network	Public-private models of financing support research in rare disease	A care and research network in Germany, connecting university hospitals and training clinician scientists researching rare disease. Funded by the Eva Luise und Horst Köhler Stiftung and the Friede Springer Stiftung.	Eva Luise und Horst Köhler Stiftung für Menschen mit Seltenen Erkrankungen, n.d. Alliance4Rare. [Online] Available at: https://www.elhks.de/en/forschung/alliance4rare/
	European Lead Factory (ELF)	Public-private models of financing support research in rare disease	Development of a compound library by eight pharmaceutical companies giving each other and the research community access to their internal libraries, alongside a public compound collection. This library can then be screened to identify which compounds may be potential starting points for medicine development	European Lead Factory, 2023. Objectives. [Online] Available at: https://www.europeanleadfactory.eu/about/objectives European Lead Factory, 2023. Partnering opportunities for charities & foundations. [Online] Available at: https://www.europeanleadfactory.eu/past-opportunities-collaboration/partnering-opportunities-charities-foundations
	BARDA Industry Day (BID)	Public-private models of financing support research in rare disease	Annual conference on medical countermeasures (MCMs) for public-private networking, awareness raising and health threat preparedness	U.S. Department of Health & Human Services, 2023. BARDA Industry Day (BID). [Online] Available at: https://medicalcountermeasures.gov/barda/barda-industry-day-2023/

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health workforce supports access to high-quality care	**Medics4RareDiseases**	People living with rare diseases provide input into medical workforce training, Medical education systems prioritise rare disease care, Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	A registered charity which advocates for and delivers rare disease training for medical students and doctors, which has a trustee that lives with a rare disease. Provides an e-learning platform – Rare Disease 101 – to teach medics about the basics of rare disease and its management in diagnosed and undiagnosed patients. Launched a mini module on rare disease clinical trials and early access programmes.	Medics4RareDiseases, 2024. The History of M4RD. [Online] Available at: https://www.m4rd.org/history/
	Postgraduate curricula as being established and implemented by ERNs Best practice	People living with rare diseases provide input into medical workforce training	The European Rare Kidney Disease Reference Network has an ERKNet Postgraduate Curriculum, a three-year online programme including case-based eLearning on patient scenarios.	European Reference Network for Rare Kidney Diseases, 2024. ERKNet Postgraduate Curriculum. [Online] Available at: https://www.erknet.org/education-training/erknet-postgraduate-curriculum-in-rare-kidney-diseases
	Health Education England & Medics 4 Rare Diseases - creation of an online resource hub about rare diseases and genomics	Education policies prioritise rare disease care	Provides a general overview of rare diseases for health professionals, including input from people living with rare diseases and their families, and the challenges they face in the health care system. Provides guidance on actions health care professionals can take and signposts them to further resources to learn more.	Health Education England (HEE), 2022. Rare disease education hub. [Online] Available at: https://www.genomicseducation.hee.nhs.uk/rare-disease-education-hub/
	Q.RARE.LI - Improving health-related quality of life in patients with rare autoimmune liver diseases by structured peer-delivered support: a transnational effectiveness-implementation hybrid trial	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	A study to assess the effectiveness and feasibility of implementing a peer-delivered support intervention for people with rare autoimmune liver diseases alongside standard care, compared to standard care alone.	Löwe, B. & Uhlenbusch, N., 2022. Q.RARE.LI - Improving health-related quality of life in patients with rare autoimmune liver diseases by structured peer-delivered support: a transnational effectiveness-implementation hybrid trial. [Online] Available at: https://rare-liver.eu/news/detail/qol-project-3
	European Reference Network Exchange Programme	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	European Commission funded exchanges for health care professionals to carry out a short secondment in another member centre of European Reference Networks, in order to spread knowledge and fill gaps in expertise. Applies to all disciplines, permits preference for particular topics that could particularly benefit from experience and knowledge sharing across centres. Staff whose centre is involved in a particular ERN (e.g. Rare Neurological Diseases) can also be seconded to a centre involved in a different ERN of relevance (e.g. Rare and Complex Epilepsies).	European Reference Network Urogenital Diseases (eUROGEN), 2023. ERN eUROGEN Exchange Programme: Now Closed but A Great Success. [Online] Available at: https://eurogen-ern.eu/ern-eurogen-exchange-programme-closed/
	European Reference Network workshops funded by the European Joint Programme on Rare Diseases	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	Clinicians and scientists get funding to organise two-day workshops for around 20 people, on innovative research, diagnostic and treatment developments of interest across rare disease areas.	EJP RD - European Joint Programme on Rare Diseases, n.d. European Reference Network workshops funded by the European Joint Programme on Rare Diseases. [Online] Available at: https://www.ejprarediseases.org/our-actions-and-services/training-and-education/ern-workshops/

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health workforce supports access to high-quality care	**European Reference Network free webinars**	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	Open access, free webinars which can be accessed by anyone with an interest in rare disease and medicine, designed for educational purposes.	European Reference Network Rare Endocrine Diseases (Endo-ERN), 2024. Overview of Webinars. [Online] Available at: https://endo-ern.eu/webinars/
	ERN EpiCARE grants for junior healthcare staff working on rare and complex epilepsies to attend major scientific congresses on neurology and epilepsy	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	Selected candidates have their expenses reimbursed up to 1000 EUR so they can present their research findings at the congresses, helping to integrate rare diseases into the wider speciality.	European Reference Network Rare and Complex Epilepsies (EpiCARE), 2023. Supporting Next Generation Epilepsy Experts. [Online] Available at: https://epi-care.eu/supporting-young-members/
	ERKNet Postgraduate Curriculum	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	Three-year online programme covering rare kidney diseases in childhood and adulthood, providing certification as a Rare Kidney Disease Specialist once the course is completed and the student has 2 years of clinical activity in the field. The course is for enrolled students only, although its webinars are also open to the public.	European Reference Network for Rare Kidney Diseases, 2024. ERKNet Postgraduate Curriculum. [Online] Available at: https://www.erknet.org/education-training/erknet-postgraduate-curriculum-in-rare-kidney-diseases
	ERN-LUNG Academy	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	Webinars for medical staff at any stage of their careers, based on webinars, online case reports, and in-person training at ERN-LUNG member centres. Open to EU and non-EU based participants. Issues a certificate of expertise.	European Reference Network Respiratory Diseases (ERN-LUNG), 2024. ERN-LUNG Academy. [Online] Available at: https://ern-lung.eu/our-expertise/education/
	ERN-Skin emergency cards	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	Rare skin disorders are not known to most health care professionals, so the HCPs and patients involved in the related ERN developed business-card sized emergency information - in multiple languages - to explain particular diseases and warn them about possible complications, precautions to take, and procedures/treatments to avoid.	European Reference Network Skin (ERN-Skin), 2024. Emergency cards. [Online] Available at: https://ern-skin.eu/emergency-cards/
	Neuropathies Rehabilitation Summer School	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	An activity accredited by the European Council for Continuing Medical Education (CME) and carrying CME credits, this ERN-endorsed summer school brings together health care professionals across disciplines and PAGs to build their knowledge of rare and complex peripheral neuropathies and establish a multidisciplinary approach to cutting-edge rehabilitation care.	European Reference Network Neuromuscular Diseases (EURO-NMD), 2023. Neuropathies Rehabilitation Summer School. [Online] Available at: https://ern-euro-nmd.eu/event/neuropathies-rehabilitation-summer-school/
	Online Genetics Course APOGeE	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases.	An ERN-led effort to develop a free online interactive textbook on medical genetics, contributing to post-graduate education in genetics and rare disease - particularly in places with fewer resources.	European Reference Network for Rare Malformation Syndromes, Intellectual and Other Neurodevelopmental Disorders (ERN-ITHACA), n.d. Online Genetics Course APOGeE. [Online] Available at: https://ern-ithaca.eu/documentation/online-genetics-course-apogee/
	Birmingham: Centre for Rare Diseases Studies (CRDS)	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	A centre of excellence for basic and applied research into the causes of rare diseases, and for multidisciplinary information sharing, teaching, and research. Works with partner hospitals treating rare diseases in the city of Birmingham to turn research into clinical impact. Provides coordinated one-stop clinics for rare disease, establishes registries, and conducts studies.	University of Birmingham, n.d. Centre for Rare Disease Studies (CRDS) Birmingham. [Online] Available at: https://www.birmingham.ac.uk/research/rare-diseases/index.aspx

