ADVANCING GENE & CELL THERAPIES BEYOND THEIR AFFORDABILITY

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ITINERARE - Innovative Therapies for Rare Diseases Symposium

University Children's Hospital, Zürich, 12 November 2021

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EURORDIS - Rare Diseases Europe

962

member patient organisations

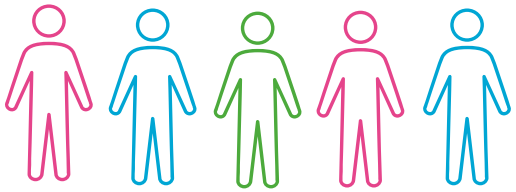
73 countries (27 EU countries)

53 National Alliances of RD Patient Organisations

79 European Federations of specific rare diseases

Founded in

1997



40+

Staff members, with offices in Paris, Brussels, Barcelona

Outreach to over

1800

patient groups

Over **+80** patient advocates

440

Volunteers

+250 moderators

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EURO RARE DISE

Investing in Health System to speed up adaption of new ATMPs

Part 1

Introduction

Advanced Therapy Medicinal Products (ATMPs) are transformative, life changing and potentially curative treatments

(18) ATMPs

13 designated as an orphan medicine product[2]

5 ATMPs withdrawals

New ATMPs

5-10 Per year

forecasted to secure market approval in the next 10 years

increase in the R&D pipeline[1]

+32%

since 2014

>1000

clinical trials globally[1] in 2019

- Ability of healthcare systems' preparedness and centres' readiness to adapt new ATMPs
- Investment in academia and manufacturing and not in healthcare systems ability to adapt.
- Affordability, pricing, and reimbursement has overshadowed debate

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[1]Reference: ARM Clinical Trials in Europe Report, 2019

"Globally, however, this is significantly higher with over 60 ATMPs approved for clinical use, specifically 34 cell therapies, 20 tissue-engineered products and 14 gene therapies (Chakravarthy R. et al., 2016; Ramezankhani R et al., 2020).

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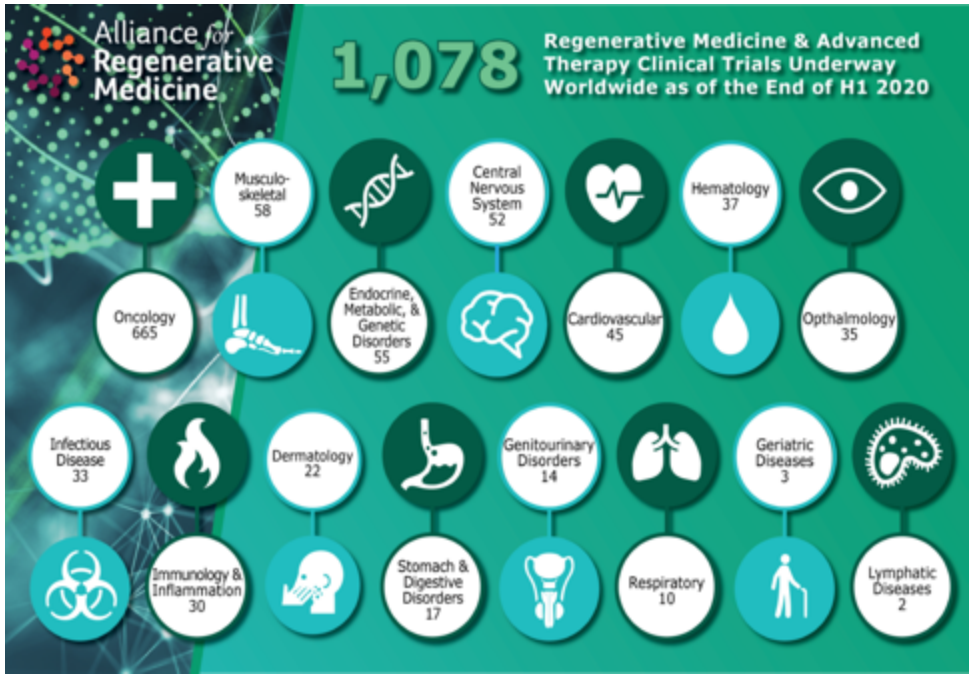
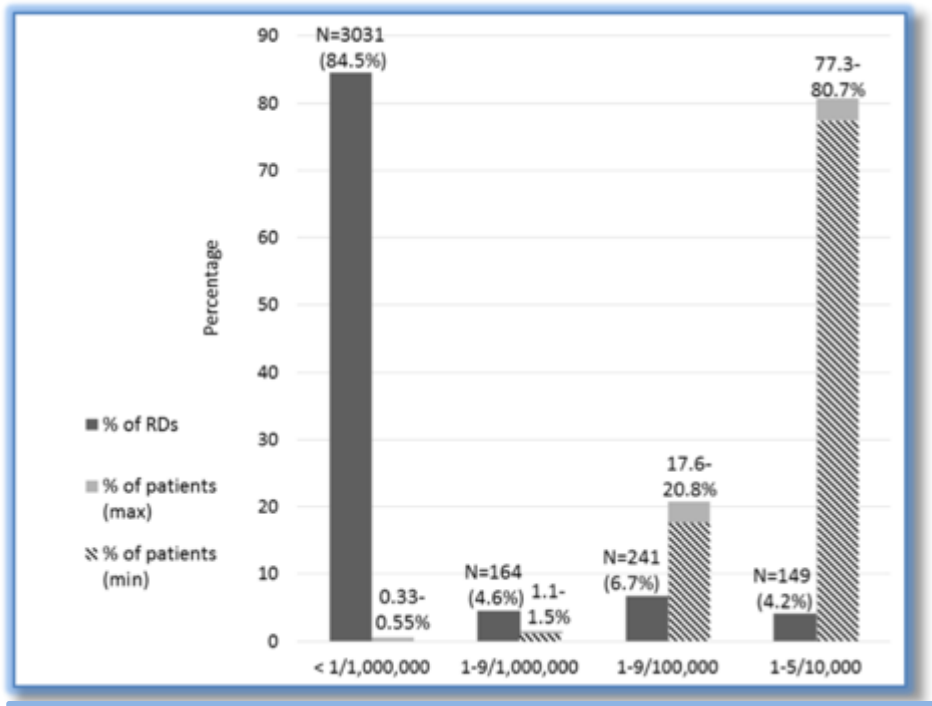
Around 270 Advanced Therapies Clinical Trials ongoing in Europe (source: ARM)



