European Rare Disease Policy

Past achievements and the drive for renewal

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National Press Foundation Rare Disease Reporting Fellowship

14th November 2023

Inserm

Co-funded by the Health Programme of the European Union

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KNOW THE RARE FOR BETTER CARE

Objectives of this session

1. Understand how the concept of RD as a public health priority with EU-added value emerged
2. Understand the evolution of EU rare disease policies
3. Understand what has been achieved to date at European level: focus on flagship initiatives (Orphanet, European Reference Networks)
4. Learn about the Rare2030 prefered policy scenario for the future of European RD Policy, and consensus recommendations
5. Understand the utility of international collaboration on RD and experience-sharing

What is a rare disease?
Why is it a public health priority?
Why is a cross-border approach needed?

Rare diseases in brief

- Prevalence <1/2000 inhabitants: European definition set by the 2000 European Orphan Drug regulation
- 6,000 + rare diseases, including the >200 rare cancers, according to Orphanet
- 30 M+ European citizens with a rare disease, around 300 million worldwide
- Most rare diseases concern a small number of patients individually
- Clinically heterogeneous, most starting in childhood (70%), chronic, disabling
- RD include, but are not limited to, rare genetic diseases (72%)
- 25% wait 5 to 30 years to be diagnosed
- 40% are misdiagnosed, thus incorrectly treated
- Poor recognition because of inappropriate coding in health information systems
- Need for specific expertise: in Europe, it resides in the European Reference Networks (ERNs)
- GPs and other health professionals cannot know each and every RD, but they should be aware of rare diseases and know how to orientate their patients towards appropriate resources and points of care

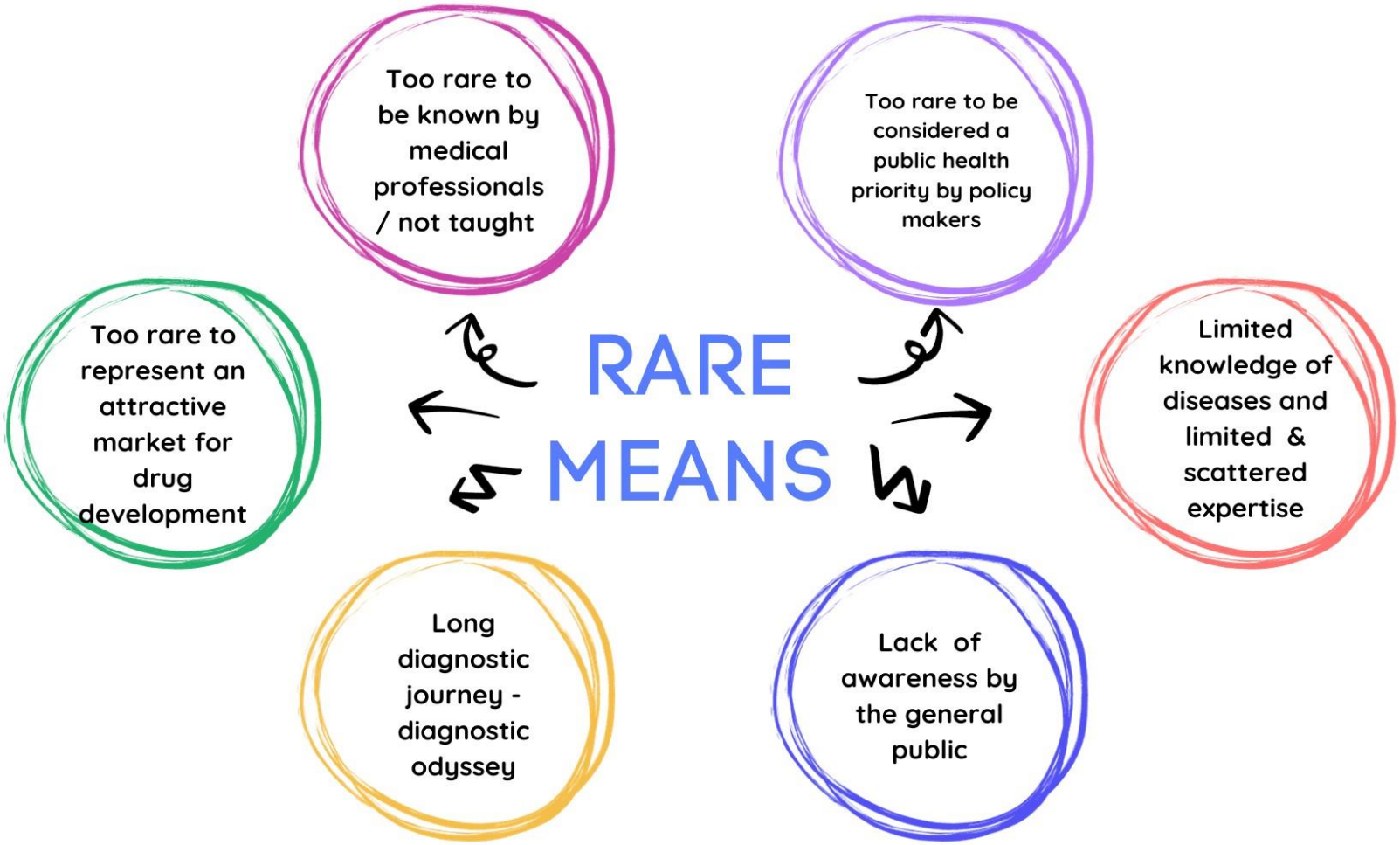
Rare disease definitions across the world

- **Low prevalence**
  - Most of policy and legislative frameworks (orphan drug regulations) define rare diseases by their prevalence (market size/population burden of disease)

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	✓	✓	✓	✓

- **For some diseases, expert groups have defined rare diseases by their incidence:**
  - 6/100 000/year for rare cancers
  - 5/10 000/year for rare infectious diseases

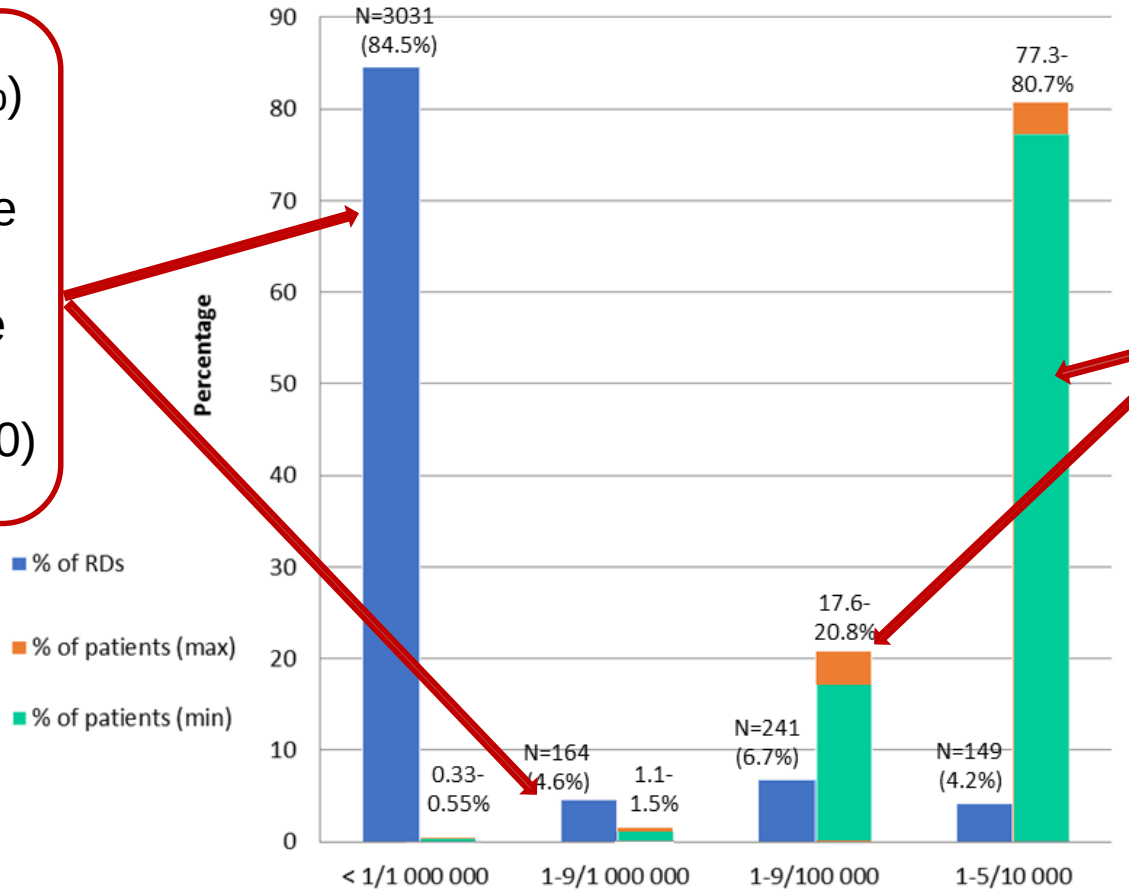
Rare diseases: a concept that describes a set of specific challenges



Further reading around the emergence of the concept of rare diseases: C Huyard "How did uncommon disorders become 'rare diseases'? History of a boundary object" Sociol Health Illn 2009

Understand global distribution of RD and PLWRD

Most (89.1%) of rare diseases are very rare (prevalence less than 1 per 100,000)



Almost all of the people with rare disease (>98%) have one of the 390 most prevalent diseases (more common than 1 per 100,000)

3.5 - 5.9% of the population (263 - 446 Million people) worldwide

Eur J Hum Genet **28,** 165–173 (2020). https://doi.org/10.1038/s41431-019-0508-0