BUILDING BLOCK	EXAMPLE	OUTCOME(S)	DETAILS	MORE INFORMATION
Health workforce supports access to high-quality care	**Newcastle Centre for Rare Disease**	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	Centre of research excellence, which cooperates with Newcastle hospitals, industry, and policy makers, involving around 100 experts from the University and NHS, as well as patient participation in designing and managing research. It established and coordinated three of the 24 ERNs while the UK was an EU Member State. 45 clinical academics and health care professionals are members of the Centre, providing multidisciplinary care and integrating social issues through care coordinators and resources to share with education providers and employers.	Newcastle University, n.d. Centre for Rare Disease: About Us. [Online] Available at: https://www.ncl.ac.uk/rare-diseases/about-us/
	London: Guys & St Thomas Rare Disease Centre	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	A rare disease multidisciplinary clinic that connects interested people living with rare diseases to research study participation opportunities.	NHS Guy's and St Thomas', 2023. Overview: Rare Diseases Centre. [Online] Available at: https://www.guysandstthomas.nhs.uk/our-services/rare-diseases-centre
	Manchester: Manchester Rare Conditions Centre	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	A virtual platform based in the Manchester University Foundation NHS Trust, which includes a centre of excellence for rare disease training courses - the MRCC Academy and clinical bioinformatics education through free online courses and formal certifications.	Manchester Rare Conditions Centre, 2024. Manchester Rare Conditions Centre. [Online] Available at: https://www.mrcc.org.uk/
	HHS Health Workforce Initiative	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	US Federal government investment in workforce training, scholarships, loan repayments and well-being programmes for the health workforce as a whole - supporting them to enter and stay in the healthcare professions.	U.S. Department of Health and Human Services, 2023. New HHS Initiative Aims to Strengthen Nation's Health Workforce. [Online] Available at: https://www.hhs.gov/about/news/2023/07/06/new-hhs-initiative-aims-strengthen-nations-health-workforce.html
	Uplifting Athletes Young Investigator Draft	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	Grants funding basic research into rare disease, including a focus on supporting researchers from underrepresented backgrounds.	Uplifting Athletes, 2024. Young Investigator Draft. [Online] Available at: https://www.upliftingathletes.org/young-investigator-draft/
	National Society of Genetic Counsellors	Healthcare professionals are trained to support people with the day-to-day realities of living with rare diseases	Provides online education for genetic counsellors and approves continuing education activities for recertification purposes. Provides practice guidelines based on clinical evidence, and practice resources for topics without such a full clinical evidence base - including certain rare diseases, based on experiences and opinions of the authors.	National Society of Genetic Counselors (NSGC), n.d. About. [Online] Available at: https://www.nsgc.org/About/About-NSGC

Bibliography

European Medicines Agency (EMA), 2023. *PRIME: priority medicines.* [Online]
Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines

Office of the National Coordinator for Health Information Technology (ONC) , 2019. *State Health Information Exchange Cooperative Agreement Program.* [Online]
Available at: https://www.healthit.gov/topic/onc-hitech-programs/state-health-information-exchange

Álvaro-Sánchez, S. et al., 2021. Current Status of Genetic Counselling for Rare Diseases in Spain. *Diagnostics* (Basel), 11(12).

118th Congress, 2023. Text - H.R.1350 - 118th Congress (2023-2024): *Cameron's Law*.. s.l., s.n.

Academy of Medical Sciences, 2016. *Improving recognition of team science contributions in biomedical research careers.* [Online]
Available at: https://acmedsci.ac.uk/file-download/6924621

Academy of Medical Sciences, 2020. *Transforming health through innovation: Integrating the NHS and academia.* [Online]
Available at: https://acmedsci.ac.uk/file-download/23932583

Ali, S. R. et al., 2021. The Quality Evaluation of Rare Disease Registries—An Assessment of the Essential Features of a Disease Registry. *International Journal of Environmental Research and Public Health*, 18(22).

Ali, S. R. et al., 2020. The EuRRECa Project as a Model for Data Access and Governance Policies for Rare Disease Registries That Collect Clinical Outcomes. *International Journal of Environmental Research and Public Health,* 17(23).

All of Us Research Program, 2024. *Data Snapshots.* [Online]
Available at: https://www.researchallofus.org/data-tools/data-snapshots/

Amelung, V. et al., 2022. *Digital Radar: Zwischenbericht Ergebnisse der ersten nationalen Reifegradmessung deutscher Krankenhäuser.* [Online]
Available at: https://www.digitalradar-krankenhaus.de/download/220914_Zwischenbericht_DigitalRadar_Krankenhaus.pdf

Asia-Pacific Economic Cooperation, 2018. *APEC Action Plan On Rare Diseases.* [Online]
Available at: https://www.apec.org/rarediseases/action-plan

Association of Public Health Laboratories, 2024. *State Profiles.* [Online]
Available at: https://www.newsteps.org/data-center/state-profiles?q=view-state-profile

Bellaiche, M. M. et al., 2021. Disparity in Access to Oncology Precision Care: A Geospatial Analysis of Driving Distances to Genetic Counselors in the U.S.. *Frontiers in Oncology,* Volume 11.

Benz, K. et al., 2022. Awareness and Knowledge of Rare Diseases in German Dentists, Dental Specialists and Oral and Maxillofacial Surgeons: A Country-Wide Survey. *Medicina,* 58(1114).

Beyond 1 Million Genomes (B1MG), n.d. *B1MG Maturity Level Model (MLM).* [Online]
Available at: https://b1mg-project.eu/resources/maturity-level-model
[Accessed 2024].

