Rare 2030

D4.1 Deliverable - Report on the rare disease knowledge base: policies, actors, initiatives

September 2019

WP Participants:

UNEW (WP Lead) ; INSERM ; EURORDIS, ISINNOVA

Deliverable 4.1 Preparation:

- Introduction (p1-9) drafted by UNEW
- Creation of the eight Knowledge Base Summaries – led by UNEW
  - Partners EURORDIS, INSERM, ISINNOVA and ICL all contributed material to the current versions of the Knowledge Base Summaries and/or reviewed content.
- Literature Review sections of each Knowledge Base Summary- elaborated by INSERM

Contents

Introduction

This deliverable consolidates the major outputs of Rare2030 WP4 between the months of January and August 2019, representing the 'building of the knowledge base'. The contents of this deliverable were elaborated for one main purpose: to elucidate the status quo of a very wide range of rare disease-related topics, and to condense these into an accessible and manageable form for the Rare2030 Panel of Experts.

Summary of this Deliverable

The main body of this deliverable is a compendium of all 8 Knowledge Base Summaries created between May and July 2019 specifically to support the activities of Rare2030. Each Knowledge Base Summary correlates to one of the eight subgroups into which the Rare2030 Panel of Experts was loosely divided.

Establishing the Panel of Experts Subgroups

A major focus of WP4 between January and June 2019 was the establishment of the Rare2030 Panel of Experts. This multidisciplinary body involved, at the end of August, **185 stakeholders from 38 countries**. The purpose of this Panel is explained in further detail in the report submitted as Milestone 4.1. The activities of the Panel of Experts (PoE) up until the end of September 2019 were as follows:

- To discuss the status quo of rare disease activities in Europe
- To identify 'past' trends related to the diagnosis, treatment and care of rare diseases
- To propose future trends likely to continue or develop in the coming years, which will have an impact on rare disease diagnosis, treatment and care in 2030 and beyond.

Because the rare disease field is so broad, and the issues likely to impact on diagnostics, treatment and care are many and varied, it was decided that the PoE should in fact discuss the above issues in smaller, more topic-specific subgroups. Eight of these were established, following partner discussions. Despite this division, the topics with which each subgroup is concerned remain very broad, and are actually quite interlinked.

PoE members were invited to self-select the subgroups into which they were enrolled: they did this by completing a short prioritisation form online, which asked them to rank the eight topics in terms of preference. They were informed that they would automatically be enrolled into their top 3 groups, and in the vast majority of cases this is indeed what happened (for a few individuals, membership was limited to only 1 subgroup, at their request, due to time commitments). A few members of the PoE failed to complete their online form: in these cases, the individuals were assigned to 3 subgroups each by the WP leader, and were informed of this: if a change was then requested, this was arranged.

The subgroup enrolment process resulted in eight subgroups populated as follows (the right-hand column shows the number of enrolled PoE members):

Sub-Group 1 – Political and strategic frameworks relevant to rare diseases	93
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Sub-Group 7 – Patient Partnerships	62
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The scope of each subgroup, in terms of the main issues to be grouped under each heading, had previously been agreed and is explained in the Milestone 4.2, as this information forms the basis of the search strategy utilized by INSERM for the literature review.

What is the purpose of the Rare2030 Knowledge Base Summaries?

Given the breadth of each subtopic (e.g. 'Research', 'diagnostics', etc.), and the heterogeneous backgrounds of the PoE members participating in each subgroup, it was necessary to try to stimulate debate **based upon an up-to-date understanding of the status quo**. This could mean an understanding of how different countries in Europe are 'performing' in a given area (e.g. how broad is the newborn screening programme, which countries have national registries for rare disease etc., and/or it could mean an appreciation of major initiatives or projects in this area and the outputs and resources they created. The partners also wished to illustrate the status quo in terms of trends observable from a review of the grey and published literature. It was decided that these various sorts of information would be consolidated as far as possible and presented in the form of a 'Knowledge Base Summary'. The content of this Deliverable, therefore, representing the fruits of 'building the knowledge base', is therefore the full series of Knowledge Base Summaries.

How were the Knowledge Base Summaries created, and what sort of information is presented?

One goal of the Knowledge Base Summaries was to present the results of the literature review performed by INSERM in accordance with the methodology detailed in Milestone 4.2. The search unsurprisingly generated a large number of peer-reviewed publications, which it would be unreasonable to expect any PoE member to read in their entirety. Instead, the INSERM team created a master-list of the individual publications resulting from their search and created a tentative summary of the trends highlighted by those publications. These summaries, entitled 'Results of the Rare2030 Literature Review' are usually approximately 2 pages in length, in addition to which references to papers which elaborate on the trend proposed are given. An example is reproduced here, to explain the concept:

"The variation in reimbursement rates and policies therefore suggests the need and prompts a call for new assessment methods and a different prioritisation of criteria for reimbursement. Our literature review showed a trend towards a re-evaluation of the standards in place challenging the most common cost-effectiveness threshold test, a gradual incorporation of social preferences, an acknowledgement of the importance of disease and socio-economic burden for decision-making as well as a desire to tailor health technology assessments to the specificities of orphan drugs (Annemans et al. 2017; Hughes-Wilson et al. 2018; Iskrov et al. 2016; Nicod et al. 2017; Rizzardo et al. 2019). Others also describe the lack of mutual understanding between payers and manufacturers and lack of transparency for orphan drug prices (Annemans et al. 2017; Waxman et al. 2019)." **(From the KBS for Sub-Group 3)**

The publications which most specifically touched upon trends and which were summarised in the Knowledge Base Summary were grouped together in a 'select bibliography' at the very end of each Knowledge Base Summary. The full list of publications found via the literature review is accessible via a link provided in each Knowledge Base Summary.

The earlier sections of each Knowledge Base Summary were compiled by the WP4 leadership team, usually with the support of partners contributing sections of material on their topics of particular expertise. Each includes the same sort of information:

- An introduction explaining what specific topics have been 'clustered' under each subgroup heading. For example, for subgroup 6 'Integrated social and holistic care' the document begins by explaining what is meant by integrated and holistic care, in this context. Often this section stipulates why the topic holds particular relevance for the field of rare diseases.
- There follows an overview of how and where this topic appears in some of the core EU policy documentation relevant to fare diseases e.g. the Commission Communication on Rare Diseases: Europe's challenges (2008) [679final], and the Council Recommendation on an Action in the Field of Rare Diseases (2009 C151/02). The purpose of this is to show what emphasis has already been placed on each topic and to remind the PoE of what stakeholders such as Member States and the European Commission have already been requested to do in each of these areas. This ostensibly facilitates the process of agreeing whether new policies are required for some topics, or whether in some cases the existing policies are actually sufficient and fit for purpose but perhaps need greater implementation. Where the EUCERD (EU Committee of Experts on Rare Diseases) or Commission Expert Group on Rare Diseases issued topic-relevant Recommendations, these are highlighted.

- Where possible, up-to-date data from the *Resource in the State of the Art of Rare Disease activities in Europe* (SotAR) is used to populate maps and tables illustrating the status quo across Europe for particular issues. This Resource has been sustained in the past by two European Joint Actions for Rare Diseases, the EUCERD JA and RD-ACTION, after being initiated in the context of the Joint Action to support the RDTF/EUCERD Scientific Secretariat, and part

of the activities are currently supported via Rare2030. Essentially, countries are asked to provide information on their national activities pertaining to rare diseases by responding to a structured survey. The questions in this survey are designed to enable countries to provide the data they pledged to submit when adopting the *EUCERD Recommendations on Core Indicators for Rare Disease National Plans and Strategies* in 2013. Across the 8 Knowledge Base Summaries created in the past couple of months for Rare2030, the following images/tables were compiled from SotAR data:

- Status of National Plans/Strategies (NP/NS) in EU/EEA countries
- Existence of dedicated bodies to oversee NP/NS implementation
- Countries with a national registry for rare diseases
- Number of OMPs with a European Union marketing authorisation available in each country
- Number of genes tested in each country (map actually generated directly from Orphanet data, not the SotAR)
- Number of diseases included in each country's newborn screening programme
- Countries with helplines for rare diseases
- Date of Rare Disease National Alliances' creation (based on SotAR)
- Number of HCPs serving as full members in the ERNs (cumulatively), per country
- Policies for development and use of Clinical Practice Guidelines for rare diseases

- Key projects or initiatives of relevance to the rare disease subgroup topic are summarised. To keep the documents reasonably short, such summaries sometimes take the form of a table of relevant initiatives and their outputs. The goal is really to show which groups and projects have been looking/are looking at these issues, and point readers towards any major outputs, such as reports, recommendations, or other forms of guidance. The purpose here is to ensure optimum dissemination of the tools and resources already available in the community, which should a) encourage PoE members to make use of these in their wider work but also b) help to assess whether new resources are necessary, by allowing the PoE to identify gaps in such resources which could be addressed by future policies
- Relevant political developments in the rare disease or complementary fields are highlighted, where possible. For instance, the discussions around revision of the Orphan and Paediatric legislation are summarised, as are the efforts to establish European-level HTA procedures.
- Key discussion questions were included near the start of each Knowledge Base Summary (see below)

How have the Knowledge Base Summaries been used to-date?