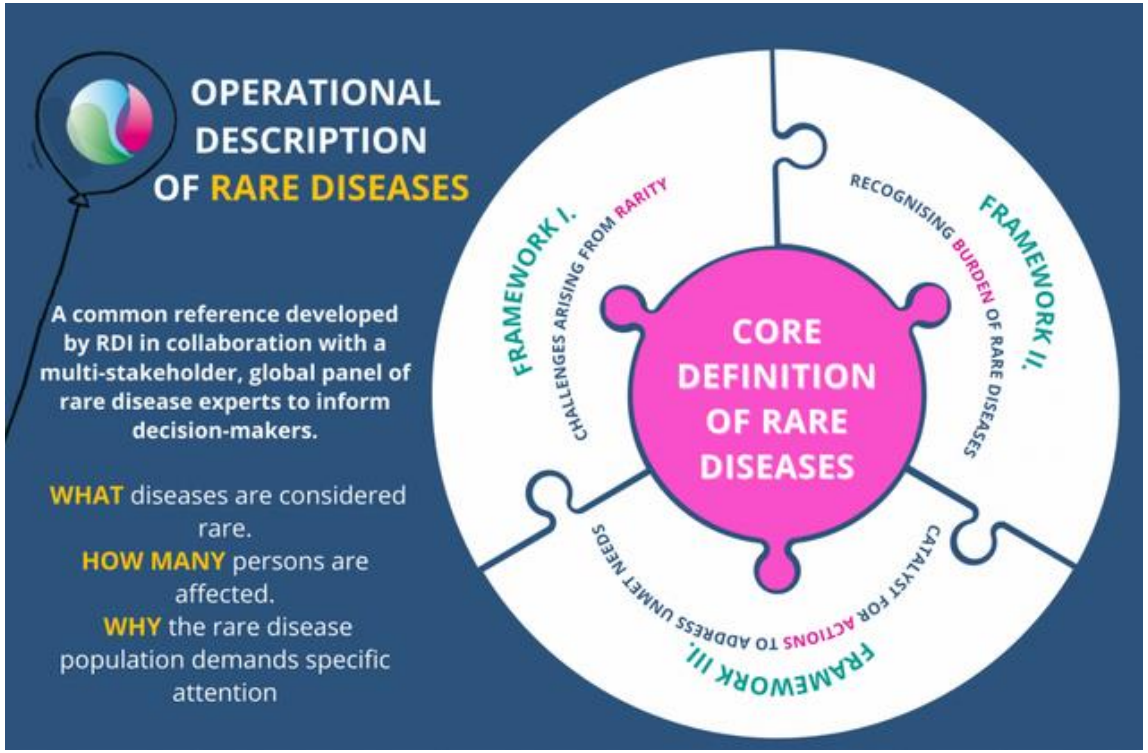
*Based on 68% of prevalent RD based on EU definition (<50/100,000), data from literature.

Endorsement of an international operational description of rare diseases

Established by a panel of global experts in collaboration with WHO-ICD

A rare disease is a medical condition with a specific pattern of clinical signs, symptoms, and findings that affects fewer than or equal to 1 in 2000 persons living in any World Health Organisation-defined region* of the world.

Read more



RARE DISEASES INTERNATIONAL

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The evolution of European policies on rare diseases

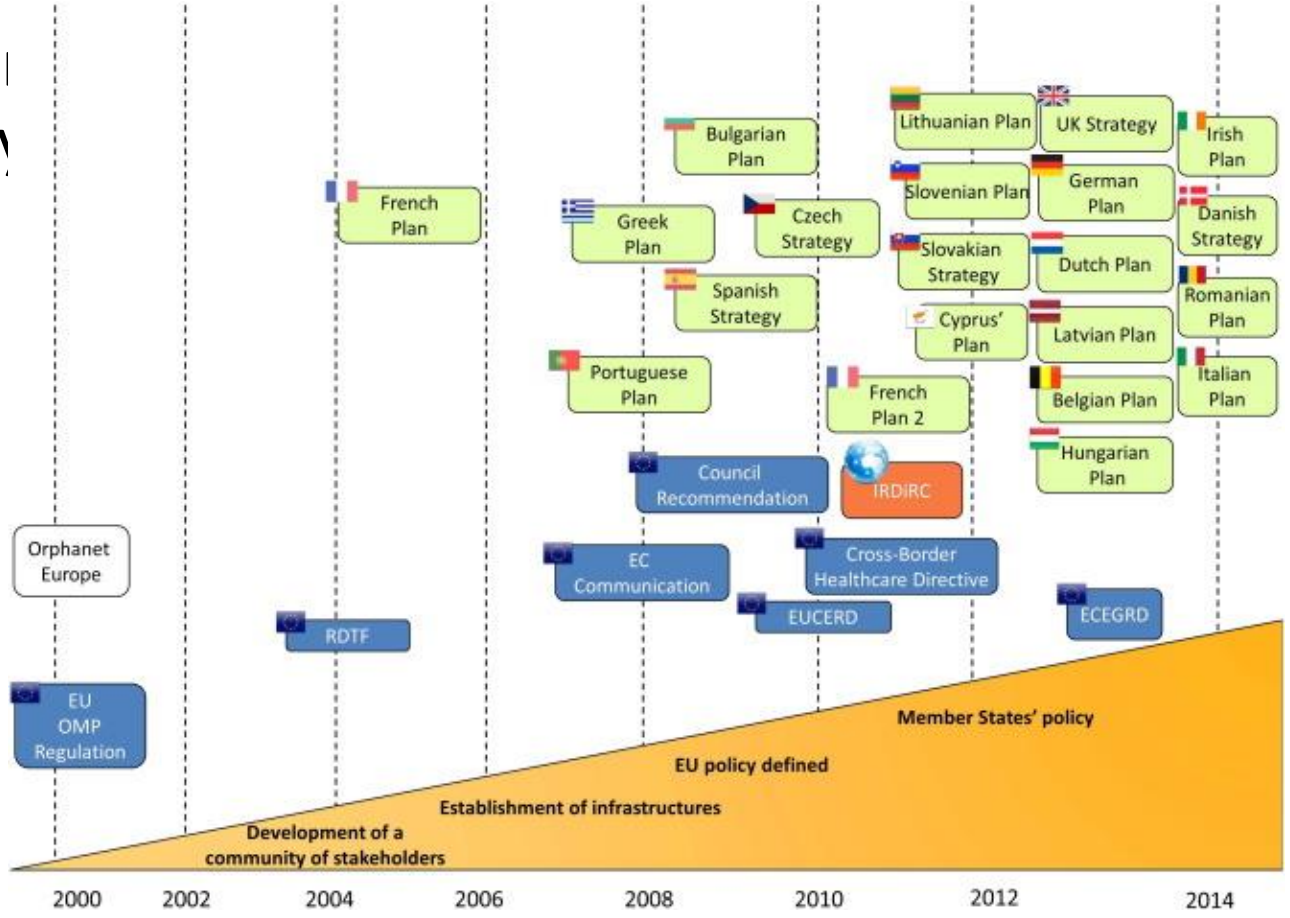
What is possible at European level

- EU treaties do not foresee a common EU health policy
- Member States can collaborate on identified public health themes if they wish
  - Instigated by the European Commission
  - Adopted by the Council of Ministers (Member States)
  - European Commission advised by ad hoc expert bodies

- Common research policies are possible, with a budget defined through codecision
- Rare diseases are a clear area of EU-added value, and the existence of the EU helped cross-border approaches in RD emerge sooner in Europe than elsewhere

An emerging, multistakeholder community driving change

- Importance of multistakeholder fora in driving policy for RD: key advocacy moments
  - Committees
  - Conferences (ECRD)
  - Rare Disease Day events
- Essential role of patient advocacy in maintaining the dynamic
  - Eurordis
  - Rare Diseases International



Rodwell & Aymé, Rare disease policies to improve care for patients in Europe, BBA Molecular Basis of Disease, 2015

The evolution of RD policy in Europe

1997:	**Creation of EURORDIS & Orphanet**
1999-2000:	**European Regulation on Orphan Drugs**
2000:	**RD included in research and health programmes (Orphanet becomes European initiative)**
2004	**Creation of EC Rare Disease Task Force & OrphaNews**
2005:	**Discussions around European Reference Networks (ERNs)**
2005:	**First French National Plan for Rare Diseases (first comprehensive RD policy plan in the world)**
2006:	**Calls for pilot ERNs**
2008:	**EC Communication «Rare Diseases: Europe's Challenges »**
2009:	**EU Council Recommendation on an Action in the field of rare diseases**
2010:	**EUCERD established – European Union Committee of Experts on Rare Diseases**
2011:	**Cross-border healthcare directive**
2011:	**International Rare Diseases Research Consortium**
2013:	**European Commission Expert Group on RD established**
2017:	**ERN European Reference Networks established**
2018:	**Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases established**
2019:	**EJP-RD European Joint Programme Rare Diseases**
2021:	**RARE 2030 Foresight results**
	Call by EURORDIS pour renewed european policy on RD in Europe
	UN Resolution for People Living With a Rare Diseases

European Reference Networks

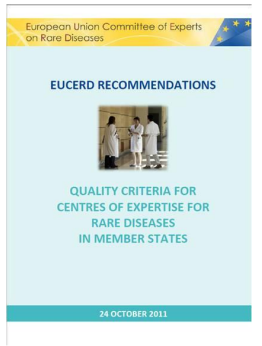
24 ERN : 900 Health care providers in 313 hospitals across 25 Member States & Norway

A community working to shape policy

Successive multistakeholder expert groups at European level (2004 – 2016) supported by EU Health Programme

EUCERD
European Union Committee of Experts on Rare Diseases

- Regular meetings and workshops: fostering knowledge-sharing and co-construction
- Recommendations
  - Centres of expertise
  - European Reference Networks
  - Registries
  - Coding of rare diseases
  - Cross-border genetic testing
  - Clinical added value of orphan drugs
  - Newborn screening
  - Specialised Social Services
- State of the art of RD reports
  - Review of European and country-level activities in the field of RD



Council recommendation on an action in the field of rare diseases (2009)

- Recommends that Member States elaborate a national plan or strategy for rare diseases by 2013
  - These plans should be comprehensive and structure the health care offer for rare diseases
  - Should identify expert centres/foster their creation – the future building blocks for ERNs
  - Should foster research on RD
  - Should consider social aspects