Black Women's Health Imperative (BWHI), Rare Disease Diversity Coalition (RDDC), Upequity, 2022. *A Report of Survey Findings: Diversity, Equity, and Inclusion Efforts in Rare Disease Organizations.* [Online]
Available at: https://21259597.fs1.hubspotusercontent-na1.net/hubfs/21259597/RDDC-DEI.pdf

Bogart, K. et al., 2022. Healthcare access, satisfaction, and health-related quality of life among children and adults with rare diseases. *Orphanet Journal of Rare Diseases,* 17(196).

Bolz-Johnson, M., Meek, J. & Hoogerbrugge, N., 2019. "Patient Journeys": improving care by patient involvement. *European Journal of Human Genetics,* Volume 28, pp. 141-143.

Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), n.d. *Alpha-ID - Identifikationsnummer für Diagnosen.* [Online]
Available at: https://www.bfarm.de/DE/Kodiersysteme/Terminologien/Alpha-ID-SE/_node.html

Bundesministerium für Gesundheit (BMG), 2021. *Tag der Seltenen Erkrankungen - Digitalisierung schafft mehr Sichtbarkeit.* [Online]
Available at: https://www.bundesgesundheitsministerium.de/ministerium/meldungen/20202021/tag-der-seltenen-erkrankungen

Bundesministerium für Gesundheit (BMG), 2023. *BMG Gemeinsam Digital – Digitalisierungsstrategie für das Gesundheitswesen und die Pflege.* [Online]
Available at: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/D/Digitalisierungsstrategie/BMG_Broschuere_Digitalisierungsstrategie_bf.pdf

Bundesministerium für Gesundheit, 2023. *Bundesgesundheitsminister legt Digitalisierungsstrategie vor: „Moderne Medizin braucht digitale Hilfe".* [Online]
Available at: https://www.bundesgesundheitsministerium.de/presse/pressemitteilungen/digitalisierungsstrategie-vorgelegt-09-03-2023.html

Bundesministerium für Wirtschaft und Klimaschutz (BMWK), 2024. *Industrielle Gemeinschaftsforschung (IGF).* [Online]
Available at: https://www.foerderdatenbank.de/FDB/Content/DE/Foerderprogramm/Bund/BMWi/industrielle-gemeinschaftsforschung.html

Bundgaard, J. S., Iversen, K. & Bundgaard, H., 2022. Patient-prioritized primary endpoints in clinical trials. *Scandinavian Cardiovascular Journal,* 56(1).

Canadian Agency for Drugs and Technologies in Health, 2018. *Drugs for Rare Diseases: A Review of National and International Health Technology Assessment Agencies and Public Payers' Decision-Making Processes.* [Online]
Available at: https://www.cadth.ca/drugs-rare-diseases-review-national-and-international-health-technology-assessment-agencies-and

Canadian Institutes of Health Research, 2011. *Canada's Strategy for Patient-Oriented Research.* [Online]
Available at: https://cihr-irsc.gc.ca/e/44000.html#f68

Centers for Disease Control, 2023. *Public Health Data Strategy.* [Online]
Available at: https://www.cdc.gov/ophdst/public-health-data-strategy/index.html

Centers for Medicare & Medicaid Services, 2023. *Medicare Promoting Interoperability Program: Frequently Asked Questions (FAQs).* [Online]
Available at: https://www.cms.gov/files/document/medicare-pi-program-faqs-2023-06-13.pdf

Centre for Innovation in Regulatory Science (CIRS), 2021. *Socio-Economic Impact Report on IMI1 projects.* [Online]
Available at: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/IMI1_SocioEconomicImpactReport_2020.pdf

Centre for Innovation in Regulatory Science (CIRS), 2023. *New drug approvals in six major authorities 2013-2022: Focus on orphan designation and facilitated regulatory pathways.* [Online]
Available at: https://cirsci.org/wp-content/uploads/dlm_uploads/2023/07/CIRS-RD-Briefing-88-6-agencies-v.1.2.pdf

Choudhury, M. C. & Chaube, P., 2022. Integrating rare disease management in public health programs in India: exploring the potential of National Health Mission. *Orphanet Journal of Rare Diseases,* 17(43).

Cleanthous, S. et al., 2021. *Myasthenia Gravis Symptoms Patient Reported Outcome (PRO) Instrument (MG Symptoms PRO).* [Online]
Available at: https://eprovide.mapi-trust.org/instruments/myasthenia-gravis-symptoms-patient-reported-outcome-pro-instrument

Clinovations Government + Health (CGH), 2016. *Final Report: Measurement of Interoperable Electronic Health Care Records Utilization.* [Online]
Available at: https://aspe.hhs.gov/sites/default/files/private/pdf/255526/EHRUtilizationReport.pdf

Costello Medical, Cambridge Rare Disease Network and Beacon, 2022. *Improving transitions to adult care for young people living with a rare disease.* [Online]
Available at: https://drive.google.com/file/d/164pML7Jrf4t4Wpz_mb9TjR8r84dNbidD/view

Critical Path Institute, 2022. *C-Path Awarded FDA Grant to Establish Public-Private Partnership to Advance Treatments for Rare Neurodegenerative Diseases.* [Online]
Available at: https://c-path.org/c-path-awarded-fda-grant-to-establish-public-private-partnership-to-advance-treatments-for-rare-neurodegenerative-diseases/

Curic, E. et al., 2023. International Undiagnosed Diseases Programs (UDPs): components and outcomes. *Orphanet Journal of Rare Diseases,* 18(348).

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V., 2022. *GKV-Finanzstabilisierungsgesetz (GKV-FinStG) hat Einfluss auf die Hämatologie / Onkologie.* [Online]
Available at: https://www.dgho.de/aktuelles/news/newsarchiv/2022/gkv-finanzstabilisierungsgesetz-gkv-finstg-hat-einfluss-auf-die-haematologie-onkologie

Directorate-General for Communication - European Commission, 2014. *Special Eurobarometer 361: European awareness of Rare Diseases.* [Online]
Available at: https://data.europa.eu/data/datasets/s842_74_3_ebs361?locale=en

Doty, M. M., Tikkanen, R., Shah, A. & Schneider, E. C., 2019. Primary Care Physicians' Role In Coordinating Medical And Health-Related Social Needs In Eleven Countries. *Health Affairs,* 39(1).