The documents were disseminated to each subgroup ahead of their first Teleconferences. The PoE members were informed ahead of time that the first (of two) Teleconference would be devoted to a quick review of the Knowledge Base Summary, with the goal of illustrating the sorts of issues falling under the scope of that particular subgroup. The PoE members were also informed that much of this

first TC would be spent debating the key discussion questions proposed on (usually) page 2 or 3 of each document. (The table below shows the full set of key discussion questions). This hopefully gave the members a chance to consider the issues and prepare some responses to those key discussion questions.

Sub-Group 1 – Political and strategic frameworks relevant to rare diseases	▪ Do we need a new action plan or EU policy framework for rare diseases? (Should the 'founding' policy documents -primarily the 2008 Commission Communication and 2009 Council Recommendation- be supplanted by new 'soft legislation' or do they simply require more effective and meaningful implementation? ▪ How do we sustain -or revive- momentum around the implementation of National Plans and Strategies for Rare Diseases? ▪ How could the European Union pave the way, strategically and practically, towards the common goal of more research, more treatments, and better quality of life for people living with RD (and thus contribute to the achievement of health-related UN Sustainable Development Goals)
Sub-Group 2 – Data collection and utilisation	▪ What actions around collecting/using data will yield the greatest progress for the field? ▪ Many activities are ongoing to make various sorts of data more interoperable/linkable: what are we missing? Where should the next emphasis (under this vast topic) be focused?
Sub-Group 3 – Accessibility and Availability of OMPs and Medical Devices	▪ How can we stimulate greater development and access to medical devices for people with rare diseases? ▪ Is the current legislation concerning OMP access fit for purpose? Where could improvements be made? ▪ What practical actions (at national and European level) would increase the accessibility and availability of OMPs
Sub-Group 4 - Basic, Clinical, Translational and Social Research	▪ How far have EU countries addressed the requests in the *2009 Council Recommendation on an action in the field of rare diseases* ▪ How do we accelerate the rate of progress for basic, clinical, translational, and/or social research? *(Please make comments on each individually, if appropriate, or else identify something which might address all)* ▪ What would be a 'game-changer' for rare disease research?

Sub-Group 5 – Diagnostics	▪ What barriers exist today to receiving an accurate diagnosis? ▪ What practical actions could address the European heterogeneity and resulting inequalities around diagnosis? Are there any topics which warrant new or updated warrant EU-level (or other supranational level) guidance, for instance? How might we improve diagnostics for rare diseases?
Sub-Group 6- Integrated Social and Holistic Care	▪ What are the biggest barriers preventing people with rare diseases and their carers from receiving holistic care? ▪ What concrete good practices promote more integrated, holistic care for people living with rare diseases? ▪ How do we build momentum in advancing this topic? At national and at European/International level?
Sub-Group 7- Patient Partnerships	▪ What does true 'patient partnership' mean? How best can patients be engaged and empowered to address rare disease issues? ▪ Are current efforts to encourage partnerships with rare disease patients sufficient? What are the bottlenecks? How can they be overcome?
Sub-Group 8 – Access to Healthcare	▪ What are our most powerful 'tools' or 'assets' to improve access to high quality healthcare for every person afflicted with a rare disease in Europe? ▪ What do you feel are the main achievements of European Reference Networks to-date, in terms of increasing access to high quality healthcare? What 'next steps' would yield the greatest progress ▪ What practical actions –at any level: local, regional, national, European and/or global) would yield the most meaningful results across this topic as a whole? Who should do what, and how?

The run-through on each teleconference highlighted the literature review section of each Knowledge Base Summary and used this to introduce the second part of the teleconference, which was dedicated to thinking back over the past few decades and trying to encourage participants to identify major moments of change and key trends they have noted. Identification of a possible trend or moment of change would then be followed by a discussion on what might have been driving that trend or change, which actors are/were involved, etc.

In short, the purpose of each Knowledge Base Summary was:

1. To act as 'food for thought' and bring all stakeholders onto the 'same page' at the start of this process
2. By illustrating where we are and what we have, to help the PoE members begin to analyse the needs of the community and the trends and changes which have led to this status quo.

It was emphasised, both by email and on the teleconferences themselves, that these Knowledge Base Summaries should be considered dynamic documents, i.e. works-in-progress. They are included as the centrepiece of this Deliverable on that basis.

Next steps for the Knowledge Base Summaries

As above, the documents were developed very quickly, to enable the PoE to commence operations and generate a sufficient number of trends for the next steps of the foresight process. They will be revised in the Autumn and early 2020, in order to produce more refined documents:

- Countries were asked to contribute their data to the SotAR in February or March of 2019. A few countries had not completed the questionnaire by the May deadline, and thus could not be included properly in the analysis used to populate the maps and tables described above. They will be contacted once more and encouraged to contribute their data, to be included in the updated Knowledge Base Summaries. Furthermore, a few countries provided data that in places could be open to interpretation; in these cases, the WP4 lead will follow-up with the data contributing committee for the countries concerned to clarify any areas requiring this. All of this will result in slightly amended maps/tables.
- During the 18 teleconferences conducted with the PoE sub-groups between June and September, several suggestions for additional content were received: panel members proposed reports, policies, pieces of legislation etc which could enrich the Knowledge Base Summaries and make these documents more comprehensive. These suggestions will be reviewed and incorporated accordingly to the revised documents
- Given the tight timelines involved in this first stage of the PoE activities, there was insufficient time for some of the Rare2030 partners to comment on the Knowledge Base Summaries and provide concrete input: this will be redressed during the next phase of activities, as targeted messages will be sent to each partner by the coordinator, requesting thorough review to identify missing sub-topics or resources.

Documents complimenting the Knowledge Base Summaries (and by extension, this Deliverable)

The 18 teleconferences generated rich debate amongst the multistakeholder PoE members. The major points of discussion and key comments raised (either vocally or via the chat function on Zoom) were captured on the 8 Shared Working Documents created for this purpose. Each Sub-Group was given one dedicated link to a GoogleDocs document, upon which all members were free to record the following types of information:

- Their responses to the key discussion questions;
- Their past trends (which could be annotated with proposed drivers and comments);
- Any nation-specific trends;

- And future trends anticipated.

In many cases, PoE members opted to contribute to these GoogleDocs documents directly (especially when unable to join the teleconferences). In addition however, the 18 teleconferences were recorded and Minutes were made for each: the WP4 lead then worked through each set of Minutes methodically, to populate the GoogleDocs documents with the comments made during the teleconferences. In this way, the WP was able to capture all feedback from the 8 sub-groups. That material will be made available as follows:

- The responses to the key discussion questions will be added as annexes to each of the revised Knowledge Base Summaries
- The tables of past trends will be curated and uploaded to the Rare2030 website, sub-group by sub-group. Meanwhile, the content will be incorporated to Deliverable 4.2 in Autumn 2019, in a synthesised form.
- The future trends tables will be reviewed by the Rare2030 partners and key overarching trends identified, to be included in a survey for the PoE (under Task 4.4)

Rare2030 Knowledge Base Factsheet

Political & strategic frameworks relevant to rare diseases

Since the 1990s, rare diseases have been a policy priority at both European Union (EU) and Member State (MS) level. A number of countries led the way in the decade leading up to the first European legislative text concerning rare diseases (the Orphan Medicinal Product Regulation of 16 December 1999): Sweden, for example, established the first centres of expertise for rare diseases in 1990 and a rare disease database and information centre in 1999. Denmark established an information centre in 1990 and then centres of expertise for rare diseases in 2001. In Italy, a decree on rare diseases came into force in 2001. And in France, Orphanet was established in 1997.