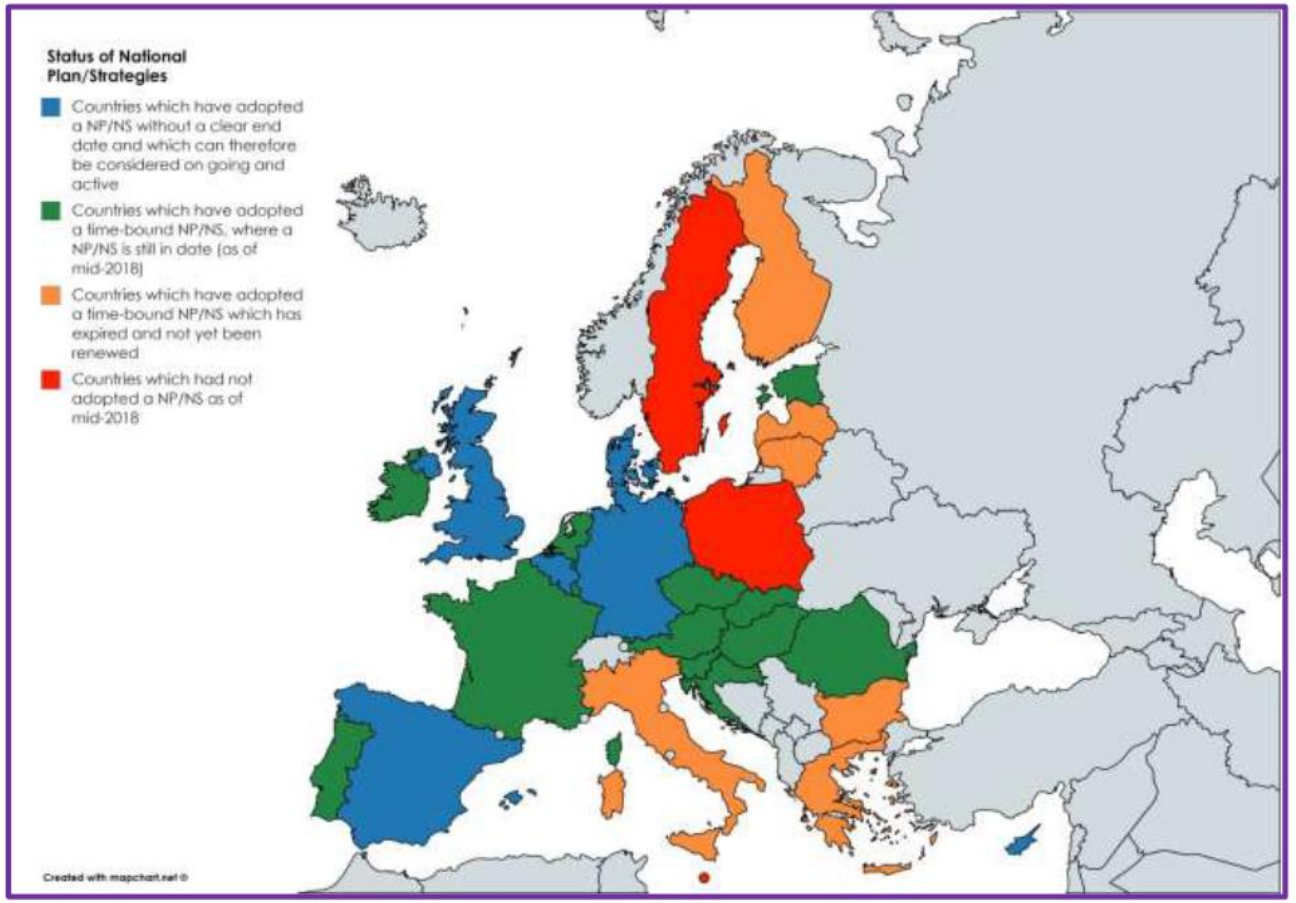
- Promotes improved codification of rare diseases (ORPHAcodes)
- Promotes gathering expertise on RD at European level
- Ambitions for the creation of European Reference Networks
- Promotes empowerment of patient organisations
- Aims to ensure sustainability of infrastructures for RD

Status of national RD policies

Outcome in 2014:

- 18 countries with an adopted plan/strategy
- 6 countries had submitted a plan/strategy to national authorities
- 4 countries in the finalisation of a plan/strategy
  - 2ème national plan in France (2011-2014)

Fig. 2: Status Quo of National Plans and Strategies for Rare Diseases in EU MS, as of July 2018

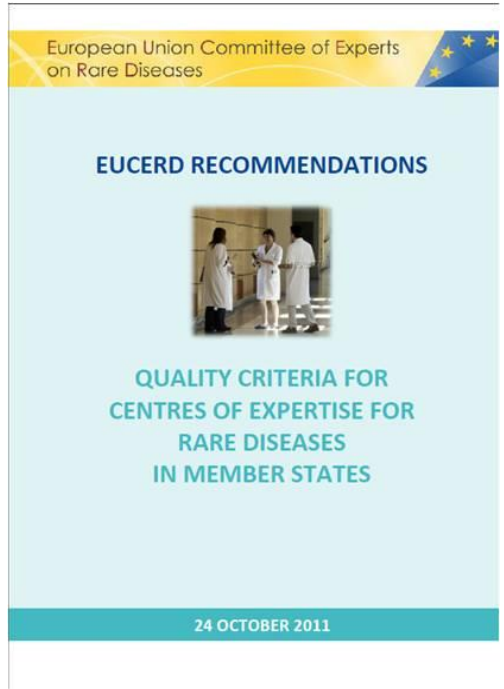


Content of the national plans

- The 18 plans adopted to date are hetrogenous
  - Some are plans that need to be transposed into concrete action plans
  - Some do not have dedicated budgets
- Most plans have established priorities
  1. Identification of centres of expertise for RD
  2. Implementation of ORPHAcodes to codify RD data
  3. RD registration (national register or database)
  4. Promoting access to information on RD – support to national Orphanet activities

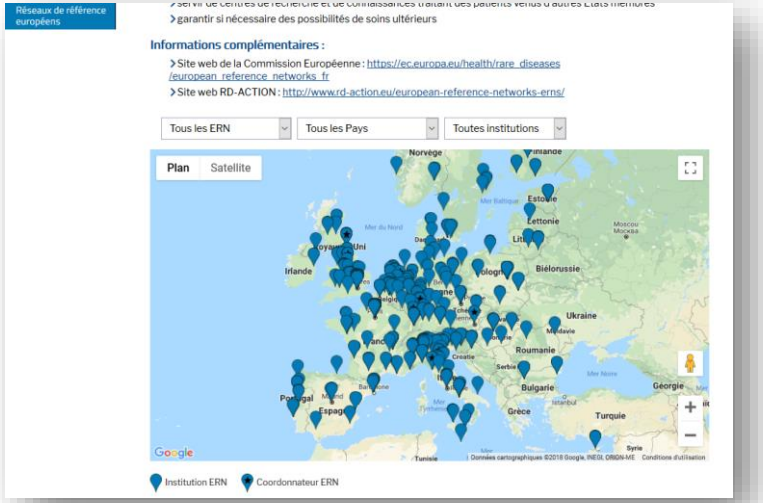
Designation of centres of expertise for RD
A success story

- Prior to the Council Recommendation & Cross Border Healthcare Directive (2011) only 6 countries in the EU had designated their RD expertise (in a non-homogenous fashion)
- Now countries have designated their expertise, guided by the *« Quality criteria for centres of expertise » (2011, EUCERD)*
  - Common understanding of what is a centre of expertise for RD
  - Prepared ground for constitution of European Reference Networks



European Reference Networks

- Created through the Cross-Border Healthcare Directive (2011) in 2017, membership extended in 2019
  - *"aim to facilitate discussion on complex or rare diseases and conditions that require highly specialised treatment, and concentrated knowledge and resources"*
  - &CPMS (Clinical Patient Management System)
- 24 networks (clinical specialties) of 900+ Healthcare Providers (HCP) in 300+ hospitals in 26 MS
  - HCP are designated by national authorities
- Supervised by a Board of Member States, coordinated on a rotating basis by one of the 24 ERN coordinators
- Flagship initiative for RD at European level, showing what can be achieved working across borders (CPMS -> Covid 19 Clinical Management Support System)



European Reference Networks

Share. Care. Cure.

ERNs' missions

Patients shouldn't travel – expertise should

- Virtual consultations
- Development of guidelines, training and knowledge exchange
- Facilitation of large clinical studies to improve understanding of diseases
- Development of new drugs and medical devices by gathering patient data
- Development of new care models, eHealth solutions and tools.
- COVID clinical care guidelines for RD