Of gene therapies up for approval over the next five years, 45% are anticipated to focus on cancer treatments and 38% are expected to treat rare inherited genetic disorders (*source: ASGCT*)

Estimating rare diseases patients' numbers

- Best minimum estimation* of the global prevalence for rare diseases:
  - 3.5-5.9% of the population (263-446 Million people) worldwide



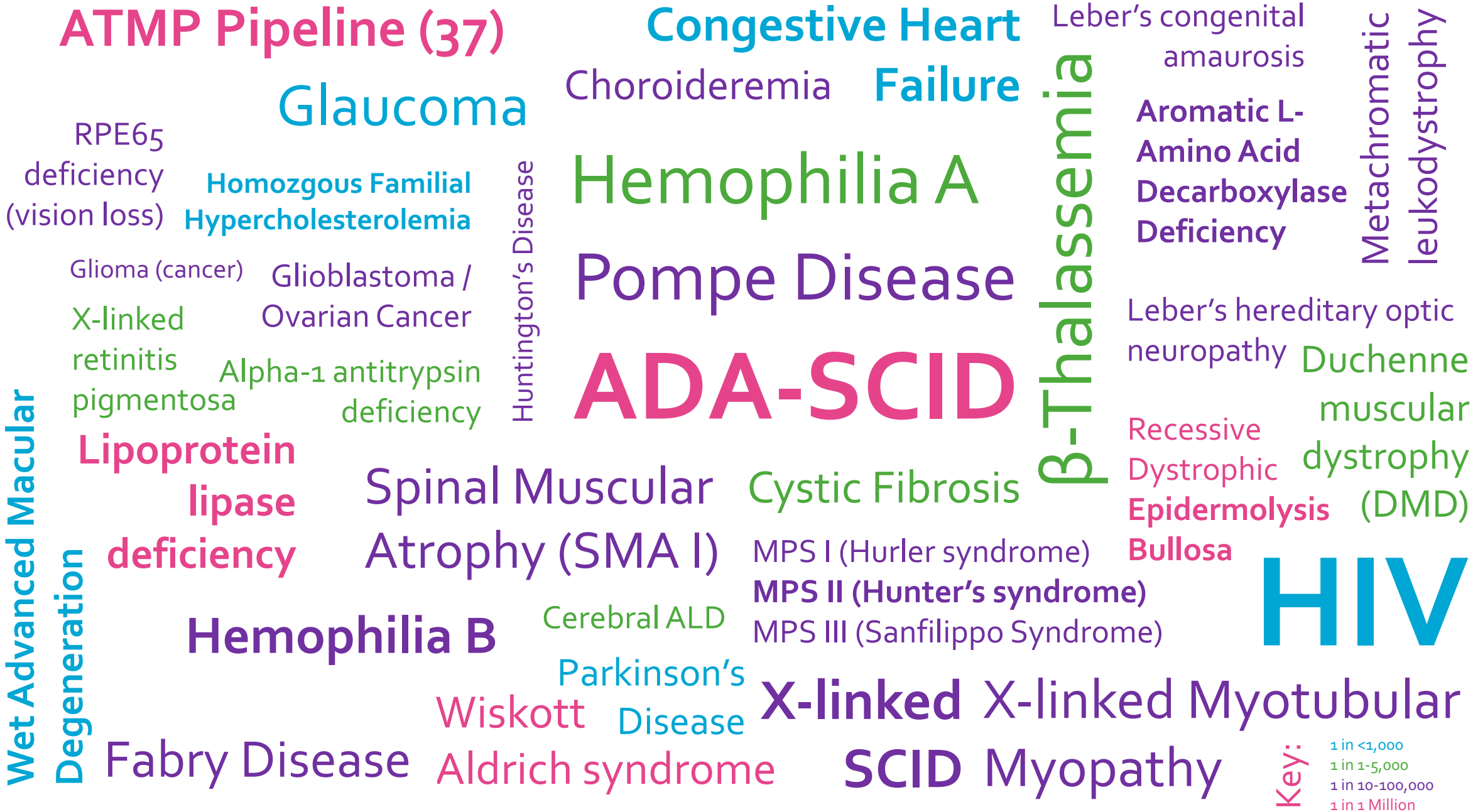
>98% of the people
have one of the 390 most prevalent diseases
(1-9/100,000 and 1-5/10,000).