In 2008 and 2009, two landmark policy documents ushered in a major period of change: the **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]** and the **Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02**. Throughout the period 2010-2016, two successive Expert Groups for Rare Disease provided a space for MS representatives, patients, Industry, and independent experts to join the European Commission in exploring avenues for cross-country collaboration around many diverse aspects of the broad 'rare disease' topic. These Groups, the EUCERD and the Commission Expert Group on Rare Diseases, were supported in their activities by two dedicated EU Joint Actions: the EUCERD JA and RD-ACTION, and issued 8 sets of topically-oriented Recommendations (see end of document) representing high-level ('soft law') commitments each country would strive to implement.

There have been several important successes for the European rare disease community in recent years, not least the realisation –after a decade of planning and preparation- of European Reference Networks (ERNs), which have a particular relevance for the rare disease field. However, there is no longer an expert group for rare diseases, and no Joint Action to allow cross-country discussion and collaboration on the full range of issues beneath the 'rare disease' heading. No dedicated forum exists to advance multistakeholder dialogue, to allow a broad analysis of the status quo, or to facilitate the search for shared solutions to common challenges around the provision of diagnosis, treatment and care for people with rare diseases. New bodies have been established with broader remits, such as the Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases (SGPP), the EU Health Policy Platform, and the Expert Group on Health Information; however, in each of these, 'rare diseases' sits amongst many other health priorities. The ERN Board of MS is a

very important stakeholder body, but its mandate specifically centred on ERNs (as opposed to all issues under the RD 'spectrum'.)

For further background on the European Policy frameworks for rare diseases, and all of the above, please see the Overview Report for the State of the Art of Rare Disease Activities in Europe.

Guiding Questions for Panel of Experts Discussion – to support the identification of Trends and drivers of change

1. **Do we need a new action plan or EU policy framework for rare diseases? (Should the 'founding' policy documents -primarily the 2008 Commission Communication and 2009 Council Recommendation- be supplanted by new 'soft legislation' or do they simply require more effective and meaningful implementation?**

2. **How do we sustain -or revive- momentum around the implementation of National Plans and Strategies for Rare Diseases?**

3. **How could the European Union pave the way, strategically and practically, towards the common goal of more research, more treatments, and better quality of life for people living with RD (and thus contribute to the achievement of health-related UN Sustainable Development Goals)?**

Concept of a national plan/strategy for rare diseases

An essential component of political and strategic frameworks for RD is the topic of National Plans or Strategies (henceforth NP/NS). The Council Recommendation of 2009 recommended that MS elaborate and adopt a national plan or strategy for rare diseases "as soon as possible, preferably by the end of 2013 at the latest". This document recommended that these NP/NS should strive "to ensure that patients with rare diseases have access to high-quality care, including diagnostics, treatments, habilitation for those living with the disease and, if possible, effective orphan drugs". They should

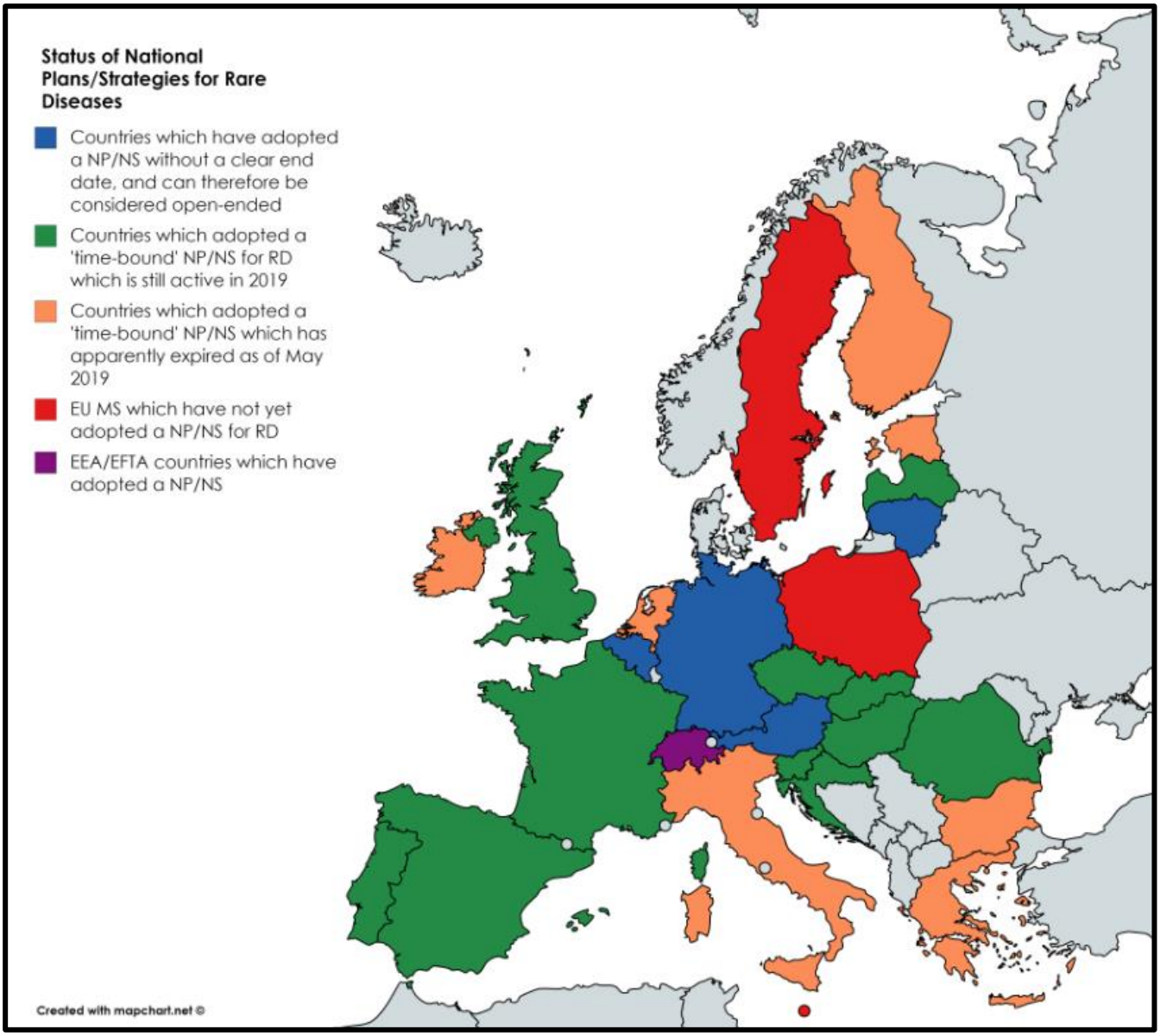
- be aimed at "at guiding and structuring relevant actions in the field of rare diseases within the framework of their health and social systems;"
- "take action to integrate current and future initiatives at local, regional and national levels into their plans or strategies for a comprehensive approach;"
- "define a limited number of priority actions within their plans or strategies, with objectives and follow-up mechanisms;"

To support countries in this activity, the EUCERD adopted a set of *Recommendations on Core Indicators for Rare Disease National Plans and Strategies*. The groundwork for this document was led by the EUROPLAN project and the EUCERD Joint Action between 2008 and 2013. The overall objective of the Recommendations was to enable the capturing of relevant data and information on the process of planning, implementing and monitoring of NP/NS. The resulting Core Indicators highlight important components for a robust and comprehensive NP/NS and their adoption was accompanied by a commitment from Member States to regularly collect this information, based around a number of fundamental questions.

Status quo of national plans/strategies for rare disease across Europe (May 2019)

The data for the following sections comes from the *Resource on the State of the Art of Rare Disease Activities in Europe*. Data for a number of countries is awaiting update; **therefore, these figures may change slightly in the coming months.**

At Member State level, there is a great heterogeneity in the state of advancement of national policies, plans or strategies for rare diseases. This map shows the status quo as of May 2019.