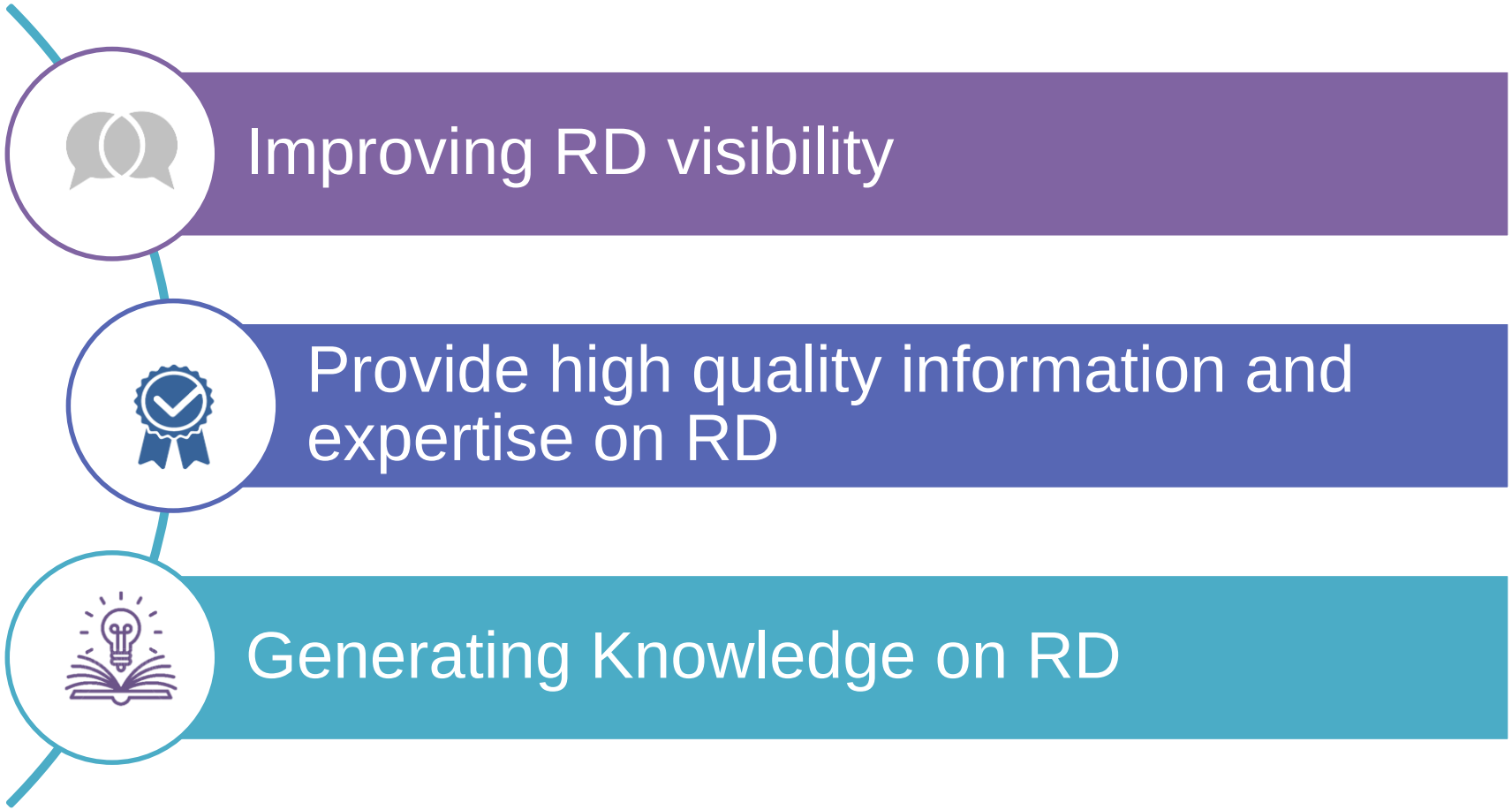
ORPHANET

The ‘ERN’ for information & knowledge on rare diseases

Orphanet in brief

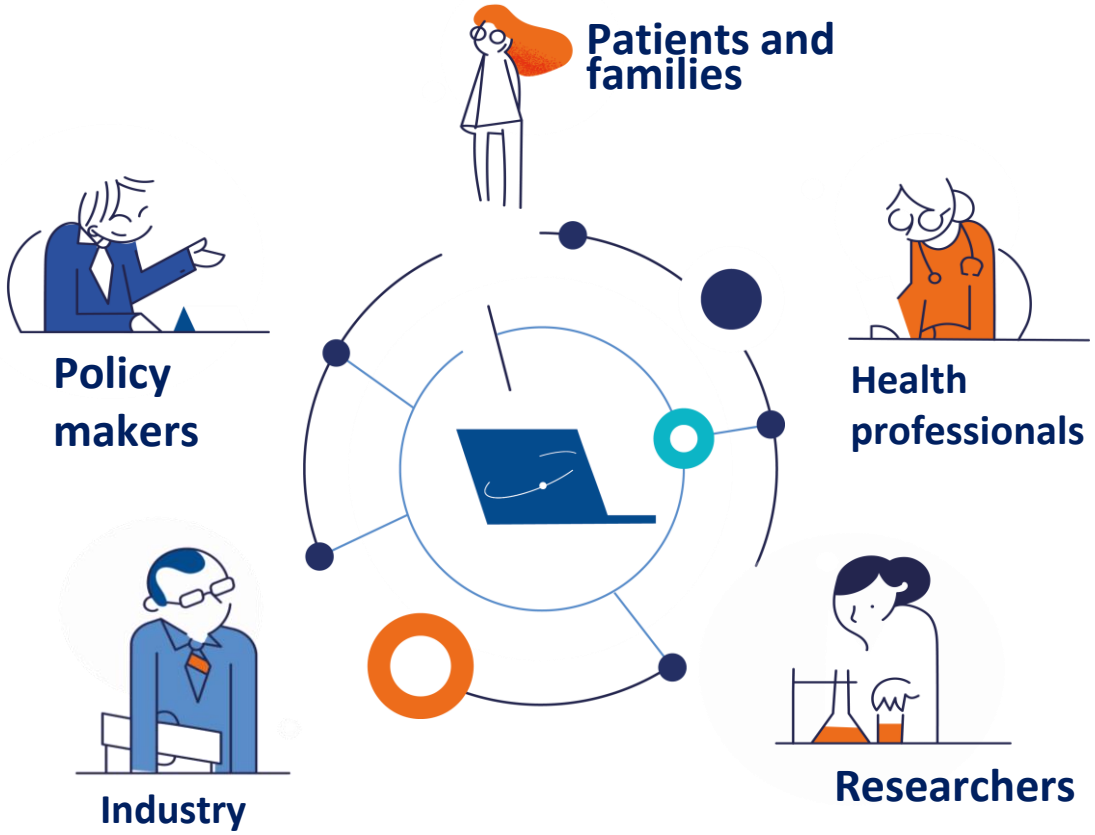
- A multilingual knowledge base on rare diseases and orphan drugs, freely available to everyone
  - A database, a portal www.orpha.net, a data source www.orphadata.com, an ontology (ORDO)
- Established in 1997, now an international network of over 40 countries
- Cooordination at French National Institute of Health and Medical Research, co-funded by the European Union's Health Programme.
- Orphanet's standard nomenclature of rare diseases (ORPHAcodes) is recognised as a best practice at EU level
- Orphanet's data platform is recognised as a Global Core Biodata Resource

Orphanet's Missions



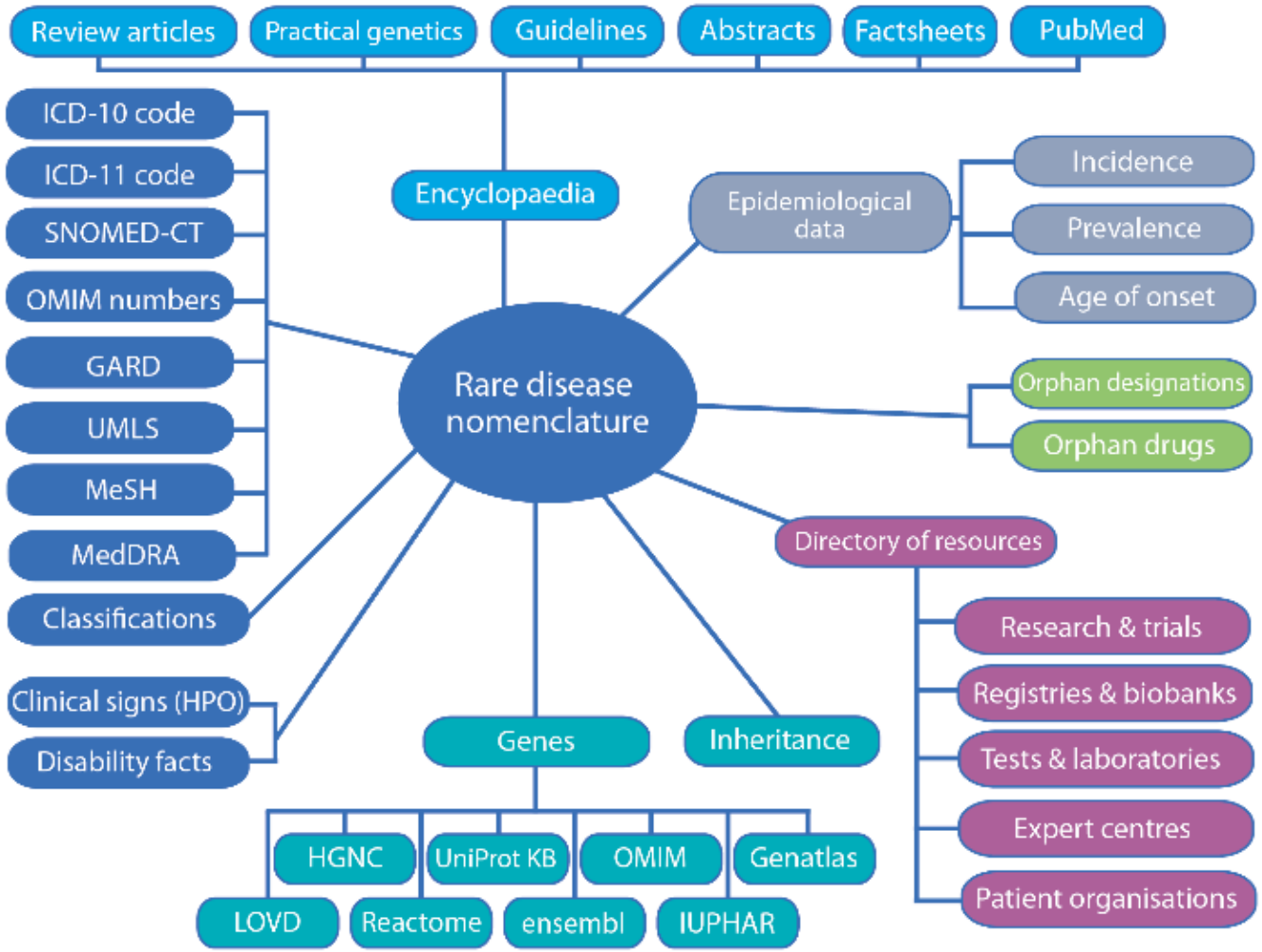
Equal access to expert RD knowledge for all

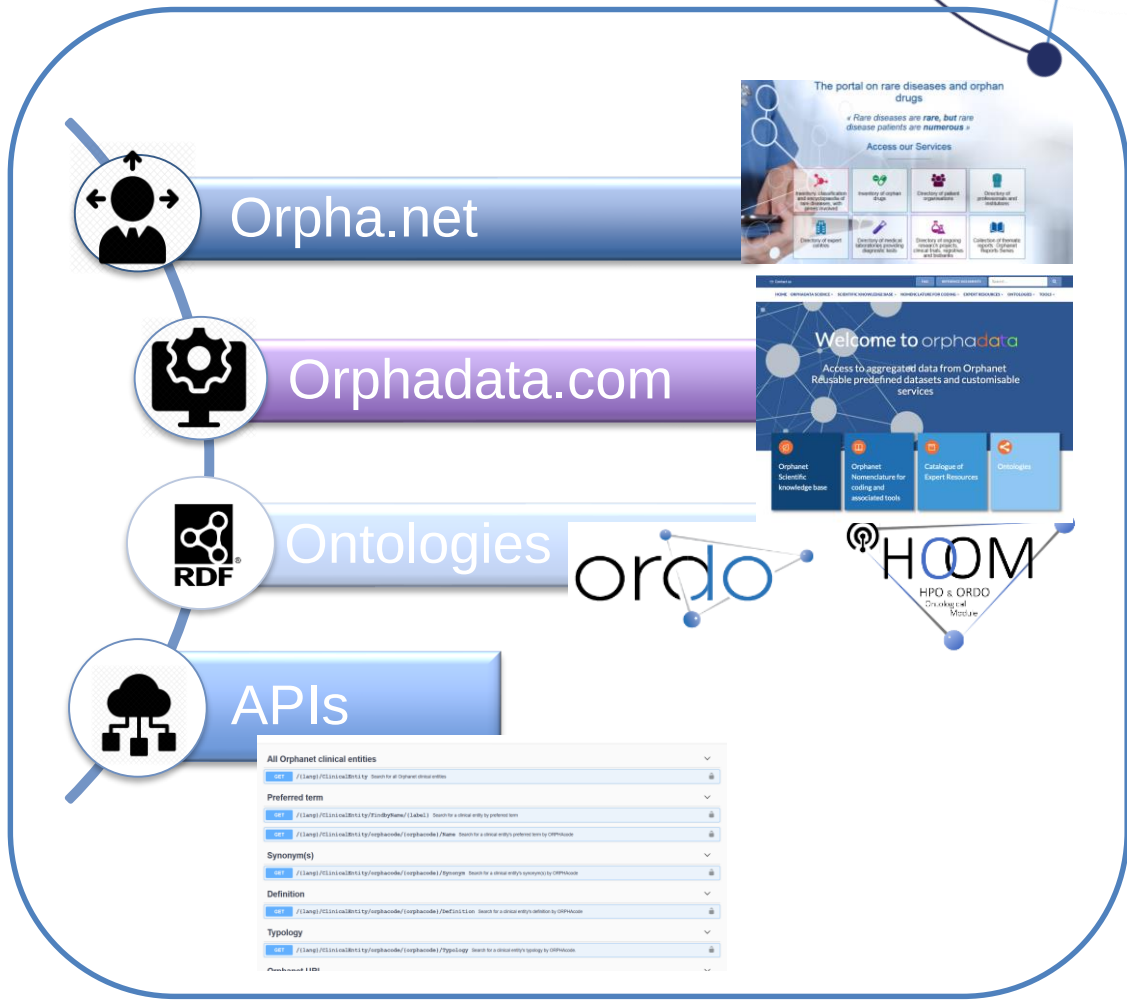
- Available for all to consult: freely accessible, no log in, no subscription fee
- Multilingual portal (9 languages) with texts & external resources in additional languages
- Gathering expertise from across the world
- A global network collecting data on expert resources in their country so that resources are visible