Country / Continent	RD Prevalence definition per 100,000	<1 /1,000,000	1-9 / 1,000,000	1-9/ 100,000	1-5 / 10,000
Korea [10]	5	✓	✓	+/-	-
Australia [11]	10	✓	✓	✓	-
Taiwan [12]	10	✓	✓	✓	-
Japan [13]	40	✓	✓	✓	✓
EU [4]	50	✓	✓	✓	✓
China [14]	76	✓	✓	✓	✓
USA [9]	80	✓	✓	✓	✓

Different RD definitions:

- Cover a largely overlapping list of diseases
- Cover a very different RD patient population

*Based on 68% of prevalent RD based on EU definition (<50/100,000), data from literature.
Estimating global point prevalence of rare diseases: analysis of the Orphanet database. BMC Public Health, submitted


ATMP Pipeline (37)
Glaucoma
Congestive Heart Failure
Choroideremia
Leber's congenital amaurosis
Aromatic L-Amino Acid Decarboxylase Deficiency
Metachromatic leukodystrophy
RPE65 deficiency (vision loss)
Homozgous Familial Hypercholesterolemia
Huntington's Disease
Hemophilia A
Pompe Disease
β-Thalassemia
Glioma (cancer)
Glioblastoma / Ovarian Cancer
X-linked retinitis pigmentosa
Alpha-1 antitrypsin deficiency
ADA-SCID
Leber's hereditary optic neuropathy
Duchenne muscular dystrophy (DMD)
Lipoprotein lipase deficiency
Spinal Muscular Atrophy (SMA I)
Cystic Fibrosis
Recessive Dystrophic Epidermolysis Bullosa
Wet Advanced Macular Degeneration
MPS I (Hurler syndrome)
MPS II (Hunter's syndrome)
MPS III (Sanfilippo Syndrome)
HIV
Hemophilia B
Cerebral ALD
Parkinson's
Wiskott Aldrich syndrome
Disease
X-linked Myopathy
X-linked Myotubular
Fabry Disease
SCID
Key::
1 in <1,000
1 in 1-5,000
1 in 10-100,000
1 in 1 Million

Overall Challenges for Therapies in Rare Diseases

The problem is simple but the solutions are complex:

- ATMPs bring hope and opportunity to people living with a rare disease
- Scientific advances are not being translated rapidly enough
- Evidence to demonstrate that a single treatment is incomplete when assessing value.
- Evidence gaps translate to uncertainty for decision-makers, making the path to patient access inefficient and unpredictable.
- Growing number of ATMPs (approval and pipeline), but majority have delayed or no access to the medicine they need.
- Availability of innovative, life-saving orphan medicinal products and advanced therapies are threatened by cost consideration

If a therapy is approved but does not reach those who need it, it is a failure of its primary purpose. We need to close the gap between innovation and access.

Uncertain & Immature Access Pathway

Assessment

- **HTA bodies struggle to interpret the evidence of clinical benefit associated with gene and cell therapies**
- Lack of real-world data on long term efficacy
- ATMPs are only approved and available in a limited number of Member States.

Availability

- **Fragmentation of the European market leads to great inequalities across and within Member States**
- Advanced engineering process requiring coordination across complex supply-chain.
- Investment in manufacturing and academia, but not in infrastructure or frontline services to support adaption




Increased health inequality & lack of availability

Affordability

- **Concern about the idea of large one-off payments; deferred payment or payment for outcomes**
- Uncertainty of Price & Reimbursement
- Significant delay in HTA approval and real risk of market withdrawal

Access

- **Limited number of Treatment Centres**
- **Lack of agreement on centralization of care**
- Existing legislation does not support access and lack of understanding of ATMP & RD by NCP
- Lack of transparency of MS decision-making process for approval
- Hospitals face significant pressure in developing new ATMP services; reimbursement doesn't cover service costs

ATMPs have been developed in a strategy and policy vacuum, with no dialogue for mutual learning.

Patient Community Action

To date, patients' access to these advanced therapies has been hampered by both practical and technical challenges, such as:

- The administrative and logistical challenges healthcare systems face in catering for advanced therapies.

- Satisfying national Health Technology Assessment (HTA) data requirements, particularly when comparative and long-term efficacy data are difficult to generate due to the nature of the diseases these therapies aim to treat.

- The requirement to adjust traditional funding models due to the once-off treatment potential of many gene and cell therapies.