Summary of the status quo:

- 25 European MS have adopted a NP/NS for rare diseases at some stage
- Most countries adopted a NP/NS with a specific chronological span i.e. are time-bound
- Of the 20 MS which adopted time-bound NP/NS at some stage:

- 1 (Austria) has since become open-ended (see below)
- The following 7 countries adopted time-bound NP/NS which, as of May 2019, appear to have ***expired*** and not to have been replaced/renewed: **Bulgaria; Estonia** (a RD Development Plan under the main National Health Plan apparently expired in 2017)**; Finland** (though a new plan is pending approval, after the first plan expired in 2017)**; Greece; Ireland; Italy; Netherlands**
- The NP/NS for the following 12 countries are apparently still active in May 2019: **Croatia; Czech Republic; France; Hungary; Latvia; Luxembourg; Portugal; Romania; Slovak Republic; Slovenia**; **Spain; UK**

- 'Open-ended' NP/NS: The following countries adopted NP/NS which were not time-bound: **Belgium, Cyprus, Denmark, Germany, Lithuania**. A 'new' addition to this category is **Austria** (which adopted a first NP for the years 2014-18 and since the beginning of 2019 extended this on an open-ended basis, with time-frames for specific actions);

- Three EU MS appear not to have adopted a NP/NS by the end of May 2019: **Poland, Malta and Sweden**

In terms of Non-MS EEA countries and Switzerland: Switzerland has also adopted a National Plan for Rare Diseases.

Implementation of National Plans/Strategies for Rare Diseases:

The Resource on the State of the Art of Rare Disease Activities in Europe (SotAR) collects information from all EU MS via a structured questionnaire. This questionnaire is designed to collect the data to which countries committed to provide via the 2013 Recommendations on Core Indicators (see above). Several questions relate not only to the existence of a NP/NS but to the level of support (financial, in particular) behind the plan or strategy, and the existence -and level of functioning- of a dedicated body to oversee the implementation and/or evaluation of the plan.

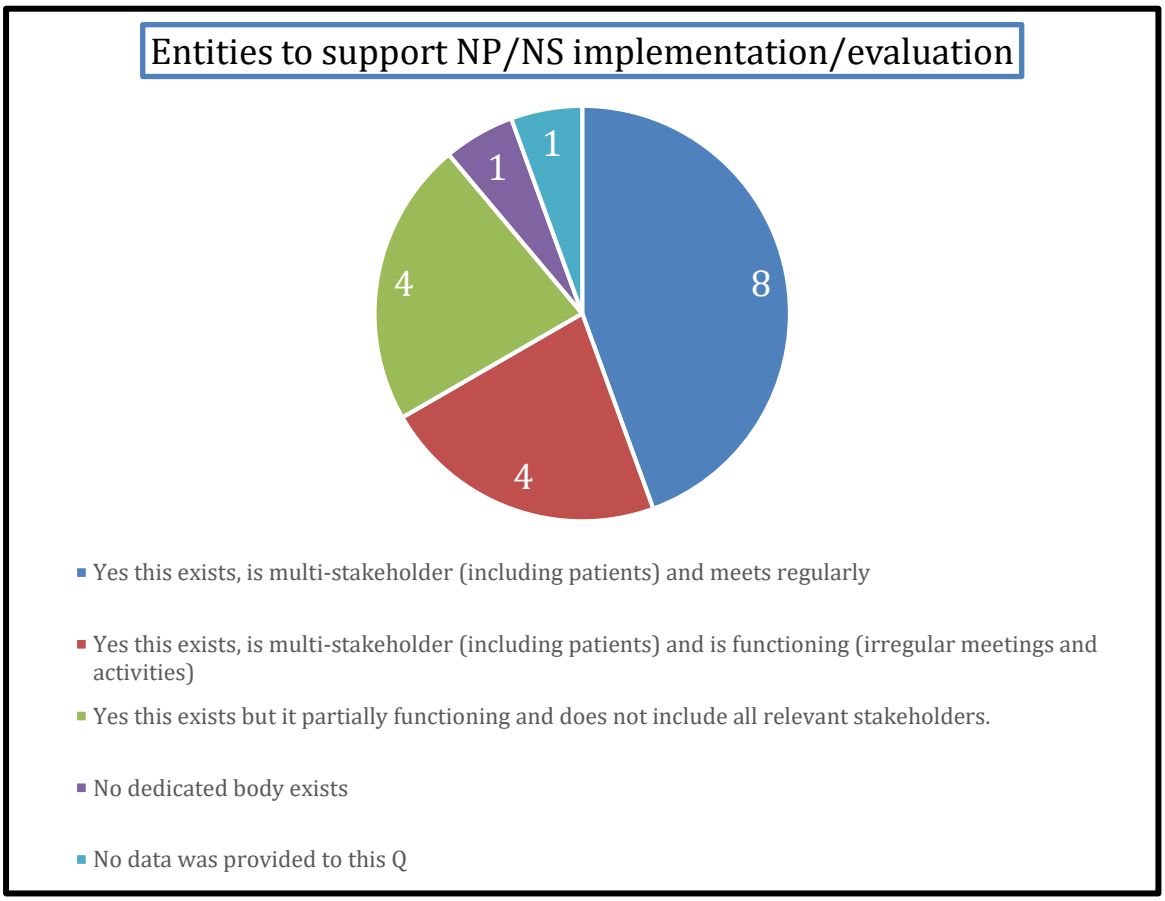
On the question of **dedicated funding for the NP/NS**:

- Many countries noted that funding was available for specific actions mentioned within the NP/NS; however
- Very few countries have dedicated funding set-aside to fund the NP/NS itself, comprehensively:
- Of the 18 EU MS with a still-active NP/NS:
  - Only 4 report having dedicated budgets to strategically support the NP/NS implementation:
    - Belgium (stipulated 15M Euros per year)
    - France (funding dedicated to the CoR – no figure provided)
    - Romania (stipulated just over 1.009 Million Euros per year)
    - Slovak Republic (stipulated 240,000 Euros per year)

It is difficult to obtain accurate and unequivocal data on the extent to which countries are investing to support their NP/NS implementation.

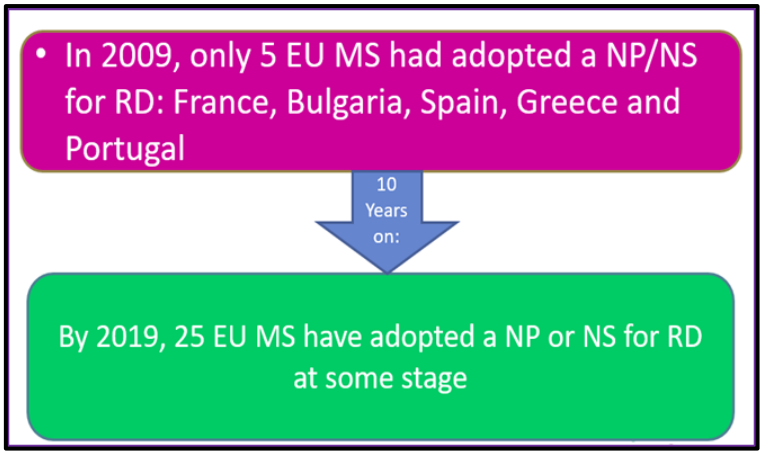
The EUCERD *Recommendations on Core Indicators for Rare Disease National Plans and Strategies* place emphasis on the need for a **dedicated multistakeholder body to support NP/NS activities**. The precise function of such a body depends upon the level of maturity of the national activities, but could include the following: shaping the development of a NP/NS (i.e. overseeing the drafting process); overseeing the NP/NS implementation, once adopted; and evaluating existing or past NP/NS to support the generation of new Plans or Strategies. The Core Indicators, whilst not delving into the granularity of possible roles for such a body, nonetheless emphasise that such entities should be multistakeholder (including patients, as well as policy-makers, academics, clinicians, and other relevant experts) and be *functional* as opposed to a 'token' body (e.g. should meet regularly).

The figure below shows the status quo in the 18 MS with **currently-active** NP/NS:



Evolution of national plans and strategies for rare diseases – European trends over the past decade

- As of 2009, 5 EU MS (Bulgaria, France Greece, Portugal and Spain) had adopted a national plan/strategy for rare diseases.
- By 2019, 25 EU MS had adopted a national plan/strategy for rare disease at some stage; this increases to 26 if one includes all EEA countries and Switzerland
- France is now in its 3rd National Plan



However: the number of expired NP/NS which have yet to be renewed is slowly increasing: as of July 2018, 6 time-bound plans had expired without replacements (and this included Austria and Lithuania, both of which are now classed as open-ended), whereas currently the figure is 7. Only 1 NP/NS for which a set time period was established appears to reach beyond 2020 (Luxembourg). It is often the case that evaluating and renewing NP/NS is a lengthy process, leaving countries without active plans or strategies for extended periods of time. **At this crucial juncture, it is imperative that a renewed focus is placed on the National Plans and Strategies for Rare Diseases in Europe**, in order to:

a) evaluate the extent to which existing NP/NS have actually been implemented in European countries;
b) encourage countries to adopt their 2nd and 3rd NP/NS, to maintain the much-needed national focus and momentum on rare diseases; and
c) define the key objectives and content for this next generation of NP/NS, by identifying good practices which have yielded results in particular countries/regions, assessing their transferability to other countries/situations, and agreeing *new* issues and topics which should be addressed via robust Plans and Strategies for the coming years.