EFPIA & IQVIA, 2023. *EFPIA Patients W.A.I.T. Indicator 2022 Survey.* [Online]
Available at: https://www.efpia.eu/media/s4qf1eqo/efpia_patient_wait_indicator_final_report.pdf

EMA, 2020. *Decision of the Executive Director: On fee reductions for designated orphan medicinal products.* [Online]
Available at: https://www.ema.europa.eu/en/documents/other/decision-executive-director-fee-reductions-designated-orphan-medicinal-products_en.pdf

EMA, 2023. *CAT quarterly highlights and approved ATMPs.* [Online]
Available at: https://www.ema.europa.eu/en/documents/committee-report/cat-quarterly-highlights-and-approved-atmps-may-2023_en.pdf

EMA, 2023. *Mid-year report 2023.* [Online]
Available at: https://www.ema.europa.eu/en/documents/report/european-medicines-agency-mid-year-report-2023-january-june-2023_en.pdf

EMA, 2023. *Orphan Medicinal Product Designation: Overview 2000-2022.* [Online]
Available at: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2022_en.pdf

EMA, n.d. *Scientific advice and protocol assistance.* [Online]
Available at: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-advice-and-protocol-assistance#

ERICA, 2022. *Patient-Centred Research (WP3).* [Online]
Available at: https://erica-rd.eu/work-packages/patient-centred-research/

ERICA, 2023. *Patient Reported Outcome Measures (PROMs) Repository.* [Online]
Available at: https://erica-rd.eu/work-packages/patient-centred-research/proms-repository/

ERN Continuous Monitoring Working Group of the ERN Coordinators Group & the Board of Member States, 2019. *Set of ERN core indicators (18) Version V.7.* [Online]
Available at: https://health.ec.europa.eu/system/files/2023-01/erns_evaluation_monitoring_en.pdf

ERN-Eye, n.d. *ERN-Eye ePAG patient advocates.* [Online]
Available at: https://www.ern-eye.eu/ern-eye-epag-patient-advocates/

Euregio Meuse-Rhine Rare Diseases (EMRaDi), 2020. *Report of Work Package 1: Report on the legal and financial situation for rare disease (RD) patients in the Euregio MeuseRhine (EMR).* [Online]
Available at: https://www.emradi.eu/assets/728c7bce-7198-4b6b-ace1-6952aa0e8e3e/emradi-wp1-legal-and-needs-en-final.pdf

Euregio Meuse-Rhine Rare Diseases (EMRaDi), 2020. *Report of WP4: Networking, training and exchanges of expertise of health professionals.* [Online]
Available at: https://www.emradi.eu/assets/af2454b9-ddd5-4659-882f-701d94495c62/emradi-wp4-en-final.pdf

European Brain Council (EBC), 2022. *Bridging Gaps and Achieving Seamless, Coordinated Care: A Joint Value of Treatment Study on Rare Neurological and Neurometabolic Disorders in Europe.* [Online]
Available at: https://www.braincouncil.eu/wp-content/uploads/2022/03/1.-VOT_RNDsReport_2022_Final.pdf

European Commission, 2019. *Commission Implementing Decision 2014/287/EU.* [Online]
Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32019D1269#d1e364-35-1

European Commission, 2019. *Study to support the evaluation of the EU Orphan Regulation.* [Online]
Available at: https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_study_final-report_en_0.pdf

European Commission, 2022. *Horizon Europe Work Programme 2023-2024: Marie Skłodowska-Curie Actions.* [Online]
Available at: https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/wp-call/2023-2024/wp-2-msca-actions_horizon-2023-2024_en.pdf

European Commission, 2022. *Study supporting the evaluation of the Directive 2011/24/EU to ensure patients' rights in the EU in cross-border healthcare.* [Online]
Available at: https://health.ec.europa.eu/system/files/2022-05/crossborder_evaluation-dir201124eu_study_frep_en.pdf

European Commission, 2023. *Funding - Key documents.* [Online]
Available at: https://health.ec.europa.eu/funding/key-documents_en?f%5B0%5D=topic_topic%3A194

European Commission, n.d. *European Reference Networks.* [Online]
Available at: https://health.ec.europa.eu/european-reference-networks_en

European Commission, n.d. *Patient Consent Form for Data Sharing in European Reference Networks for Rare Diseases.* [Online]
Available at: https://cpms.ern-net.eu/cms/media/consent/EN_InformedConsent.pdf

European Health and Digital Executive Agency (HaDEA)., 2019. *Technical Toolbox: overview of Annexes for the Evaluation process.* [Online]
Available at: https://health.ec.europa.eu/system/files/2023-01/erns_evaluation_toolbox_en.pdf

European Reference Network VASCERN, 2023. *Pregnancy: recommendations for care.* [Online]
Available at: https://vascern.eu/groupe/pregnancy-2/recommendations-for-care/

EURORDIS - Rare Diseases Europe, 2020. *How has COVID-19 impacted people with rare diseases?.* [Online]
Available at: https://www.eurordis.org/publications/how-has-covid-19-impacted-people-with-rare-diseases/

EURORDIS, 2009. *Experiences and Expectations of Rare Disease Patients on Diagnosis and Care in Europe.* [Online]
Available at: https://www.eurordis.org/wp-content/uploads/2009/12/EURORDISCARE_FULLBOOKr.pdf

EURORDIS, 2017. *Juggling care and daily life: The balancing act of the rare disease community - A Rare Barometer survey.* [Online]
Available at: https://download2.eurordis.org/rbv/2017_05_09_Social%20survey%20leaflet%20final.pdf

EURORDIS, 2018. *Rare disease patients' participation in research.* [Online]
Available at: https://download2.eurordis.org/rbv/2018_02_12_rdd-research-survey-analysis.pdf

EURORDIS, 2019-2020. *Developing a Patient Satisfaction Questionnaire.* [Online]
Available at: http://download2.eurordis.org.s3.amazonaws.com/epag/ePAG%20Good%20practice_ERN-Skin_FINAL_Patient%20Satisf%20Quest.pdf

EURORDIS, 2019. *Achieving Holistic Person-Centred Care to Leave No One Behind.* [Online]
Available at: https://download2.eurordis.org/positionpapers/Position%20Paper%20Holistic%20Care%20for%20Rare%20Diseases_Final.pdf

EURORDIS, 2021. *Key findings from a survey on patients' and carers' experience of medical care for their rare diseases.* [Online]
Available at: https://download2.eurordis.org/rbv/HCARE/HCARE_FS_long.pdf

EURORDIS, n.d. *EURORDIS Open Academy School on Medicines Research & Development.* [Online]
Available at: https://openacademy.eurordis.org/summer-school/

EURORDIS-Rare Diseases Europe, 2021. *Rare 2030 – the future of rare diseases: A Rare Barometer survey.* [Online]
Available at: https://download2.eurordis.org/rare2030/RARE2030_survey_public_report.pdf

Eurostat, 2023. *Unmet health care needs statistics.* [Online]
Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Unmet_health_care_needs_statistics#Unmet_needs_for_services_related_to_health_care_due_to_financial_reasons

EveryLife Foundation for Rare Diseases, 2023. *The Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study.* [Online]
Available at: https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf

EveryLife Foundation for Rare Diseases, n.d. *Challenges to Diversity in Rare Diseases.* [Online]
Available at: https://everylifefoundation.org/rare-advocates/rare-diversity-hub/disparities-in-public-health/

FDA, 2009. *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.* [Online]
Available at: https://www.fda.gov/media/77832/download

FDA, 2019. *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products Guidance for Industry.* [Online]
Available at: https://www.fda.gov/media/131797/download

FDA, 2022. *Action Plan for Rare Neurodegenerative Diseases including Amyotrophic Lateral Sclerosis.* [Online]
Available at: https://www.fda.gov/media/159372/download