EURORDIS has initiated a patient-focused collaboration to stimulate multi-stakeholder discussions in order to improve patients' access to these therapies

- RARE IMPACT -

RARE IMPACT is a consortium of manufacturers of gene and cell therapies and umbrella organizations

Who are we?

EURORDIS RARE DISEASES EUROPE + DOLON

Manufacturers:

BIOMARIN
NOVARTIS
Takeda
VERTEX
ultragenyx pharmaceutical
Sangamo THERAPEUTICS
Pfizer
Spark THERAPEUTICS
SAREPTA THERAPEUTICS
Chiesi People and ideas for innovation in healthcare
SANOFI
Celgene
GILEAD Creating Possible
REGENXBIO
bluebirdbio
AUDENTES THERAPEUTICS
PTC THERAPEUTICS
Orchard therapeutics

Non-profit organisations:

FONDAZIONE GENETHON CURE THROUGH INNOVATION
Telethon
AFMTÉLÉTHON INNOVER POUR GUÉRIR

Trade associations:

efpia European Federation of Pharmaceutical Industries and Associations
Alliance for Regenerative Medicine
EUCOPE European Confederation of Pharmaceutical Entrepreneurs AISBL

RARE IMPACT.

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Rare Impact

The RARE IMPACT initiative aims to identify and validate the challenges to patients' access to gene and cell therapies through multi-stakeholder engagement incl. HTA agencies, regulatory bodies, payers, patient groups, clinicians, manufacturers and other experts across Europe.

Phase I

- Definition of the challenges to patient access to the advanced therapies "4 As" (assessment, affordability, availability and accessibility)

- Stimulate multi-stakeholder discussion to ensure patients obtain better access to the gene and cell for rare diseases in Europe
- Deliverables: x10 Country Reports & EU Report - proposing actionable solutions to address these challenges

Phase II

Further gather information and propose solutions to improve patients' access to gene and cell therapies, under 3 core activities:

- Price and the economics of ATMPs: Enabling a stakeholder dialogue in support of patient access and innovation (WS 1).
- Evidence generation for ATMPs: Building consensus among stakeholders to accelerate patient access (WS 2).
- Processes and criteria of selection of Centres of Expertise for ATMPs (WS 3).

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Rare Impact website: https://rareimpact.eu/why-rare-impact

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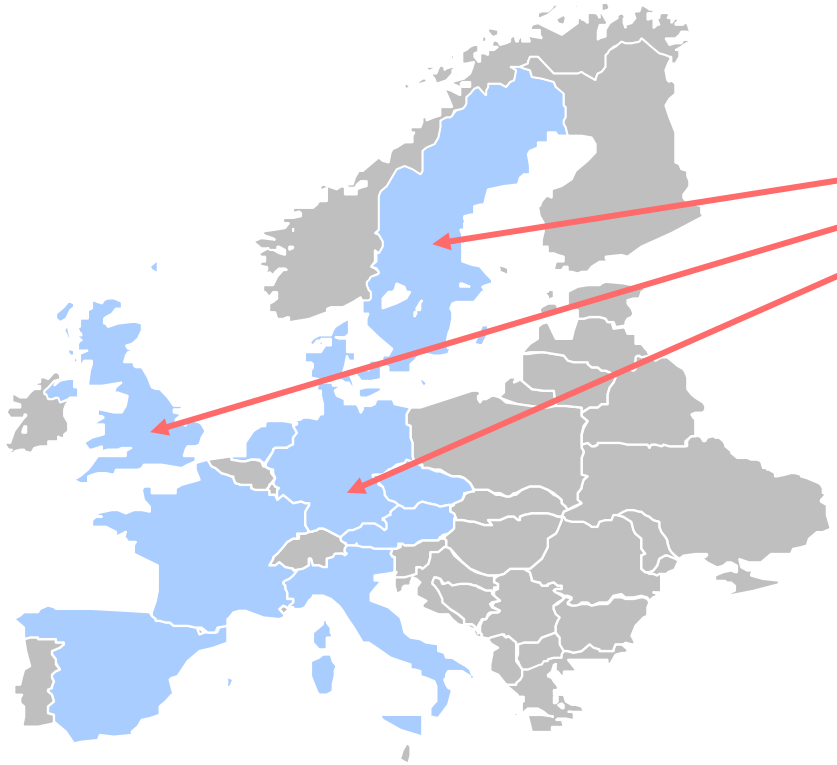
Country level reports have required the focus to be on country-level engagement across 10 countries

What have we done?



1. Report development:

- Direct calls with country-level patient associations, payers, policymakers and academics (>35 interactions)

2. Report sharing:

- Calls and meetings with country-level patient associations
- Multi-stakeholder in-country meetings
- Website

Geographic scope

European level report: challenges and solutions proposed

Assessment

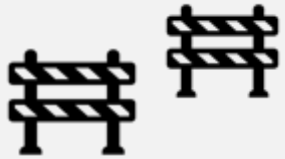
Regulators

HTA agencies

1. *There is a gap between regulators and HTA bodies in evidence criteria*
2. *Registry-type data required for post-approval regulatory requirements differs from that required by payers for managed entry agreements or other innovative payment models*

Solutions:
1. EMA, in collaboration with HTAs, HMAs **issue guidance on ATMP assessment** with focus on **methodological uncertainty** (incl. long-term evidence generation, use of pan-European natural history datasets) building on existing initiatives to form a framework for assessment at the country level.
2. Collaboration between the stakeholders on **registries** (real world evidence).