Video: https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanet.php?lng=EN

Orphanet, added-value knowledge base for all users





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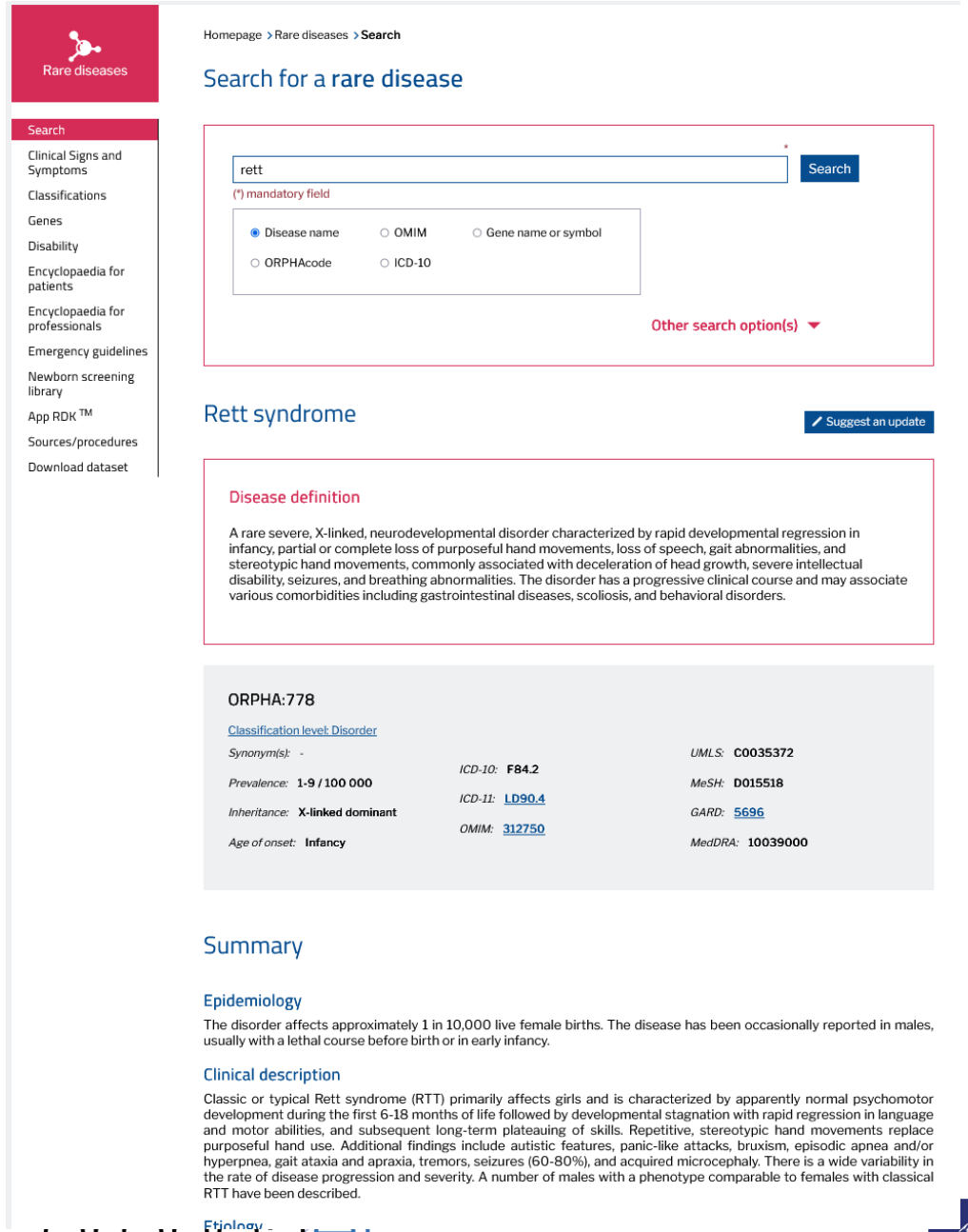


A summary on this disease is available in Deutsch (2021) Español (2021) Français (2021) Nederlands (2021) Português (2004) Italiano (2007) Slovak (2007, pdf) Greek (2007, pdf) Polski (2007, pdf)

Detailed information

Search for a disease and consult associated resources

Français (2006, pdf) - *Orphanet*
Svenska (2019) - *Socialstyrelsen*
Deutsch (2021, pdf) - *Kindernetzwerk e.V.*

Guidelines

Emergency guidelines
Français (2020, pdf) - *Orphanet Urgences*
Español (2020, pdf) - *Orphanet Urgences*

Clinical practice guidelines
Français (2017) - *PNDS*
Français (2019) - *PNDS*

Anesthesia guidelines
Czech (2015) - *Orphananesthesia*
English (2015) - *Orphananesthesia*
Español (2015) - *Orphananesthesia*

English (2005, pdf) - *Eur J Hum Genet*
English (2019) - *GeneReviews*

Diagnostic criteria
English (2010) - *Ann Neurol*

Disability

Disability factsheet
Français (2018, pdf) - *Orphanet*
Dansk (2018) - *Sjaeldne Diagnoser*

Genetic Testing

Guidance for genetic testing
Français (2012, pdf) - *ANPGM*

produced/endorsed by ERN(s) produced/endorsed by FSMR(s)

Additional information

Further information on this disease
- Classification(s) (2)
- Gene(s) (1)
- Disability
- Clinical signs and symptoms
- Publications in PubMed
- Other website(s) (16)

Patient-centred resources for this disease
- Expert centres (473)
- Networks of expert centre (10)
- Diagnostic tests (216)
- Patient organisations (162)
- Orphan designation(s) and orphan drug(s) (17)

Research activities on this disease
- Research projects (55)
- Clinical trials (3)
- Registries/biobanks (45)
- Network of experts (4)

Specialised Social Services
- Eurordis directory

Newborn screening
- Newborn screening library

International catalogue of expert services

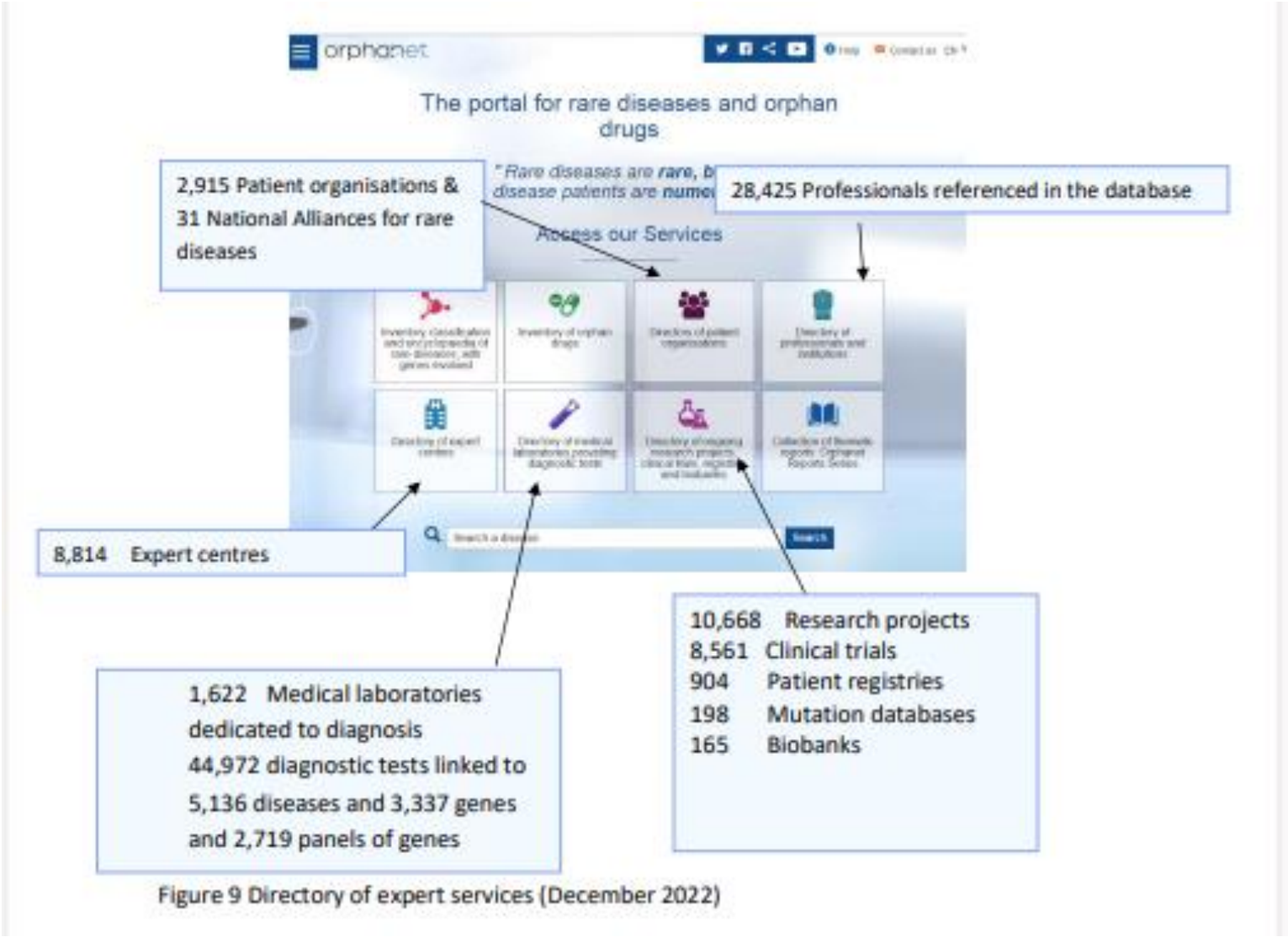


Figure 9 Directory of expert services (December 2022)

Why is it important to improve visibility of rare diseases with improved coding of rare diseases?