FDA, 2022. *Focus Area: Patient-Reported Outcomes and other Clinical Outcome Assessments.* [Online]
Available at: https://www.fda.gov/science-research/focus-areas-regulatory-science-report/focus-area-patient-reported-outcomes-and-other-clinical-outcome-assessments

FDA, 2023. *Approved Cellular and Gene Therapy Products.* [Online]
Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

FDA, 2023. *FDA's Overview of Catalyst Pharms., Inc. v. Becerra.* [Online]
Available at: https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/fdas-overview-catalyst-pharms-inc-v-becerra

FDA, 2023. *Transcript: Emerging Technology Program.* [Online]
Available at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/transcript-emerging-technology-program

FDA, 2024. *Rare Disease Endpoint Advancement Pilot Program.* [Online]
Available at: https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program#Frequently%20Asked%20Questions

FDA, 2024. *Search Orphan Drug Designations and Approvals.* [Online]
Available at: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm

Federación Española de Enfermedades Raras, 2022. *Últimos avances y próximos retos: FEDER analiza el informe ReeR 2022.* [Online]
Available at: https://www.enfermedades-raras.org/actualidad/noticias/ultimos-avances-y-proximos-retos-feder-analiza-el-informe-reer-2022

Fergusson, D. et al., 2018. The prevalence of patient engagement in published trials: a systematic review. *Research Involvement and Engagement,* 4(17).

Food and Drug Administration (FDA), 2022. *Designating an Orphan Product: Drugs and Biological Products.* [Online]
Available at: https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products

Food and Drug Administration, 2022. *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials: Guidance for Industry.* [Online]
Available at: https://www.fda.gov/media/157635/download

Gahl, W. A. et al., 2021. Essential list of medicinal products for rare diseases: recommendations from the IRDiRC Rare Disease Treatment Access Working Group. *Orphanet Journal of Rare Diseases,* 16(308).

Gemeinsamen Bundesausschusses, 2023. *Richtlinie des Gemeinsamen Bundesausschusses über die Früherkennung von Krankheiten bei Kindern (Kinder-Richtlinie).* [Online]
Available at: https://www.g-ba.de/downloads/62-492-3190/Kinder-RL_2023-05-12_iK-2023-07-13.pdf

Genomics England, 2023. *NHS genomic medicine service data release v2 (28/02/2023).* [Online]
Available at: https://re-docs.genomicsengland.co.uk/current_gms/

German Biobank Node, n.d. *German Biobank Directory.* [Online]
Available at: https://directory.bbmri.de/menu/main/app-molgenis-app-biobank-explorer/biobankexplorer#/catalogue
[Accessed 2024].

German Federal Institute for Drugs and Medical Devices, n.d. *Orphan Medicinal Products.* [Online]
Available at: https://www.bfarm.de/EN/Medicinal-products/Licensing/Medicines-for-rare-diseases/_artikel.html
[Accessed 2023].

German Society for Neonatal Screening (DGNS), 2020. *National Screening Report Germany 2020.* [Online]
Available at: https://www.screening-dgns.de/Pdf/Screeningreports/DGNS-Screeningreport-e_2020.pdf

Gesellschaft für Telematik (gematik), n.d. *How It Works.* [Online]
Available at: https://www.das-e-rezept-fuer-deutschland.de/en/how-it-works
[Accessed 2024].

Ghent University, 2023. *Ghent University pioneers with non-competitive basic funding for professors.* [Online]
Available at: https://www.ugent.be/en/news-events/non-competitive-basic-funding.htm

Global Alliance for Genomics & Health, 2021. *Data Access Committee Guiding Principles and Procedural Standards Policy (v1.0).* [Online]
Available at: https://www.ga4gh.org/document/data-access-committee-guiding-principles-and-procedural-standards-policy-v2/

Halbisen, A. L. & Lu, C. Y., 2023. Trends in Availability of Genetic Tests in the United States, 2012–2022. *Journal of Personalized Medicine,* 13(4), p. 638.

Health Education England: Genomics Education Programme, n.d. *Rare disease education hub.* [Online]
Available at: https://www.genomicseducation.hee.nhs.uk/rare-disease-education-hub/#intro

HealthData@EU Pilot, 2023. *HealthData@EU Pilot identifies common elements for health data access and data use within the legal frameworks of the participating nodes.* [Online]
Available at: https://ehds2pilot.eu/news/healthdataeu-pilot-identifies-common-elements-for-health-data-access-and-data-use-within-the-legal-frameworks-of-the-participating-nodes/

Hedley, V., Rodwell, C. & Simon, F., 2019. *Rare 2030 Knowledge Base Summary on Access to Healthcare for Rare Diseases.* [Online]
Available at: https://www.rare2030.eu/our-work/

Hedley, V., Rodwell, C. & Simon, F., 2019. *Rare 2030 Knowledge Base Summary on Rare Disease Diagnostics.* [Online]
Available at: http://download2.eurordis.org.s3.amazonaws.com/rare2030/Knowledge%20Based%20Summaries/Knowledge%20Base%20Summary%20-%20Rare%20Disease%20Diagnostics%20%281%29.pdf

Horgan, D. et al., 2024. Tackling the implementation gap for the uptake of NGS and advanced molecular diagnostics into healthcare systems. *Heliyon,* 10(1).

Innovative Health Initiative, 2024. *Project factsheets.* [Online]
Available at: https://www.ihi.europa.eu/projects-results/project-factsheets

Institute for Clinical and Economic Review (ICER), 2017. *Assessing the Effectiveness and Value of Drugs for Rare Conditions: A Technical Brief for the ICER Orphan Drug Assessment & Pricing Summit.* [Online]
Available at: https://icer.org/wp-content/uploads/2020/10/ICER_Assessing-the-Value-of-Drugs-for-Rare-Conditions_051017.pdf

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) , n.d. *ICH Guideline Implementation.* [Online]
Available at: https://www.ich.org/page/ich-guideline-implementation
[Accessed 2024].

International Rare Diseases Research Consortium (IRDiRC) , 2022. *RD Metrics.* [Online]
Available at: https://irdirc.org/resources-2/rd-metrics/

IQVIA Institute for Human Data Science, 2020. *Orphan Drugs in the United States: Rare Disease Innovation and Cost Trends Through 2019.* [Online]
Available at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/orphan-drugs-in-the-united-states-rare-disease-innovation-and-cost-trends-through-2019/orphan-drugs-in-the-united-states.pdf

IQVIA Institute for Human Data Science, 2023. *Supporting Patients through Research Collaboration: Interactions between Patient Organizations and Life Sciences Companies.* [Online]
Available at: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/supporting-patients-through-research-collaboration

Jarosławski, S. et al., 2018. Patient-reported outcome claims in European and United States orphan drug approvals. *Journal of Market Access & Health Policy,* 6(1).

Kobau, R. & Zack, M. M., 2021. Knowledge of and familiarity with epilepsy in U.S. adults: Results from the 2017 ConsumerStyles Online Panel Survey. *Epilepsy & Behavior,* 114(A).

Maruszcyk, K. et al., 2022. Implementation of patient-reported outcome measures in real-world evidence studies: Analysis of ClinicalTrials.gov records (1999–2021). *Contemporary Clinical Trials,* Volume 120.