Affordability

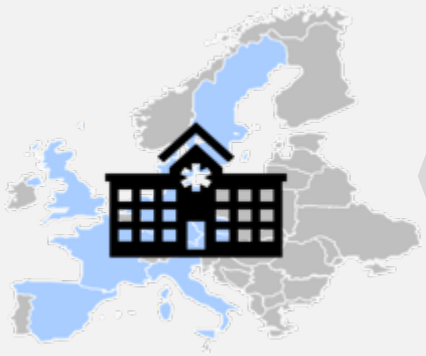


1. *There are concerns about the sustainability of prices and poor understanding on the role of price.*
2. *There are barriers to annuity payments and innovative funding options across Member States.*

Solutions:
1. **Education** of stakeholders on the ATMP development cycle, costs and incentives.
2. Collaboration with stakeholders at the national level to remove barriers to annuity and innovative payment models

European level report: challenges and solutions proposed

Availability



1. *Variability in the use of cross-border healthcare legal provisions (Form S2) across Member States and the sustainability of this pathway is uncertain*
2. *Hospital exemption legislation interpretation can vary across Member States which impacts patient access to available treatments*

Solutions:

1. Coordinate and issue **formal guidance on cross-border pathways** at the European level to facilitate access to different ATMPs
2. **Seek clarification from EC on the appropriate use of the hospital exemption** in the ATMP Regulation and introduce oversight by the EMA Pharmacovigilance Risk Assessment Committee

Accessibility

Clinical expertise, ICU and other resource requirements and the short shelf life of ATMPs require patients to be treated in specialist centres that require manufacturer, and increasingly, country-level certification

Solution: Assess and educate around the existing system in place for treatment centre qualification. Encourage stakeholder dialogue to explore options to **reduce administrative burden** and **ensure consistency across Member States.**

Rare Impact: Call for EU Action

Legalisation & Access

- Improve legal pathways to access care abroad either a 3rd route or one entry point
- Increased transparency of MS decision-making process
- Adapt an EU policy for centralization of cases as associated treatments
- Enlarge the role of ERNs to validate referral eligibility

Price & Reimbursement

- European innovation fund linked to joint-EU HTA assessment, to fund the therapy, clinical services
- Implement 'managed access pathways' to collect real-world data across EU Member States, in order to reduce clinical uncertainties.
- Price isn't a stumbling block (as inline with existing treatments e.g.: ERT); Upfront costs challenging with high uncertainty of sustained clinical benefit

Health Systems

- Member States to adopt a common model for qualification incl. minimum expertise threshold & patients involvement.
- Greater collaboration between EU MS on establish European ATMP Treatment Centres with designated hubs for eastern countries
- Investment into centre and drive standardisation
- Hub and spoke model to administer an ATMP & FU

Hospital Service

- Reimbursement of an advanced care model is urgently needed.
- Patient care coordinator to support navigate system, legal requirements, travel logistics and living
- Qualified Treatment Centers should take part in a learning system
- Research to demonstrate the value and impact of the clinical experience on treatment outcome.

Strategic Investment to Speed Up Adoption

Current Situation

- Complex therapies requires highly specialised clinical competences, complex logistic, training and qualification of a few expert centres
- ATMPs are only approved and available in a limited number of Member States
- Lack of transparency of quality and safety of treatment centre and standards for qualification
- Qualification is a 'shared competency'
- Quantifying the 'experience' is subjective and not objective
- Invest in frontline services to support adaption and development of common product standards for ATMPs
- Coordination across complex supply-chain
- Reimbursement tariffs does not cover healthcare
- Clinical experience impact on the outcome of treatment

Best Practice Approach

- Establish European ATMP Treatment Centres and centralization of treatment for small patient populations
- EU Hub + Spoke model to administer an ATMP & Follow Up (inc. real-world data collection)
- Member States to adopt a common model for qualification incl. minimum case threshold (incl. in EMA scientific advice)
- Pilot joint qualification of ATMP Treatment Centres
- Patients involved in design of standards and decision.
- Investment into NHS infrastructure to adopt ATMP and greater standardisation (FAST, Catapult)
- Patient care coordinator to support the holistic needs of the family
- Reimbursement of care is urgently needed
- Continue support and training to qualified ATMP Centres and participation in a learning system / network

Connecting Treatment Centres under Networks

Part 2

"RD Gaining Momentum as a Key UN Policy Area"

H. E. Toshiya Hoshino - Ambassador and Permanent Representative of Japan to the UN, March 2021

"No country can claim to have achieved universal healthcare if it has not adequately and equitably met the needs of those with rare diseases"

Helen Clark, United Nations Development Program (2016)

"WHO's top priority is to support countries on the path towards universal health coverage, with the aim of ensuring that all people can access the health services they need. […] **This includes access to diagnosis and treatment for people who suffer from rare diseases**."