(For a schema showing adoption schedule for EU MS, please see below)

What other policy areas influence rare diseases and rare-disease policy-making?

Rare disease policy-making lies at the crossroads of a multitude of policy areas, rendering the development of comprehensive policies challenging. Due to the diverse nature of conditions included under the RD definition, many policies and programmes include rare diseases. For example, RD are present in cancer policies as rare cancers belong to both categories (31): indeed, for the area of rare cancers, the main challenge is to ensure that rare cancers do not fall between the two stools of 'rare diseases' and 'cancers'. Following on from the 2009 *Commission Communication on an action against cancer*, the European Partnership on an action against cancer (EPAAC), worked to raise awareness of the challenges faced by rare cancers and to insist on the need for tailored policies. The work on rare cancer policy has continued under the Joint Action on Rare Cancers (2016) which, amongst other work streams, strives to build a coherent policy framework for the management of rare cancers in Europe,

and notably structures its work around the two rare-cancer focused European Reference Networks (ERN EURACAN, ERN PaedCan). The global effort towards universal healthcare is also a major influential factor for rare disease policy and the emphasis on equity, quality, responsiveness, efficiency, resilience should very likely contribute to a better inclusion of rare diseases in national health policy planning (cf. UHC2030).

A number of disability policies also include rare diseases and shape part of the rare disease political framework (33); for example, the European Union disability policy includes measures for rare disabilities (EURORDIS 2011). Genomic and precision medicine programmes and initiatives (2; 3; 18) are also policy areas of interest to rare diseases. In addition, the specificities of rare diseases, implying the need for exchange of information and innovative data management/discovery techniques, make eHealth policies and the legislation around the use of artificial intelligence for medical and healthcare purposes, critical. This is particularly important as regards to the development of tools and services that have a high potential of promoting rare disease research, care and treatment opportunities (8).

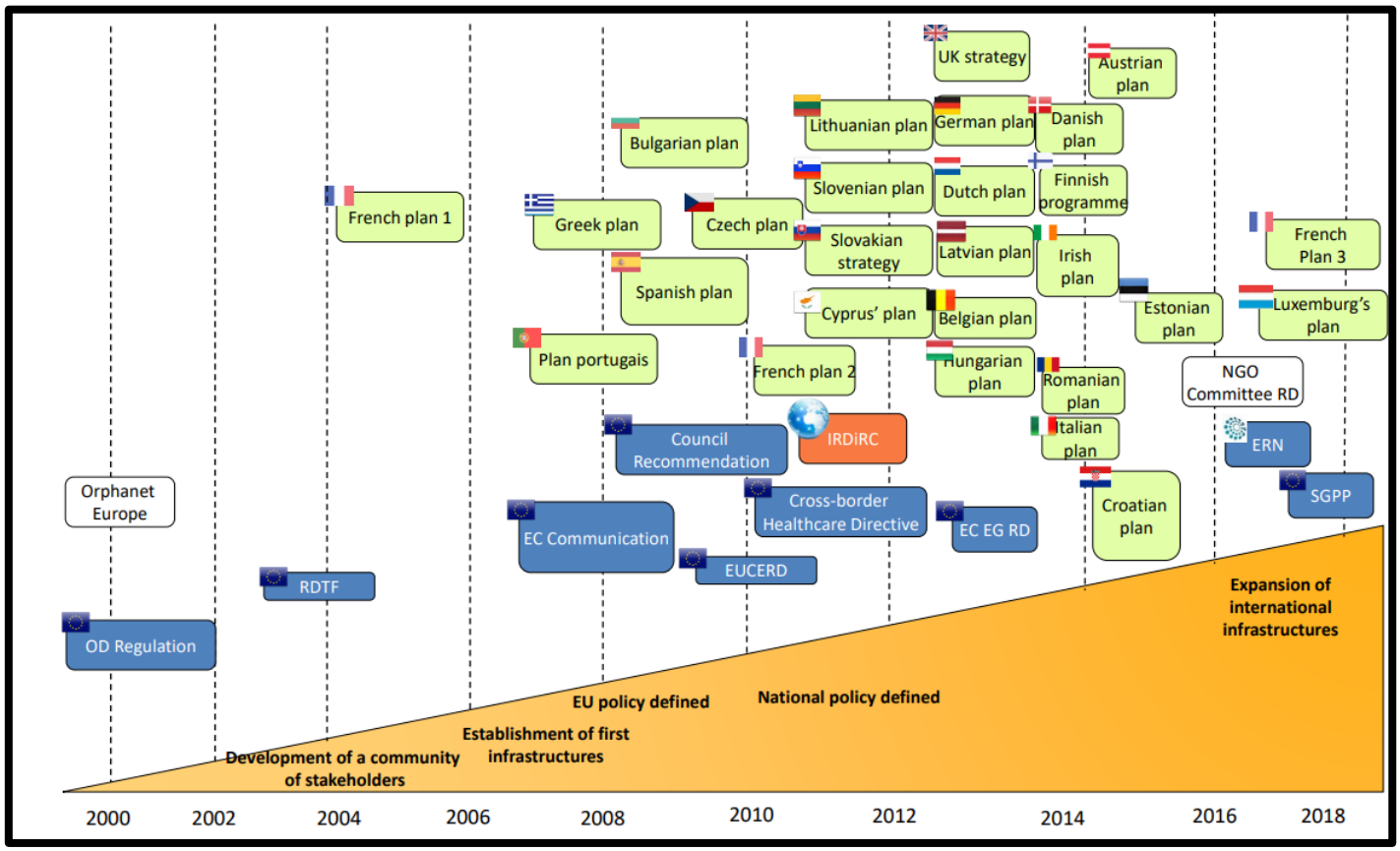
In addition, the quality of healthcare and policy actions for rare diseases is clearly linked to the global and national economic context and larger economic policies, and thus is significantly influenced by budget constraints, which might act as a hurdle to rare disease policy development (9; 10). In the future, we are sure to see a mutual influence and interaction between rare disease policy and the UN Sustainable Development Goals, which are both concerned with ensuring that no citizen of the world is left behind.

Results of the Literature Review: Observed Trends

Observed trends in Europe

Firstly, the most striking trend at the European level is the **emergence of rare diseases as a concept** (13), and the **official recognition of the challenges in the field of rare diseases**, leading to the **development of a European policy framework with an impact on the emergence of rare disease policies in Member States**. Indeed, the first legislative text in the field of RD, the Orphan Medicinal Product Regulation of 1999, was followed by the creation of the Rare Disease Task Force in 2004 and the multi-stakeholder drafting of the two first keystone documents at European level: the Commission Communication in 2008 and the Council Recommendation in 2009. These texts, and the policy support mechanisms provided in the form of the EUCERD/Commission Expert Group on RD and associated Joint Actions, have proven to be critical in e**nhancing policy change and the adoption of RD legislation at EU and Member State level** (20; 21). They have **provided the rare disease field with increased visibility**, the assurance of support and guidance at the EU level, and a basis for cooperation. Furthermore, the **European Commission has actively shaped the policy field** and the implementation of legislation by maintaining, and even increasing, the priority level of the issue over the years (21,28) and through its active **financial and administrative support of projects dedicated to the advancement of RD research, information and structuration of networks**. Some authors even mention a process of harmonisation taking place and **a certain relative policy coherence** in the region with common

definitions and legislations as well as **transnational actions** (16; 30). The European Commission has also contributed to the **structuration of rare disease research policy** via its EU Framework Programme for Research and Innovation. Indeed, under the Seventh Framework Programme for research, from 2007 to 2013, €620 million was allocated to over 120 collaborative research projects on rare diseases, and the EU commitment on this path continues with the Horizon 2020 programme (5; 7). This trend continued with **European support to the International Rare Disease Research Consortium and its ambitious goals** (from 2012) with the support of the EC and the NIH.