Miller, K. L. & Lanthier, M., 2024. Orphan Drug Label Expansions: Analysis Of Subsequent Rare And Common Indication Approvals. *Health Affairs,* 43(1).

Mueller, T. et al., 2016. Characteristics of patients contacting a center for undiagnosed and rare diseases. *Orphanet Journal of Rare Diseases,* 11(81).

Myrick, K. L., McNeal, M. & DeFrances, C., 2022. QuickStats: Percentage of Office-Based Physicians Using Telemedicine Technology, by Specialty — United States, 2019 and 2021.. *Morbidity and Mortality Weekly Report (MMWR),* 71(49), p. 1565.

National Human Genome Research Institute (NHGRI), 2023. *The Undiagnosed Diseases Program.* [Online]
Available at: https://www.genome.gov/Current-NHGRI-Clinical-Studies/Undiagnosed-Diseases-Program-UDN

National Institute for Health and Care Excellence (NICE), 2023. *Transition from children's to adults' services: Quality standard [QS140].* [Online]
Available at: https://www.nice.org.uk/guidance/qs140/

National Institutes of Health (NIH), 2021. *Bespoke Gene Therapy Consortium.* [Online]
Available at: https://www.nih.gov/research-training/accelerating-medicines-partnership-amp/bespoke-gene-therapy-consortium

National Institutes of Health (NIH), 2023. *Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC).* [Online]
Available at: https://report.nih.gov/funding/categorical-spending#/

National Institutes of Health, n.d. *Genetic and Rare Diseases (GARD) Information Center.* [Online]
Available at: https://rarediseases.info.nih.gov/about
[Accessed 2024].

National Organization for Rare Disorders, Inc. (NORD), 2023. *Congress should protect the intent of the Orphan Drug Act and pass the RARE Act.* [Online]
Available at: https://rarediseases.org/pass-the-rare-act/?pt=post

National Society of Genetic Counselors, 2023. 2023 *Professional Status Survey: Executive Summary.* [Online]
Available at: https://www.nsgc.org/Portals/0/2023%20PSS%20Executive%20Summary.pdf

Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen, 2013. *National Plan of Action for People with Rare Diseases.* [Online]
Available at: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/N/NAMSE/National_Plan_of_Action.pdf

Nguyen, M. T. et al., 2019. Model consent clauses for rare disease research. *BMC Medical Ethics,* 20(55).

NHS England, 2023. *Working in partnership with people and communities: Statutory guidance.* [Online]
Available at: https://www.england.nhs.uk/long-read/working-in-partnership-with-people-and-communities-statutory-guidance/#b1-public-involvement-legal-duties

NHS England, n.d. *Rare disease collaborative networks.* [Online]
Available at: https://www.england.nhs.uk/commissioning/spec-services/highly-spec-services/rare-disease-collaborative-networks/

NORD – National Organization for Rare Disorders, Inc., 2020. *NORD RareInsights® COVID-19 Community Survey Report.* [Online]
Available at: https://rarediseases.org/wp-content/uploads/2022/10/NRD-2061-RareInsights-CV19-Report_v2.pdf

NORD, 2020. *Barriers to Rare Disease Diagnosis, Care, and Treatment in the US: A 30-Year Comparative Analysis.* [Online]
Available at: https://rarediseases.org/wp-content/uploads/2022/10/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf

NORD, 2022. *NORD Statement on Passage of the Inflation Reduction Act.* [Online]
Available at: https://rarediseases.org/nord-statement-on-passage-of-the-inflation-reduction-act/

NORD, 2023. *NORD Rare Disease Centers of Excellence.* [Online]
Available at: https://rarediseases.org/center-of-excellence/

NORD, n.d. *NORD Centers of Excellence.* [Online]
Available at: https://rarediseases.org/rare-disease-centers-of-excellence/
[Accessed 2024].

NORD, n.d. *NORD State Report Card: Newborn Screening.* [Online]
Available at: https://rarediseases.org/policy-issues/newborn-screening/
[Accessed 2024].

NORD, n.d. *Rare Disease Advisory Council – State Map.* [Online]
Available at: https://rarediseases.org/rare-disease-advisory-councils/map/
[Accessed 2024].

Northwestern University, 2023. *PROMIS® (Patient-Reported Outcomes Measurement Info.* [Online]
Available at: https://www.healthmeasures.net/explore-measurement-systems/promis

OECD, 2022. *Federal research and experimentation (R&E) tax credit.* [Online]
Available at: https://stip.oecd.org/innotax/incentives/USA1
[Accessed 2023].

OECD, 2022. *R&D tax credit (Forschungszulage).* [Online]
Available at: https://stip.oecd.org/innotax/incentives/DEU1
[Accessed 2023].

OECD, 2023. *Government budget allocations for R&D.* [Online]
Available at: https://stats.oecd.org/Index.aspx?DataSetCode=GBARD_NABS2007

Office for Life Sciences (OLS) , 2022. *Genome UK: 2022 to 2025 implementation plan for England - Annex A: high-level metrics.* [Online]
Available at: https://www.gov.uk/government/publications/genome-uk-2022-to-2025-implementation-plan-for-england/annex-a-high-level-metrics

Office of Management and Budget, 2020. *Federal Data Strategy.* [Online]
Available at: https://strategy.data.gov/overview/

Office of the Assistant Secretary for Planning and Evaluation (ASPE), n.d. *Health Data Standards Principles.* [Online]
Available at: https://aspe.hhs.gov/health-data-standards-principles
[Accessed 2024].

Office of the Assistant Secretary for Planning and Evaluation, n.d. *Making Electronic Health Record (EHR) Data More Available for Research and Public Health.* [Online]
Available at: https://aspe.hhs.gov/making-electronic-health-record-ehr-data-more-available-research-public-health
[Accessed 2023].

Office of the National Coordinator for Health Information Technology (ONC), n.d. *Health IT Legislation.* [Online]
Available at: https://www.healthit.gov/topic/laws-regulation-and-policy/health-it-legislation
[Accessed 2024].

Oregon Health & Science University, n.d. *Rare Disorders Research Consortium.* [Online]
Available at: https://www.ohsu.edu/human-genetics-initiative/research-consortium

Orphanet Urgences, 2018. *« Bonnes pratiques en cas d'urgence » Myasthénie autoimmune.* [Online]
Available at: https://www.orpha.net/data/patho/Emg/Int/fr/Myasthenieautoimmune_FR_fr_EMG_ORPHA589.pdf

Orphanet, 2020. *COVID-19 and Rare Diseases.* [Online]
Available at: https://international.orphanews.org/newsletter-en/editorial/nl/id-200327.html#oa_orphanet-is-collecting-expert-recommendations-and-services-concerning-covid-19-and-rare-diseases

Patel, D. et al., 2023. Equality, diversity, and inclusion in oncology clinical trials: an audit of essential documents and data collection against INCLUDE under-served groups in a UK academic trial setting. *BMC Medical Ethics,* 24(105).