Dr Tedros Adhanom Ghebreyesus, WHO Director General (2018)

"Vision set out in the agenda (proposed UN Resolution for RD) is a **world free of fear and violence, of universal literacy, of equitable and universal access** to quality education, health care and social protection […] is a **beacon of hope for people with rare diseases**."

Ms. Leslie Wade – Chief, Intergovernmental Support and Coordination for Sustainable Development, DESA (2021)

"we must work together to ensure an **equitable and affordable access to quality health services and medicines for everyone** especially […] **people living with rare diseases** among others while ensuring that they **do not face financial hardship or fall back into poverty.**"

H. E. Vitavas Srivihok – Ambassador and Permanent Representative of Thailand to the UN (2021)

Why a UN Resolution at the UN General Assembly in New York?

The **impact** of going through life with a rare disease goes far **beyond only health concerns, and affects the whole family.**

Persons living with a rare disease and their families experience **stigma, discrimination, and lack of visibility and recognition in society.**

Targeted adoption of Resolution by the UNGA (December 2021)

Core Group

Brazil

Qatar

Spain

France

Early Co-Sponsors

Italy

Portugal

Central African Republic

Equatorial Guinea

Our Vision 4 Collaborative Global Network

People living with a rare disease no matter where they live can reach a network of expertise to access appropriate diagnosis, care and treatment

SDG Agenda 2030

UHC Implementation

Cover **2 billion people** with hubs in major cities ➔ **85 million people living with a rare disease**

- **Break down barriers accessing care**:
  - open and direct self referral to RD Hubs
  - healthcare pathways

- **Strengthen healthcare systems**
- **Expedite and provide accurate diagnosis**:
  - reduce misdiagnosis
  - diagnosis in < 1 year after 1st contact with a doctor

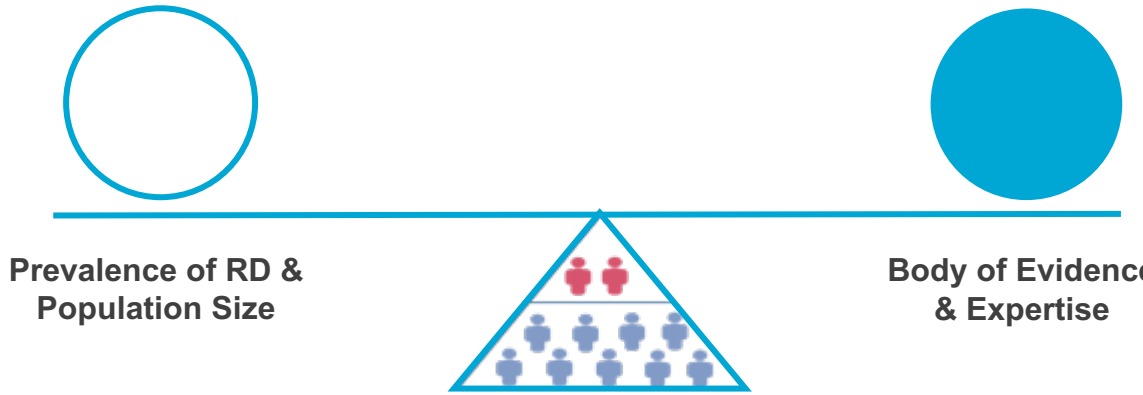
Evolution in Healthcare 4 RD

Prevalence of RD & Population Size

- >98% population of PLWRD are affected by 390 rare diseases (>1 per 100,000),
- 2% population are affected by one of >6000 rarer condition (<1 per 100,00)
- Globally, 15 most populated countries have >65% of the global population; 73/ Countries have a population less than 5M

Body of Evidence & Expertise

- Relationship between caseload volume and prof experience with health outcomes
- Care have evolved from an MDT to Networked Care
- Virtual care allows the possibility to access high-quality care incl. remote locations
- Informed by the global expertise and experience from across a Network



Improving Patient Outcomes

- Collaborative working improves health outcomes.
- Learning together as a key part of the success of effective networks
- Clinical networks as learning systems improve outcomes of treatment of the participants
- Growing number of clinical networks for rare diseases (China, EU, France, Japan, US,, etc.)