Nevertheless, despite this relative unity, **differences exist between Member States and some are further ahead of others in terms of national implementation of rare disease legislation** (21; 28). For instance, **France is often cited as a model,** having adopted the first comprehensive national plan for rare diseases in the world in 2004; today, France is implementing its third national plan and is seen as an instrumental actor and a leading figure for European policy on this matter (5; 17; 28; 30). This suggests the existence of a **trend of rare disease policy emerging as the result of exchange of experiences at national level, notably through a certain number of fora at European level**, such as the Rare Disease Task Force, the European Union Committee of Experts on Rare Diseases, the Commission Expert Group on Rare Diseases, and the current Steering Group on Prevention and Promotion of Health. The supportive role of the EC has facilitated this trend, as has the **willingness of stakeholders, including national competent authorities, to share experiences**.

Moreover, over the years more space has been allocated for the **involvement of rare disease patients and advocacy groups in policy decision-making**. Local stakeholders are cited and recognised as key

players and **drivers for the implementation of policies** (22). Indeed, the role of patients and patient advocates in the political and economic system over time has evolved (35) and they were increasingly included in strategic, multi-stakeholder committees and expert groups such as the RDTF, EUCERD, and Commission Expert Group on RD (12; 19; 21). Their role is gradually becoming more central to the decision-making process, **making the patient voice integral to the policy-making process** (1). This has ultimately led some advocates to play the role of broker between patient organisations, national and supranational structures, the media and health services (35).

Observed trends at the global level

For a summary of national -and regional- policy frameworks beyond Europe, see the 2018 Overview Report for the State of the Art of Rare Disease Activities in Europe (pages 23-45).

When examining supranational bodies and their approach to rare diseases, one can note the **growing interest and official recognition of the challenges posed by rare diseases,** which are now included in the **health priorities of global entities such** as the WHO. Examples include the recent mention of rare diseases at the 71st World Health Forum and the **establishment of a NGO Committee for Rare Diseases at the United Nations**. Moreover, **actors in regions such as Latin America and Asia-Pacific are currently in the process of developing their national and regional frameworks,** exchanging experiences in the process. Nevertheless, regions like Russia or Africa lag behind even within the more cohesive regions, thus a **discrepancy regarding rare disease definitions and implementation of policies is observable** (16; 21; 26).

On a global scale, some authors also highlight the trend of the **emergence of collaborative networks** in the last ten years. Such **organisational models tend to embrace a wide range of stakeholders** such as decision-makers, healthcare professionals, patient organisations and private entities such as biopharmaceutical laboratories. This multidisciplinary approach allowing a variety of perspectives to meet has gained momentum recently and seems to **garner support as a means to inform policy-making.** In addition to such horizontal networking, a **vertical form of networking** has been highlighted, with links made between players at the local, regional, national and supranational level (15).

Linked to such phenomena is the fact that **organisations have displayed a tendency to unify and gain an international dimension in order to increase their influence at the international level** (5). Indeed, it is stated that the **specificities of rare disease policy require actions at the highest institutional level** and a maximum level of international cooperation in order to set the agenda and promote action in the field (6). There seems to be a growing emphasis on *regional* collaboration, as evidenced by transnational initiatives, which help to promote the case for rare diseases in areas such as the Asia-Pacific region (16; 36).

A pertinent element of rare disease planning, particularly with reference to national plans, is the attention paid to the **sustainability of the policies and systems elaborated and adopted**. Not only does the model need to ensure equity, fairness and accessibility for all, but the plan/strategy/policy must be manageable, to put as little constraint on the budget as possible and guarantee its resilience over time (see above) (9; 10).

Finally, the **importance of societal values** when devising rare disease policy is evident from the literature. This type of discourse shifts the balance to the population's rather than the policy-makers' preferences and embraces the citizens' perspective and priorities for health decisions (Shirizzo et al; 25). It leads to distinctive results regarding priority rankings and has significant consequences for rare disease policy-making.

For consideration by the Panel of Experts: potential Trends for this topic and possible drivers of change

Potential **Trends:**

- Harmonisation of the concept and definition of a RD
- International recognition of RD challenge
- Multi-stakeholder policy-making, with EC support
- Patients/advocacy groups as brokers in policy making process
- Regional collaboration (Europe, Asia Pacific, South American)
- Consideration for sustainability of healthcare systems/resilience of healthcare systems
- Undiagnosed disease networks/ approaching RD from the challenge of finding a diagnosis

  ...

Potential **drivers:**

- European Commission prioritisation of RD as a policy priority & support to multi-stakeholder fora
  - Establishment of common policy framework
- International recognition of RD challenge
- Experience/best practices exchange: information exchange
  - Influence of the USA Orphan Drug legislation on other world regions
  - Influence of France's 'pioneer' experience
  - Influence of European example on other world regions
- Societal values: caring for all members of society
- Patients as brokers in policy making process and actors of change
- …

References from the Rare Disease Field Literature Review

Full list of articles/publications found in the literature review:

- https://docs.google.com/spreadsheets/d/1SRXASsFiD9sdQz286SVo860XdTpGaOIncyjIhGphULI/edit?usp=sharing

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Knowledge Base Summary

Data Collection and Utilisation

Contents:

Introduction to the topic: How can data can support advances in the diagnosis, treatment and care of rare disease?

The topic of 'data collection and utilisation' is extremely broad. This document therefore contains *select* (i.e. far from exhaustive) summaries of the status quo in a few key areas, including registration, inventorying and coding of diseases, data interoperability, and ethical legal and social issues (ELSI). Other aspects of the topic, for instance those more relevant to diagnostics, will appear in alternative subgroup documents.

Data on any rare condition is extremely precious. No single country will see a sufficient number of patients with any very rare disease to fully understand the condition, in terms of its epidemiology (e.g. how many cases exist in any given population), the range of symptoms observed, the development of the disease over time, and the likely outlook for newly-diagnosed patients. Capturing structured data, based upon field-appropriate standards and ontologies, is particularly important in diagnostics (see

Knowledge Base Summary on Diagnostics). Rare disease patient data, especially if collected in a standardised form, takes on greater power to serve what one may loosely term 'secondary purposes', particularly in the case of registry data.
These topics appear in some of the 'foundational' European policy documents in various ways:

Coding and Inventorying:

Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final] Section 3.1. Improving Recognition and Visibility on Rare Diseases:
"To improve diagnosis and care in the field of rare diseases, appropriate identification needs to be accompanied by accurate information, provided and disseminated in inventory and repertory formats adapted to the needs of professionals and of affected persons.[..] The Commission therefore aims to put in place a thorough coding and classification system at European level…"

Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02.
II. ADEQUATE DEFINITION, CODIFICATION AND INVENTORYING OF RARE DISEASES

- Use for the purposes of Community-level policy work a common definition of rare disease as a disease affecting no more than 5 per 10 000 persons.
- Member States (MS) were asked to "ensure that rare diseases are adequately coded and traceable in all health information systems"
- MS were also asked to "Contribute actively to the development of the EU easily accessible and dynamic inventory of rare diseases based on the Orphanet network and other existing networks as referred to in the Commission Communication on rare diseases"

In 2014, the Commission Expert Group on Rare Diseases adopted a ***Recommendation on Ways to Improve Codification for Rare Diseases in Health Information Systems***

In 2017 and 2018, RD-ACTION – the EU Joint Action for Rare Diseases- generated several practical outputs to build upon this Recommendation and support countries in implementing the OrphaCode.

Registries:

Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]
Section 5.11. "Registries and databases constitute key instruments to increase knowledge on rare diseases and develop clinical research … A key issue will also be to ensure the long-term sustainability of such systems, rather than having them funded on the basis of inherently precarious project funding."

The Council Recommendation of 2009 asked Member States to "Consider supporting at all appropriate levels, including the Community level, on the one hand, specific disease information networks and, on the other hand, for epidemiological purposes, registries and databases, whilst being aware of an independent governance"

One of the eight sets of Recommendations adopted by the EUCERD and Commission Expert Group for Rare Diseases was dedicated to registration and patient data collection. The ***EUCERD Recommendations on Rare Disease Patient Registration and Data Collection*** (2013) remain an important compendium of high-level principles for judicious creation and operation of registries.