- Rare disease data is rare and scattered
- Critical mass = solid epidemiological data
- Produce data for public health and health economics
- Document natural history of rare diseases
- Identify patients in electronic health records for clinical research

Orphanet nomenclature of RD

ORPHA CODES

PREFERRED TERM

Fanconi-Bickel syndrome

Suggest an update

DEFINITION

Disease definition

A rare glycogen storage disease due to a deficiency in solute carrier family 2, facilitated glucose transporter member 2 and characterized by hepatorenal glycogen accumulation leading to severe renal tubular dysfunction and impaired glucose and galactose metabolism.

ORPHAcode

ORPHA:2088

Classification level: Disorder

SYNONYMS

Synonym(s):

GSD due to GLUT2 deficiency

GSD type 11

GSD type XI

Glycogen storage disease due to GLUT2 deficiency

Glycogen storage disease type 11

Glycogen storage disease type XI

Glycogenosis due to GLUT2 deficiency

Prevalence: Unknown

Inheritance: Autosomal recessive

Age of onset: Infancy, Neonatal

ICD-10: E74.0

OMIM: 227810

UMLS: C3495427

MeSH: -

GARD: 2268

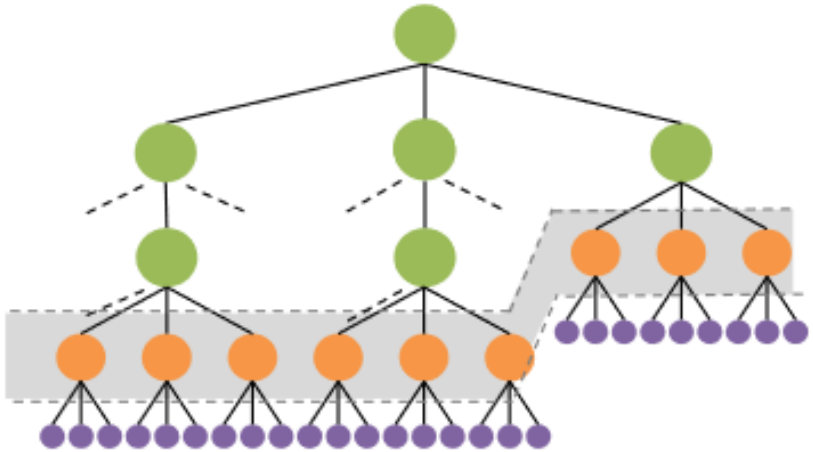
MedDRA: -

Representing rare diseases: ORPHA CODES

A MEDICAL TERMINOLOGY SPECIFIC TO RARE DISEASES (<1 in 2000 cases)

Clinical definition:

Disorders are clinically homogeneous entities described in at least two independent individuals, confirming that the clinical signs are not associated by fortuity.



Group

Disorder

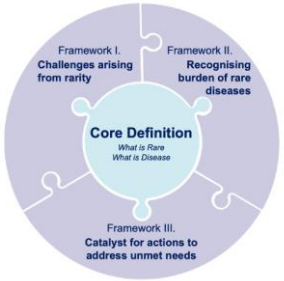
Subtype

9,449 clinical entities

2,124 groups

6,313 disorders

1,012 subtypes

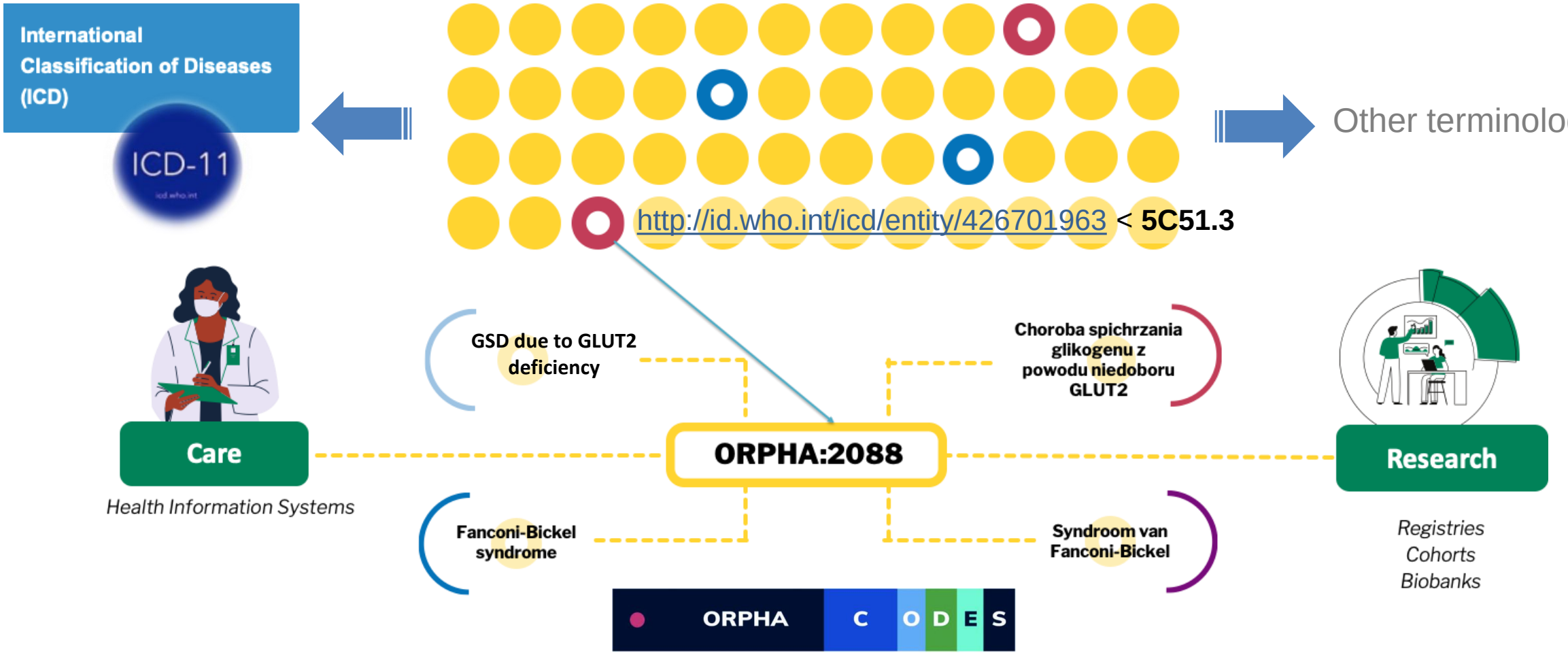


"Classification level"

ENG FR SP DE IT NL PG PL RU CHN TUR

Comprehensive, standardized, evidence-based, interoperable, versioned, computable and free (CC-BY 4.0)

Towards general interoperability for RD



Reinforce the national level to add European value

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- National hubs
  - Information & data
  - ORPHAcode implementation support

European Reference Networks

National nodes
- Care and research activities
- CPGs
- ORPHAcode implementation

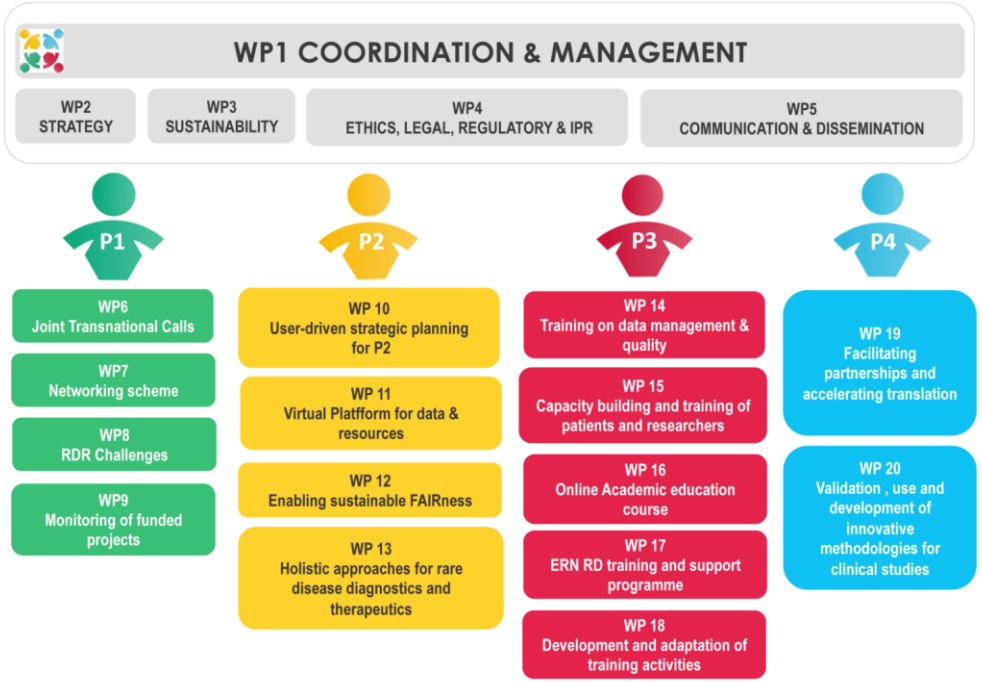
European Health Data Space

National nodes
- Hospitals' data
- EHRs
- ORPHAcode implementation

Structuring the European RD Research Ecosystem

- Up to 2019, some RD-specific calls funded by EU, with some transnational calls (organised by the eRare) ERA-NET.
- European Joint Programme on RD (EJP-RD) : 5 year project to structure the RD research ecosystem
- 130+ institutions & ERNs dans 35 pays structured into 4 main pillars:
  - Funding/transnational calls
  - Coordinated access to data & services
  - Training & empowerment
  - Innovation and clincial trials support
- To **improve the integration, the efficacy, the production and the social impact of research on RD** through the development, demonstration and promotion of Europe/world-wide sharing of research and clinical data, materials, processes, knowledge and know-how
- To **implement and further develop an efficient model of financial support for all types of research on RD (**fundamental, clinical, epidemiological, social, economic, health service) coupled with accelerated exploitation of research results for benefit of patients.
- Will be followed by an ambitious 7-year European Partnership for RD (ERDERA)