Network Model

Collaborative Global Network (CGN) will **connect existing networks and collaborative hubs** of expert centres and patient organisations ➔ to form a **'network of networks'**

National Hubs
network locally

- National Endorsed Single or Multi-Centers as National Hubs, mandated to strengthen health systems competency in RD
- Internationally recognized as a 'lighthouse' for rare diseases
- Progressively increase National Population & RD Coverage (%)
- Knowledge 'adaptors' to access global knowledge for their national health system to 'plug-in and play'

Regional Hubs
cooperate across regions

- Virtual multi-centre Network or Collaborative Hubs connecting across regions
- Partnership of the National Hubs & Patient Ogranisations
- Defined locally to demonstrate equality, diversity and inclusion
- Scale up diagnostic capacities and connect to an Undiagnosed Disease Programme
- Provide the platform to supports collaboration

CGN4RD Network
collaborate Globally

- Network of Regional Hubs (x18-20 Hubs) & International Federations
- Disease Cluster Working Groups to offer expert advice and coordinate 'community actions'
- Inform global strategy and guidelines e.g.: WHO roadmap for rare diseases
- Exploit advancements in technology to share data, information, practice to build global knowledge thro[illegible]

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Expansion of the ERNs

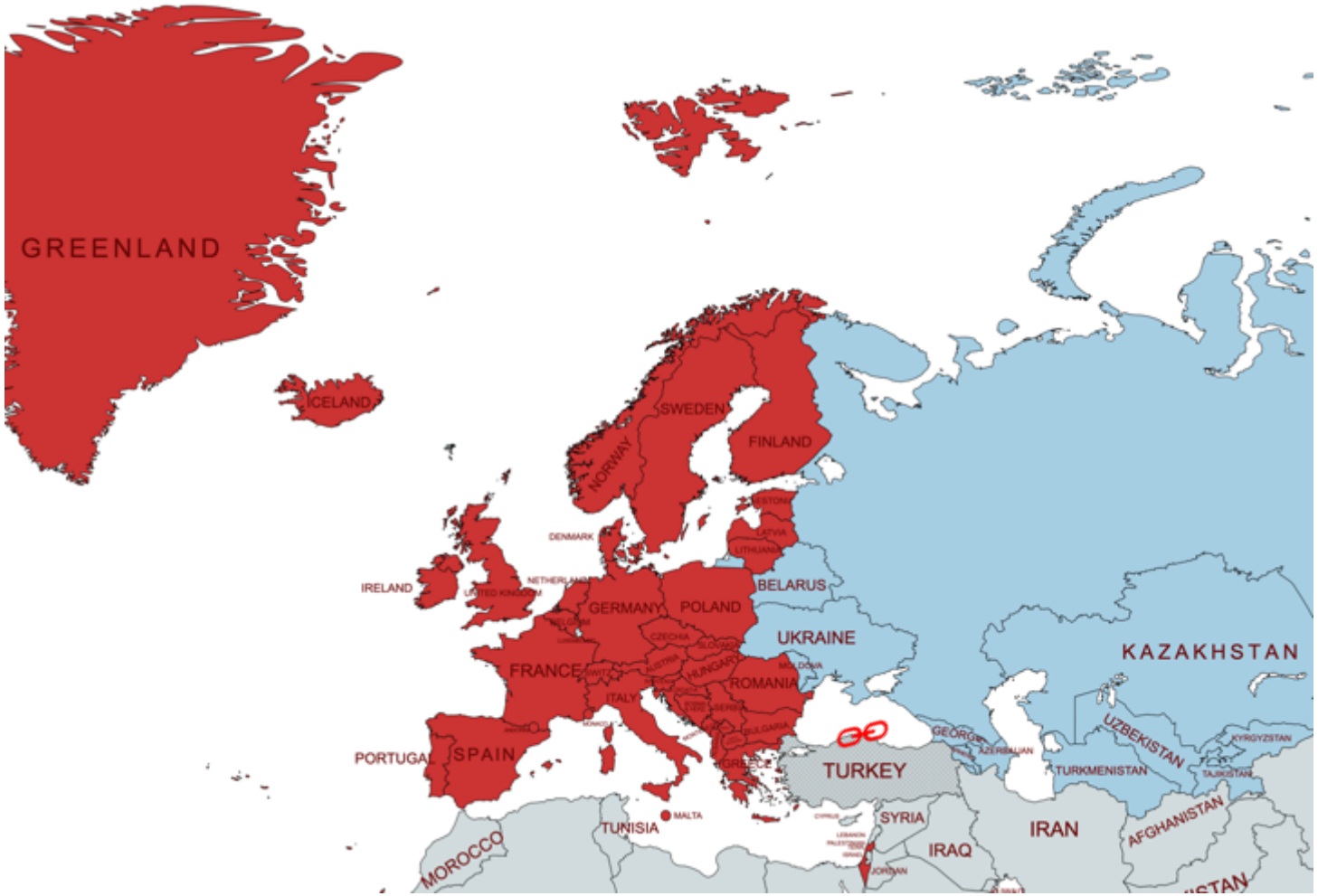
ERN Networks should collaborate closely at national and international level with other Centres of Expertise and Networks

- exchange and disseminate knowledge and best practices
- communication tools
- develop clinical guidelines and protocols
- exchange clinical information
- develop training alternatives and models and operation and coordination practices, etc.