NB. Naturally, there is an ***extensive*** list of policies, Regulations and Directives with a bearing upon this broad topic which, whilst not RD-specific, should obviously be considered 'core' to this subject; for instance

- the General Data Protection Regulation ((EU) 2016/679) which came into force in May 2018
- the Directive on the Application of Patients' Rights in Cross-border healthcare (Directive 2011/24/EU), from the perspective of data moving across borders
- the 2018 *Commission Communication on enabling the digital transformation of health and care in the Digital Single Market; empowering citizens and building a healthier society*

Guiding Questions for Panel of Experts Discussion – to support the identification of trends and drivers of change

1. **What actions/approaches around collecting and using data will yield the greatest progress for the rare disease field?**
2. **Many activities are ongoing to make various sorts of data more interoperable/linkable: what are we missing? Where should the next emphasis (under this vast topic) be focused?**

Rare Disease Registries

Registries have traditionally been viewed as an excellent way to collect and pool patient data. The WHO defines a registry as "a file of documents containing uniform information about individual persons, collected in a systematic and comprehensive way, in order to serve a pre-determined scientific, clinical or policy purpose". Registries collect information on patients afflicted by a particular disease or group of diseases. By combining data on as many patients as possible, at the regional, national, European or global level, the power of the data increases exponentially. Registries, particularly when used by many different centres, enable researchers to accrue a so-called 'critical mass' of patients which would often otherwise be impossible.

What purposes can Registries serve?

- By collecting data over a long period of time, registries can elucidate the natural history of a disease (i.e. how the symptoms develop and progress, what the prognosis might be, etc.);
- Registries can focus upon the epidemiology of the disease i.e. how the disease is caused/what are its origins and its impact in any given population (including its rarity). Such epidemiological information is very valuable in assessing disease threats and informing the appropriate planning of health services;
- Registry data can demonstrate the efficacy of different management and therapeutic options, presuming information on treatment regime and clinical outcomes is captured.
- Registries -if established in a certain way - can support the post-marketing surveillance of (conditionally) approved orphan medicinal products
- The correlation between certain genetic mutations and corresponding clinical presentation (phenotype) may be elucidated by registry data. Sometimes patients with the same condition

and the same genetic mutation exhibit very different symptoms and experience the disease with varying severity: only by capturing this information routinely and robustly are researchers better able to understand rare conditions and their prognoses by correlating patients' genotypes and phenotypes (in other words, understanding how different combinations of genetic anomalies result in particular clinical presentations).

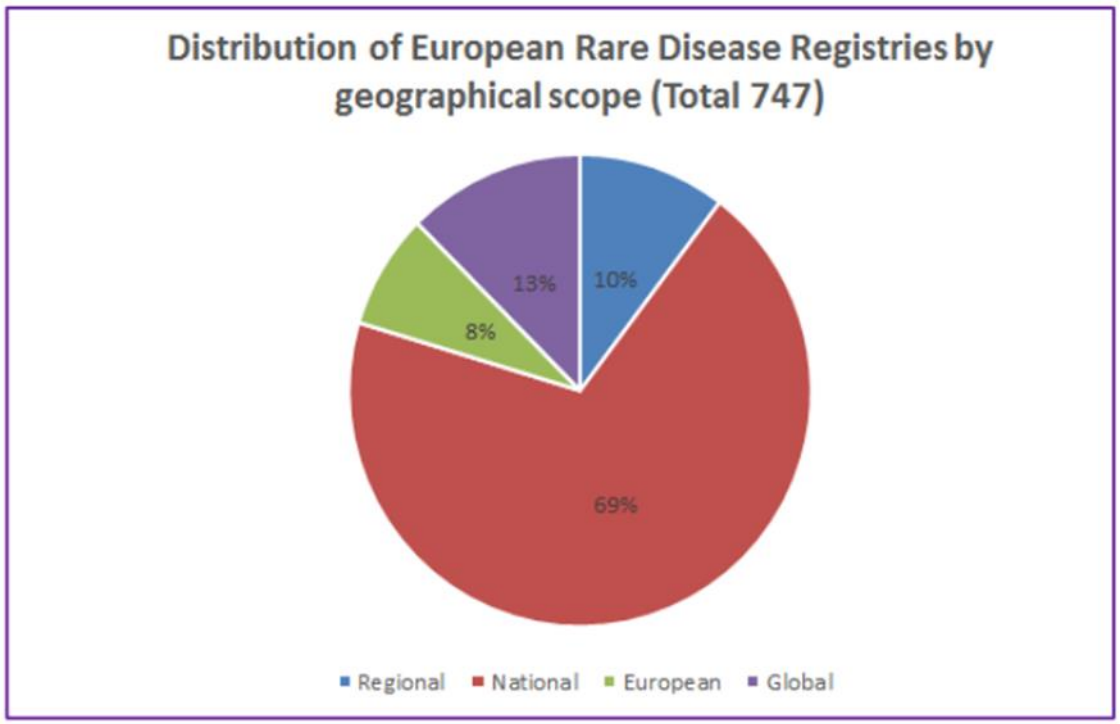
- Registries are a significant enabler for clinical research, for instance by supporting an assessment of the feasibility of conducting a trail in the first place, and later by facilitating the recruitment of patients. This is particularly useful when registries record an accurate genetic diagnosis (i.e. they stipulate the particular mutation responsible for causing the condition). As medicines and interventions become more personalised, clinical trials often target a specific mutation and therefore need to recruit a particular sub-set of patients. The existence of detailed genotypic information enables a sponsor to assess the number of trial participants they could potentially recruit, and where they are based.

What is the status quo of rare disease registration in Europe?

Information of the European status quo regarding rare disease registration is available in several fora (with more information likely to emerge through overarching initiatives such as the EU Joint Programme Co-Fund for RD Research, ERN mapping exercises, etc.)

According to the May 2018 Orphanet Report Series report 'Rare Disease Registries in Europe' (2019 update due very soon!) **there are 747 disease registries in Europe: 51 operate at the European level; 93 Global; 518 National and 77 Regional.**

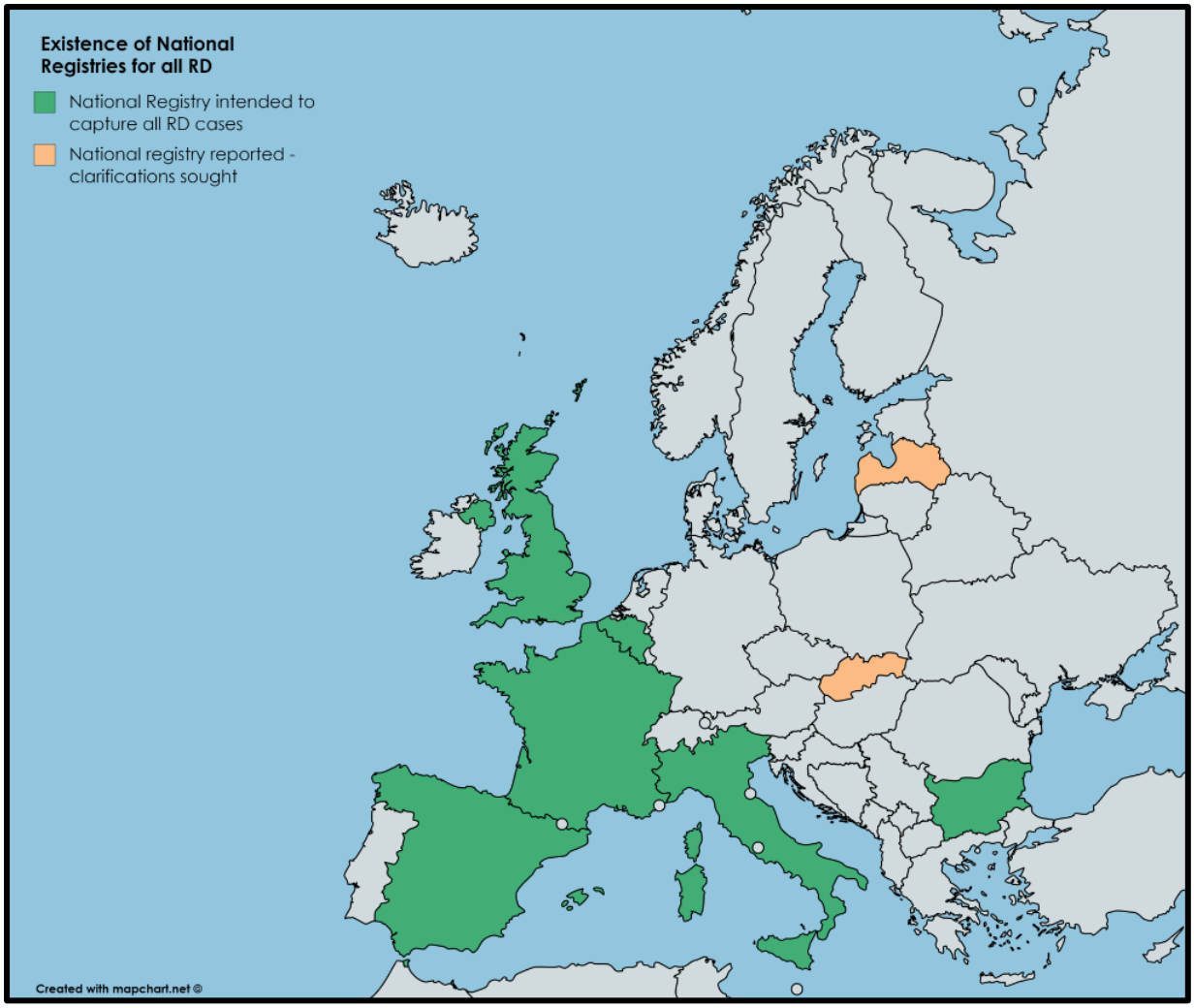
Most of the registries are established in academic institutions. A minority are managed by pharmaceutical or biotech companies, with others being run by patient organisations. A full list, based upon the data contained in the Orphanet database, is available here - http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf.