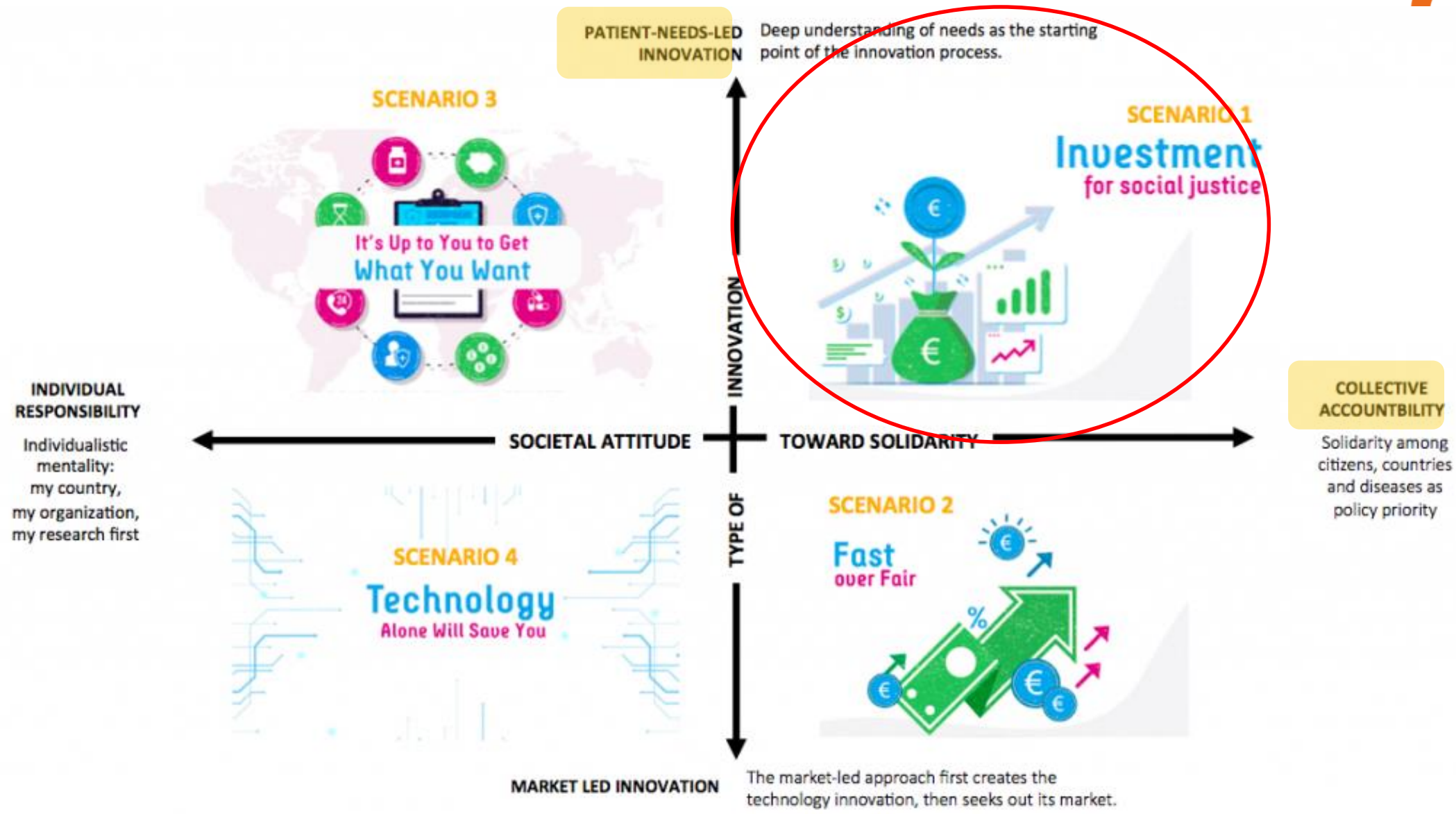
EUROPEAN JOINT PROGRAMME RARE DISEASES



A new policy scenario for 2030

- Project mandated by European Parliament in 2018
  - Take stock of evolutions of 20 years of European policy
  - Issue a vision for a renewed European policy for next 10/20 years
  - Suggest recommendations of how to achieve this goal
- 300+ experts and young citizens worked towards a set of recommendations for a renewed European policy
  - Recommendations
  - Knowledgebase factsheets
  - Scenarios Video

Rare2030
Foresight in Rare Disease Policy


PATIENT-NEEDS-LED INNOVATION
Deep understanding of needs as the starting point of the innovation process.
SCENARIO 3
It's Up to You to Get What You Want
SCENARIO 1
Investment for social justice
INDIVIDUAL RESPONSIBILITY
Individualistic mentality: my country, my organization, my research first
INNOVATION
SOCIETAL ATTITUDE
TOWARD SOLIDARITY
COLLECTIVE ACCOUNTBILITY
Solidarity among citizens, countries and diseases as policy priority
TYPE OF
SCENARIO 4
Technology Alone Will Save You
SCENARIO 2
Fast over Fair
MARKET LED INNOVATION
The market-led approach first creates the technology innovation, then seeks out its market.

"The health of 30 million people living with a rare disease in Europe should not be left to luck or chance"

Long-term, integrated European & national plans and strategies	*Earlier, faster, more accurate diagnosis*	*Access to high quality healthcare*	*Optimising data for patient & societal benefit*
Integrated & person-centred care	*Partnership with patients*	*Innovative & needs-led research & development*	*Available, accessible & affordable treatments*

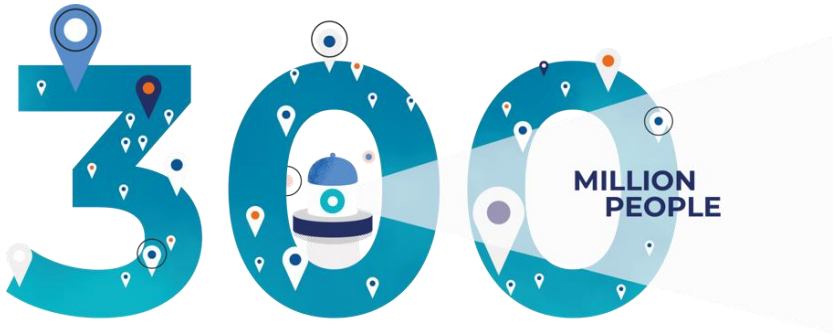
Call for a European Action Plan on RD (2021)

- Following from Rare2030, call launched by EURORDIS in 2021 for a « European Action Plan on RD »
  - #30millionreasons for European to take action on rare diseases
  - Call for a renewed EU policy for RD supported by the French & Czech EU Presidencies (2022)
    - Czech EU Presidency Call to action at EPSCO Council Meeting endorsed by 21 MS (December 2022)
  - High-level conference during Spanish presidency (2023)

On the issue of Orphan Drugs:

- Review of EU of OD and paediatric legislation (from 2020)
  - Positive impact BUT lack of medicines in areas where need for medicines is the greatest (including childhood diseases)
- Current revision of the EU pharmaceutical legislation (perspectives for RD)

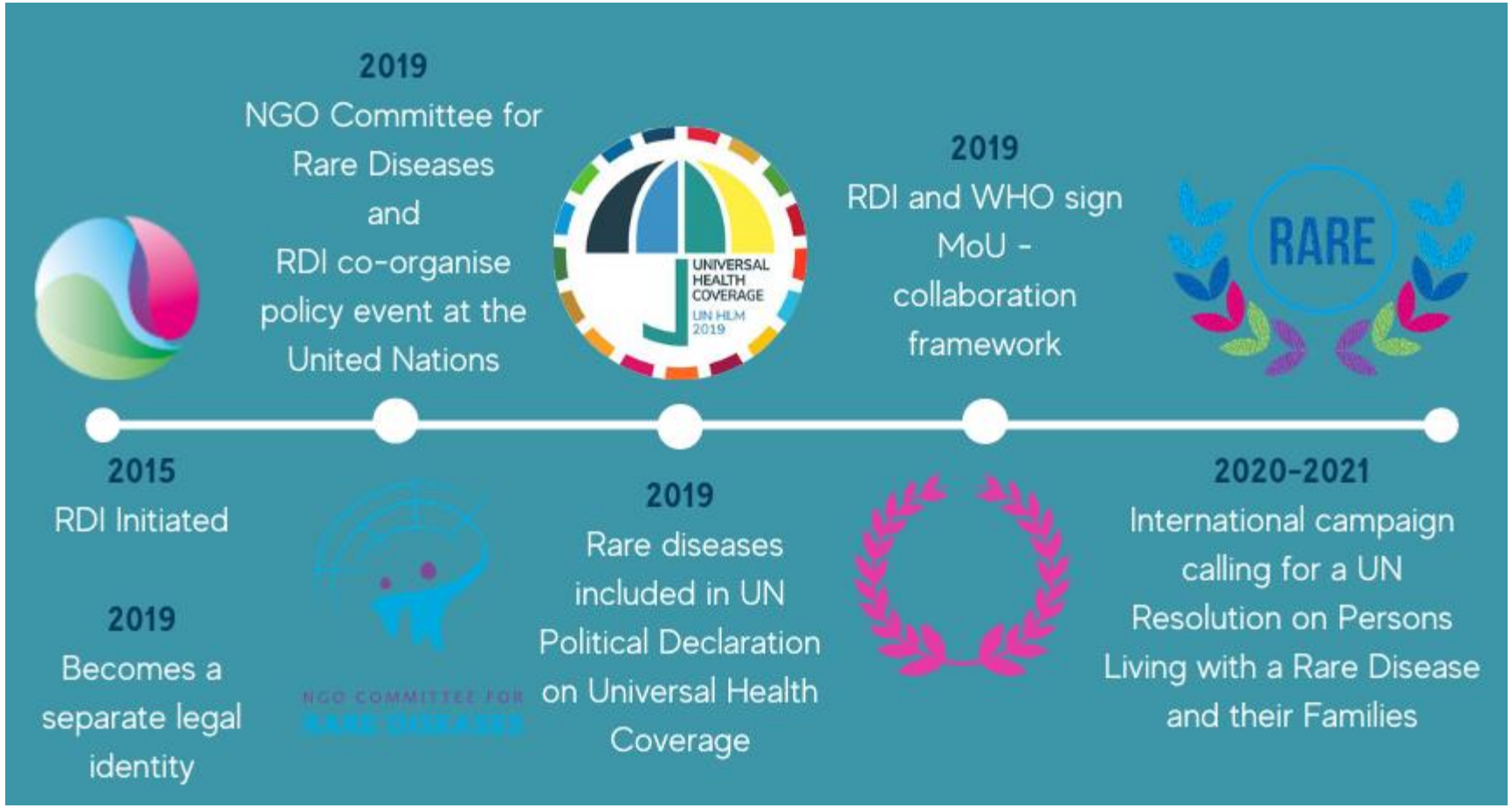
Europe in the global RD context & sharing lessons learned



The global RD community : stronger year by year

- **Rare Disease Day** (from 2008) : key advocacy moment coordinated by EURORDIS
- **ICD-11 Revision process**: Orphanet lead RD work (c 2009->)
- **IRDiRC** (2011)
  - EU/NIH: International Rare Disease Research Consortium
- **Rare Diseases International** (2015)
  - Launched by EURORDIS & NORD: Alliance of RD patient organisations
  - Mandated by the WHO to work on a global operational definition of RD (2022)
- **NGO Committee on RD @ UN** (2019)
  - Initiative of EURORDIS & Agrenska Foundation
  - Mission: Advocacy @ UN
  - Key in generating momentum to 2021 UN Resolution on PLWRD