Membership: Full & Affiliate Member; as well as a Collaborative Partner (not including in the legal definition

Source: EC Delegated Decision (2014) Annex I: Criteria & Conditions to be fulfilled by the Networks (7)

Switzerland in a 'European Hub'



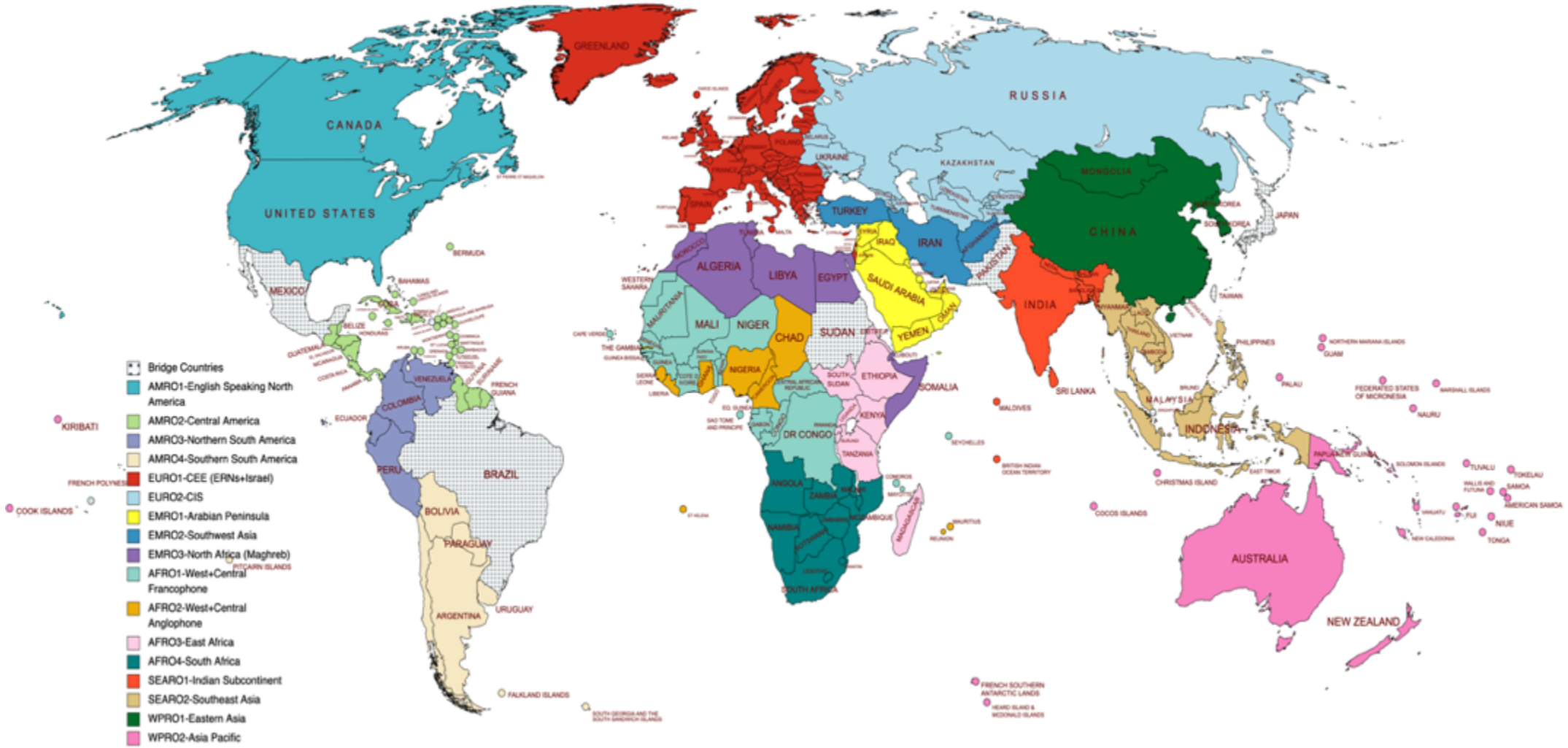
EURO Regional Hubs Proposal: <u>2 hubs</u>

- EURO 1: Central and Western Europe:
- EURO 2: Eastern Europe

Additional considerations around hub distribution:

- EURO 1: ERNs + Israel, Turkey, Switzerland & UK
- EURO 2: Commonwealth of Independent States (CIS)
- Turkey (EURO-EMRO) is a bridge country

Existing Networks & Collaborative Hubs



Regional Hubs Configuration (n.17)

AMRO (4), EURO (2), AFRO (4), EMRO (3) and SEARO/WPRO (4)

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Key messages

1. "The ambition of EURORDIS is to have 3 to 5 times more new rare disease therapies approved per year, 3 to 5 times cheaper than today by 2025"
2. European innovation fund linked to joint-EU HTA assessment, to fund the therapy, clinical services
3. Implement 'managed access pathways' to collect real-world data across EU Member States, in order to reduce clinical uncertainties
4. Improve legal pathways to access healthcare abroad
5. Investment into NHS infrastructure to adopt ATMP and greater standardisation
6. MS approve based on a common assessment & standards, establish European ATMP Treatment Centres with designated hubs for eastern countries
7. Qualified Treatment Centers should take part in a learning system in order to improves safety and outcomes
8. Learning together as a key part of the success of effective networks
9. Foster development of clinical networks within Switzerland, and progress discussions to connect across the WHO European Region

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Thank you for your attention

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