Patterson, A. M., O'Boyle, M., VanNoy, G. E. & Dies, A. K., 2023. Emerging roles and opportunities for rare disease patient advocacy groups. *Therapeutic Advances in Rare Disease,* Volume 4.

Pavan, S. et al., 2017. Clinical Practice Guidelines for Rare Diseases: The Orphanet Database. *PLoS ONE,* 12(1).

Pieroni, F. et al., 2023. The Tuscany Regional Network for rare diseases: from European Reference Networks' experience to registry based organisation and management model for rare diseases. *Orphanet Journal of Rare Diseases,* 18(324).

Prader-Willi Syndrome Association USA, n.d. *Save the Orphan Drug Tax Credit!.* [Online]
Available at: https://p2a.co/DdkLL6r
[Accessed 2024].

Rady Children's Institute: Genomic Medicine, 2023. *Payer Policy and Advocacy.* [Online]
Available at: https://radygenomics.org/clinical-genome-services/payer-policy-advocacy/

Rare Diseases International, n.d. *Rare Diseases International.* [Online]
Available at: https://www.rarediseasesinternational.org

RARE-X, 2022. *Strategic Directions and Recommendations: Diversity, Equity, and Inclusion Scoping Review.* [Online]
Available at: https://rare-x.org/wp-content/uploads/2022/02/dei-020722.pdf

Rees, C. A., Pica, N., Monuteaux, C. M. & Bourgeois, T. F., 2019. Noncompletion and nonpublication of trials studying rare diseases: A cross-sectional analysis. *PLOS Medicine,* 16(11).

Reillon, V., 2017. *European Parliament Members' Research Service Briefing: Public-private partnerships in research.* [Online]
Available at: https://www.europarl.europa.eu/RegData/etudes/BRIE/2017/603934/EPRS_BRI%282017%29603934_EN.pdf

Reimer, A., Bruckner-Tuderman, L. & Ott, H., 2018. Mapping health care of rare diseases: the example of epidermolysis bullosa in Germany. *Orphanet Journal of Rare Diseases,* 13(197).

Research For Rare, n.d. *Zentren für seltene Erkrankungen.* [Online]
Available at: https://www.research4rare.de/zentren-fuer-seltene-erkrankungen/
[Accessed 2024].

Schmidt, T. et al., 2020. Die aktuelle Versorgungssituation von Patientinnen und Patienten mit seltenen Knochenerkrankungen an Universitätskliniken in Deutschland. *Osteologie,* 29(04), pp. 266-274.

Sciensano, n.d. *Central Registry of Rare Diseases.* [Online]
Available at: https://rarediseases.sciensano.be/en/registry

SE-Atlas, 2023. *Deutsche Referenznetzwerke.* [Online]
Available at: https://www.se-atlas.de/drn?ln=de_DE

Social Security Administration, 2023. *Compassionate Allowances.* [Online]
Available at: https://www.ssa.gov/compassionateallowances/

Soussand, L. et al., 2022. Impact of the COVID-19 pandemic on the care of rare and undiagnosed diseases patients in France: a longitudinal population-based study. *Orphanet Journal of Rare Diseases,* 17(430).

Speckmann, C. et al., 2023. Prospective Newborn Screening for SCID in Germany: A First Analysis by the Pediatric Immunology Working Group (API). *Journal of Clinical Immunology,* Volume 43, pp. 965-978.

Stabsstelle Patientenbeteiligung des G-BA, n.d. *Patientenvertreterinnen und Patientenvertreter beim G-BA.* [Online]
Available at: https://patientenvertretung.g-ba.de/wer-wir-sind/patientenvertreterinnen-und-patientenvertreter-beim-g-ba/
[Accessed 2024].

Surescripts Network Alliance, 2022. *2022 National Progress Report.* [Online]
Available at: https://surescripts.widen.net/s/mvtqvvf5sd/2022-national-progress-report

Taruscio, D. et al., 2014. The Current Situation and Needs of Rare Disease Registries in Europe. *Public Health Genomics,* 16(6), pp. 288-298.

Toledano-Alhadef, H. et al., 2020. Role, function and challenges of multidisciplinary centres for rare diseases exemplified for neurofibromatosis type 1 syndrome. *Child's Nervous System,* Volume 36, pp. 2279-2284.

Triebold, M. et al., 2021. Geographical analysis of the distribution of certified genetic counselors in the United States. *Journal of Genetic Counselling,* 30(2), pp. 448-456.

United States Government Accountability Office, 2018. *ORPHAN DRUGS: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue,* s.l.: United States Government Accountability Office.

Universitätsklinikum Gießen – Marburg, 2022. *Zentrum für unerkannte Krankheiten.* [Online]
Available at: https://www.ukgm.de/ugm_2/deu/umr_zuk/27241.html

Ward, A. J. et al., 2023. Genetic services survey—experience of people with rare diseases and their families accessing genetic services in the Irish Republic. *Journal of Community Genetics,* Volume 14, p. 583–592.

Wiendl, H. & Meisel, A., 2022. Diagnostik und Therapie myasthener Syndrome, S2k-Leitlinie. *Deutsche Gesellschaft für Neurologie (Hrsg.), Leitlinien für Diagnostik und Therapie in der Neurologie*, p. www.dgn.org/leitlinien.

Yang, G. et al., 2022. The national economic burden of rare disease in the United States in 2019. *Orphanet Journal of Rare Diseases,* 17(163).

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

Zhang, H. et al., 2022. Increased COVID-19 mortality rate in rare disease patients: a retrospective cohort study in participants of the Genomics England 100,000 Genomes project. *Orphanet Journal of Rare Diseases,* 17(166).

Glossary

TERM	DEFINITION
Access funds	Public funding that supports people to access healthcare
Additional benefit	A medicine is shown to have an advantage over others in the same class, which is beneficial for patients
Advanced Therapeutic Medicinal Products (ATMPs)	Cell, tissue, and gene therapies
Age of diagnosis	The age at which the person is diagnosed
Age of onset	The age when a disease begins
Alpha-ID	A German system of coding medical diagnoses, which has a coding set for rare diseases (Alpha-ID-SE)
Biobank	A storage space for biological samples held for research purposes
Building blocks	Overarching pillars of a health system fit for rare diseases
Centre of Excellence	A medical institution or group of medical institutions which can treat a wide range of rare diseases in children and adults, with staff from all relevant medical specialties, and which carries out rare disease research
Clinical academic	A healthcare professional who also works in academic research, with roles at both kinds of institution
Clinical outcome assessments	A measure assessing patient symptoms, feelings, function, or survival, often used in clinical trials
Clinical Patient Management System	The European Reference Networks' system for sharing patient data between clinicians
Clinical trial endpoints	The variable being measured in a clinical trial e.g. five-year survival
Cohesion funds	Public funding destined to reduce geographic inequalities
Comparative Effectiveness Research	Research that compares two treatments/strategies etc. in terms of their benefits and harms
Comparator	The product used as the baseline for comparing it to a new product
Continuing Medical Education (CME)	Ongoing courses to help healthcare professionals keep up to date
Cost-effectiveness	A comparison between how much a product costs and the health impact that product has
Cross-border care	Travelling to a different country to receive healthcare
Data access committee (DAC)	A group set up to assess requests to use the health data its organization holds
Diagnostic odyssey	The lengthy, difficult journey to obtaining a diagnosis.
Disaggregated data	Data that has been broken down into sub-categories e.g. disease prevalence in men and women
Dried blood spot (DBS) samples	Cards containing blood samples from a pinprick, which can be used for rare disease screening
E-prescriptions	Electronic prescriptions – the digital version of a printed script for medicine
Electronic health records (EHRs)	A digital version of a patient's health records
EU Orphan Regulation	Regulation (EC) No 141/2000, which sets out rules and incentives for developing orphan medicines
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)	The European trade association for small and medium enterprises in the pharmaceutical and biotech industries
European Medicines Agency	The EU-level regulator assessing applications for market authorisation of medicines and medical devices
European Reference Networks (ERNs)	Virtual networks connecting doctors and researchers to share rare disease expertise and assess patient cases
EURORDIS – Rare Diseases Europe	The European-level patient advocacy organization on rare diseases
FAIR principles	International guidelines on making data Findable, Accessible, Interoperable and Reusable to support research