RD advocacy at international level



International Rare Diseases Research Consortium

- 2 main initial goals: to contribute to the development of 200 new therapies and the means to diagnose most rare diseases by the year 2020
- New goals (2017-2027)
  - **Goal 1**: All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline
  - **Goal 2**: 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options
  - **Goal 3**: Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients

IRDiRC
INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

IRDiRC goals by 2027

- Develop the means to diagnose patients with suspected rare diseases within one year of coming to medical attention
- Develop 1,000 new therapies for rare diseases, and particularly for diseases *with no approved treatment*
- Create methods for assessing the impact of diagnoses and therapies on rare disease patients

Members

Constituent Committees

Scientific Committees

Funding organizations and companies invest more than $10 mln in 5 years in research projects
Patient organizations represent the broad patients' interests for all rare diseases

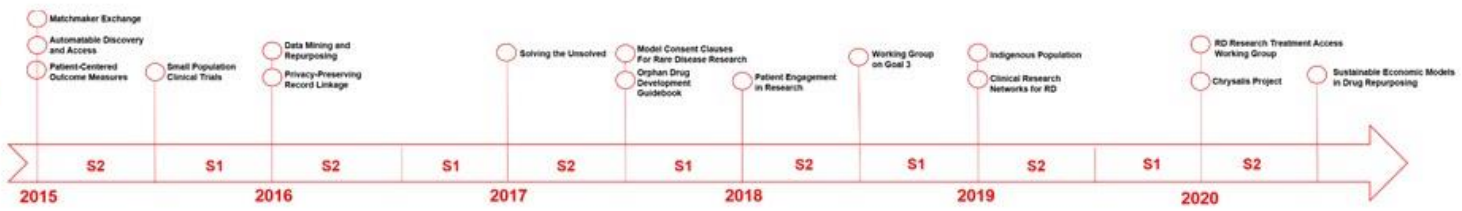
Members have balanced expertises and represent academia, patient organizations, diagnostics, pharmaceutical industry, and regulatory bodies

IRDiRC activities & resources

IRDiRC organizes several activities and provides many resources to the international rare diseases research community

IRDiRC Task Forces

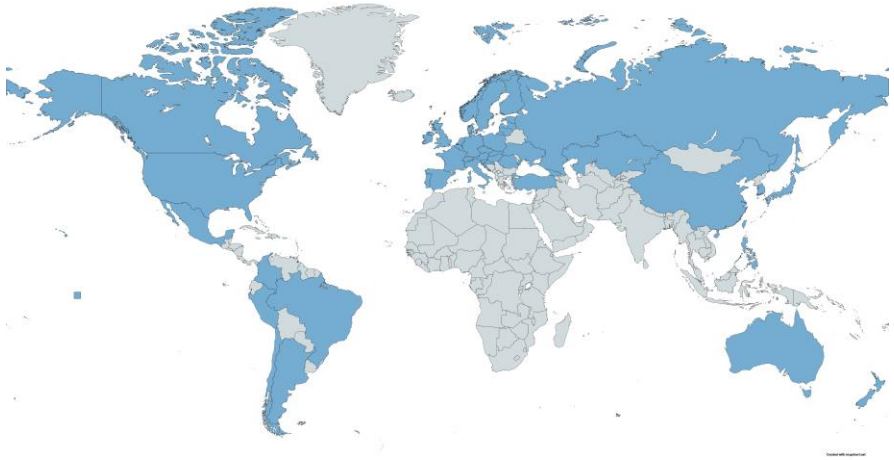
IRDiRC *recruits* experts and key players throughout the world to populate its Scientific Committees and Task Forces.
The Task Forces may operate either solely as IRDiRC initiatives or jointly with partner groups that wish to collaborate and address similar issues.



Task Forces are created to *tackle* specific time-limited topics within rare diseases research proposed by the Consortium's Constituent and/or Scientific Committees.
Task Forces develop solutions through policy recommendations and/or technical applications including platforms, tools, standards and guidelines

How are RD policies evolving outside of Europe

- Countries outside of Europe were the pioneers in shaping policy for rare diseases
- A range of legislative texts prior to European RD policy, mostly focused on providing incentives for orphan drug development
  - Japan: Nan-byo/intractable diseases (1972)
  - US Orphan Drug Act (1983)
- Increasing number of comprehensive RD plans and recommendations for plans across the world, organisation of communities and advocacy led by patients



Countries with legislative texts concerning rare diseases (some mainly around orphan drugs)

Lessons learned Europe can share with the international community

The European experience can help inform the development comprehensive plans/stategies for rare diseases, and demonstrates the utility of regional/cross-border approach

- It is essential to share experiences and lessons learned : the European plans could serve as a model for some countries
- The **Rare 2030 Recommendations** can provide ideas and lessons learned from 20 years of experience of rare disease policy in Europe and possibly help avoid pitfalls
- Remember the importance of the patient voice, the impact of the patient narrative, the place of the patient as an expert of their own diseas and the essential role of patient advocacy in driving change (capitalise on Rare Disease Day in raising awareness for change)

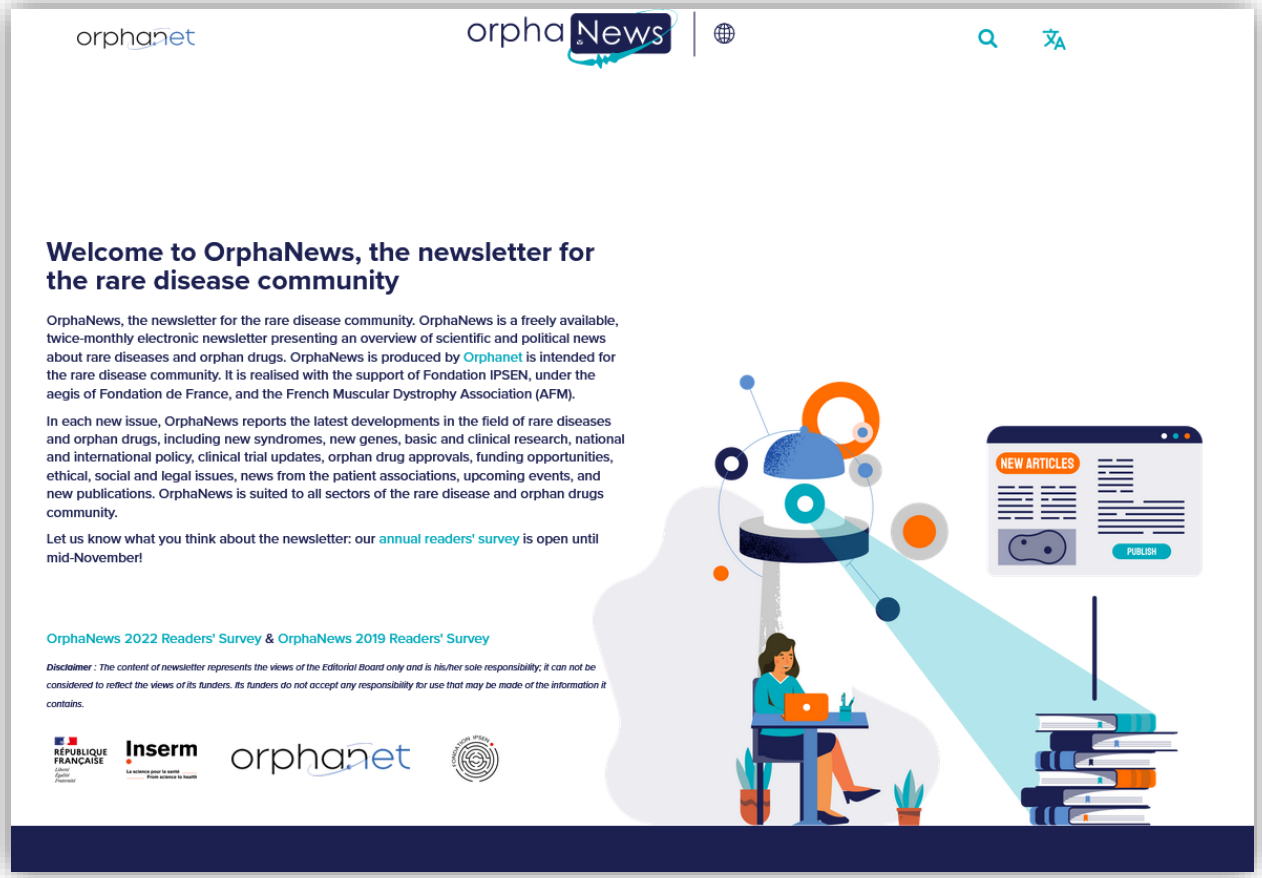
Want to learn more?

www.orpha.net

Charlotte.rodwell@inserm.fr

YouTube

@orphanet



How can you leverage Orphanet resources

- **Basic reference numbers/statistics** : Orphanet/Eurordis 2020 publication on global prevalence of RD
- **Information on a specific rare disease**: Orphanet
- **Find a professional or patient organisation to interview** : Orphanet
- **Keep up to date on priority topics, evolutions**: OrphaNews **Search background of issues**: OrphaNews & Rare 2030 Knowledge Base
- **Massive data sets for analysis for reporting**: Orphadata

Other references

- OrphaNews
- EURORDIS Website
- Rare2030 Knowledge Base
- Rare2030 Recommendations
- European RD Expert Committee's archives
- International Rare Disease Research Consortium website
- RD-Action State of the Art of Rare Diseases 2018 Report
- Nguengang Wakap, **"Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database",** *Eur J Hum Genet* **28,** 165–173 (2020). https://doi.org/10.1038/s41431-019-0508-0
- C Huyard **"How did uncommon disorders become 'rare diseases'? History of a boundary object"** Sociol Health Illn 2009, 10.1111/j.1467-9566.2008.01143.x
- Rodwell & Aymé, **"Rare disease policies to improve care for patients in Europe,** BBA Molecular Basis of Disease 2015, https://doi.org/10.1016/j.bbadis.2015.02.008

Rare disease activities around the world: recent publications

- Brazil Initiatives to promote access to medicines after publication of the Brazilian Policy on the Comprehensive Care of People with Rare Diseases
- Australia: Implementing the National Strategic Action Plan for Rare Diseases - May 2023 status report
- Managing rare diseases: examples of national approaches in Europe, North America and East Asia
- Quebec : Politique québécoise pour les maladies rares
- Evaluation of rare diseases policy performance of OECD countries using MCDM methods
- A civil society view of rare disease public policy in six Latin American countries
- Overview on social security system of rare diseases in China
- A compilation of national plans, policies and government actions for rare diseases in 23 countries
- Review of 11 national policies for rare diseases in the context of key patient needs
- Advancing rare disease policy in Latin America: a call to action
- Asia-Pacific Economic Cooperation launches Rare Disease Action Plan
- Philippines: Rare Disease Act
- State of rare disease management in Southeast Asia

Video: Orphanet – Know the rare for better care

or

Video: ORPHAcodes