Genetic counselling	Working with a genetics specialist to understand your rare disease and receive support in doing so
Genomic medicine	Using genetic information as part of someone's treatment
Genomics	The study of genetic material
Good practices	Real-world actions that successfully support outcomes
Health Technology Assessment (HTA)	The process in which a country decides whether and how much it is willing to pay for a health technology
Healthcare Professionals (HCPs)	People who work in the medical field and provide health services/ treatments
HIMSS Electronic Medical Record Adoption Model (EMRAM)	A method of measuring progress towards implementing digital records in hospitals
Incremental cost-effectiveness ratio (ICER)	A statistic used to measure cost-effectiveness vs a competitor, which records the extra cost paid per extra unit of health effect and can be used to compare products based on price-per-improvement
Interdisciplinary	Including other specialties in the project work
International Classification of Diseases 10th edition (ICD-10)	A global coding system for diseases and health conditions
International Organization for Standardization (ISO) accreditation	When a third party examines an organization to certify it is compliant with internationally recognized standards for a particular task
International Rare Diseases Research Consortium (IRDiRC)	A network of governmental, non-profit, private sector, and patient advocacy organisations, alongside scientific researchers, which works to boost rare diseases research worldwide.
Interoperability	The capacity of digital systems to connect to and 'talk' with each other
Marketing authorisation	The process of obtaining permission to sell a medicine
Measures	Data points used to assess outcomes
Medicaid drug utilization review (DUR)	A requirement for US states to continually assess the use of medicines in practice
Metadata catalogue	Metadata describes other pieces of data, and a metadata catalogue collates all the ways data is described to facilitate locating particular kinds of information
Multi-stakeholder	Bringing many actors interested in a topic together to work on it
Multidisciplinary	Involving several disciplines/specialties
National Organization for Rare Disorders (NORD)	A USA-based non-profit representing people living with rare diseases and their families.
Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen (NAMSE)	Germany's network of government organisations and rare disease patient advocates, responsible for the national rare disease action plan
Natural history (of disease)	The course of a disease in practice, from start to finish, in the absence of treatment/care
Newborn screening (NBS)	The process of testing children at birth for a series of diseases, some of which are rare, usually conducted as a pinprick blood test – but which could also include genetic screening
Non-competitive research	Research funded through block grants without having to make competitive applications
Orphacodes	A method of classifying rare diseases with unique codes to be used in health and research information systems
Orphan devices	Medical devices used to treat rare conditions
Orphan Medicinal Products (OMPs)	Medicines that diagnose/prevent/treat life-threatening/very serious conditions which affect no more than 5/10,000 people
Orphanet	An online portal collating resources and information on rare diseases
Out-of-pocket costs	Direct payments, made for health services, which are not covered/ reimbursed by the national health system
Outcomes	Descriptions of what a health system fit for rare diseases can deliver to patients

Patient advocacy groups (PAGs)	Organisations that campaign for and raise awareness of the needs of people with their disease
Patient Journeys	Pathways mapped out by patients setting out the stages of a disease and the different experiences and needs they may have at each stage
Patient navigators	Professionals who assist patients in navigating the health system to get the most benefit from it
Patient reported outcomes (PROs)	Self-reported information from patients about their health status
Patient-centred outcomes research (PCOR)	Research that assesses healthcare products and interventions with reference to questions and outcomes highlighted by those affected by the condition in question
Patient-meaningful endpoints	A variable that matters to patients being measured in a clinical trial
Patient-meaningful outcomes	Clinical trial outcomes that matter to patients (regardless of who reports the outcomes)
Patient-Reported Experience Measures (PREMs)	Ways of recording how patients experience their engagement with the health system
Patient-Reported Outcome Measures (PROMs)	Ways of measuring patients' self-reported health status e.g. questionnaires
Payers	Organisations that pay for healthcare services
Pharmacy and Therapeutics (P&T) committee	A committee of healthcare professionals and administrative staff which makes recommendations to its organization about procurement and use of medications
Precompetitive research	Research conducted by multiple companies cooperating to make discoveries that no one company could do by itself, which can then be used to develop products in competitive research
Prevalence	The number of people who have a disease in the population at a particular time
Pricing and reimbursement	The processes of determining whether a product is available in a particular health system, and of establishing its price
Public-private partnerships (PPPs)	Agreements between government and private sector organisations to conduct a particular task/project together
Quality-adjusted Life Years (QALYs)	A statistic which measures the extra years of life gained from a treatment, as well as the quality of life experienced in those years
Rare 2030	An EU-funded study into future policy scenarios for rare disease and options for action
Rare disease plan	A government strategy setting out planned actions and goals for rare disease policy
Real-world data	Data collected about the way the treatment works in practice e.g. patient outcomes, diagnosis, treatments, test results
Registry	Databases collating, for one or more rare diseases, health data on people living with one of the diseases they focus on.
Regulatory exclusivity	The period of time for which a product is protected from generic alternatives competing with it
Regulatory fees	The money that developers must pay regulatory bodies for their services
Research and development expenditure	The amount of money that public and private actors spend on research and producing new products/processes/etc.
Secondary use	The use of health data for purposes other than that which it was first collected for
Sick funds	Health insurer
Surrogate endpoints	A marker which does not directly measure the targeted variable in a clinical trial, but which can be used to substitute for it where it is impractical to measure
Syndromes Without a Name (SWAN)	A patient organization for people living with extremely rare, unnamed diseases.
Telegenetics	Genetic counselling via telephone or online
Telemedicine	Appointments with a medical professional conducted over the telephone or online
Unmet (medical) needs	A situation in which existing services/treatments/products etc. are not capable of fully addressing an issue faced by patients
Whole Genome Sequencing (WGS)	A method of sequencing someone's entire genome, for medical testing purposes – usually used in rare diseases and cancer
World Health Organisation (WHO)	A United Nations agency responsible for health policy and health promotion worldwide.