Information on national activities concerning RD registries is also elicited from each EU country via the *Resource on the State of the Art of Rare Disease Activities in Europe*. According to the latest collection (as of May 2019 - data is still being updated in some countries), there is quite a heterogeneous reality across Europe as regards **national registries** designed to capture all cases of a rare disease in the national territory:

The following countries reported the existence of a **national-level registry established/evolved specifically for RD patient cases (i.e. to register any patient with a RD):**

- **Belgium**: The national level Central Registry for Rare Diseases (CRRD) is prospectively collecting a limited set of variables, having started with a proof-of-concept phase in two genetic centres after which the other six recognized genetic centres came on-board.
- **Bulgaria**: In 2017, a project was established to create a National Register of Patients with Rare Diseases. The registry appears operational as it is already collecting a number of data items including patient's name, date of birth, leading diagnosis, accompanying diagnosis, examinations, studies, consultations, etc. family history, etc.
- **France**: Has the project named BNDMR (Banque Nationale de Données Maladies Rares-National National Rare disease Bank). This was initially intended to develop and accelerate research projects; however, the concept is being further developed and it will be possible to allow mapping of patients' needs and healthcare received, and to facilitate patients' recruitment for clinical and epidemiological studies and clinical trials. BNDMR is populated via two main data streams: BAMARA, which is a care data collection; and DPIs (a DPI is the Patient Medical File each hospital completes)
- **Italy**: Has a national registry for RD, functionally linked to regional and interregional registries of RD. This was established through Art. 3 of the Ministerial Decree of the 18th May 2001 No 279. The National registry is based at the National Institute of Health. Regional/interregional registries are managed by Regional Health authorities.
- **Spain**: In 2011 the Carlos III Institute of Health (ISCIII) joined the International Rare Disease Research Consortium (IRDiRC) and launched an internal and strategic IRDiRC call for Spain, which resulted in the consolidation of the Spanish Registry Network for Research for Rare Disorders (SpainRDR). More recently, the passage of Royal Decree 1091/2015 created and regulated the *State* Registry of Rare Diseases.
- **UK**: In 2015 the long-standing congenital anomalies registry network evolved into the broader National Congenital Anomaly & Rare Disease Registration Service (NCARDRS).
- **Slovak Republic**: The national registry for rare diseases was created in January 2014: it is capturing all cases of hereditary diseases, chromosomal anomalies and genetic syndromes (*new data: more details will be gathered*)
- **Latvia**: Since 2015, rare disease registration is implemented under the Register of congenital anomalies, which is apparently broadened to include all RD cases (*new data: more details will be gathered*))



Several other countries reported in their 2019 updates that concrete steps towards a national registry were now underway e.g.

- **Croatia** has begun to collect data for a potential registry and the Croatian Society for Rare Disease and the Croatian Medical Association has funded the creation of the software needed for a national rare disease registry.
- **Hungary** also began development of National RD registry software
- **Malta** is seeking to link all cases of RD appearing in their other existing national registries

Beyond Europe, several countries have established national RD registries, for instance, **Colombia** now has a national registry for rare diseases. In the **USA**, the Office of RD Research launched a pilot project in 2012 to establish the Global Rare Diseases Patient Registry and Data Repository (GRDR). By 2016, the GRDR had agreed Common Data Elements (CDEs) organized into 10 categories that include required and optional elements, and has launched consent forms and information resources. In 2017, the GRDR changed its name to the Rare Disease Registry (RaDaR) Program

(*Please inform the project of national registries in your country*) A more detailed summary of European national registry activities will be published later in 2019 using the data from the State of the Art Resource

What initiatives are supporting rare disease registration, and in what way?

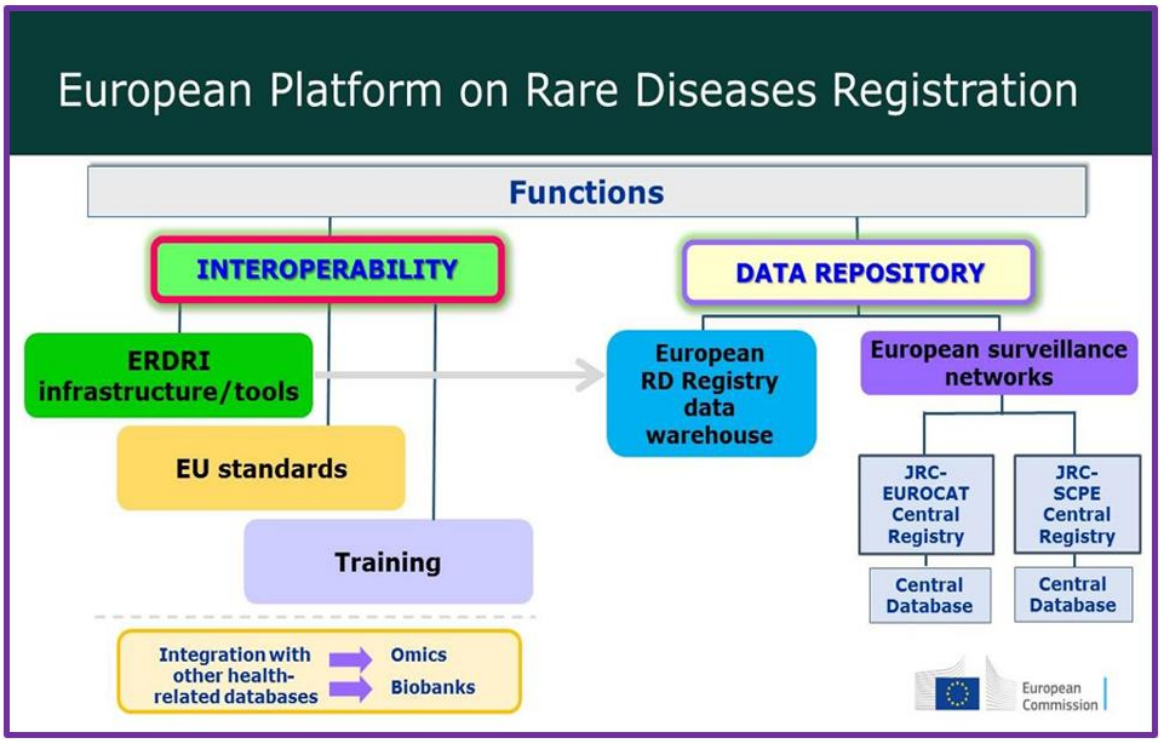
(Please note that this table is selective – for a more exhaustive summary see for instance Overview Report on the State of the Art of Rare Disease Activities in Europe, 2018 Page 65 onwards)

Initiative/Project	Brief Outline	Key Resources/Contribution to the field
EC Joint Research Centre	Signed an Agreement in 2013 to establish a European Platform on RD Registration. Actions are ongoing and are RD-specific Main goal – addressing the lack of interoperability in Europe's RD registries	• Resources to support the various elements of the ERDRI (EU RD Registration Infrastructure), including: • Common Data Set for RD Registries (based on EUCERD Joint Action, RD-Connect, and EPIRARE outputs) • ERDRI User Access Guide • (see further, below)
EMA Patient Registries Initiative	Established in 2015. Actions are ongoing Not RD-specific. Main Goal - facilitating interactions between registry coordinators and potential users of registry data, both at an early stage of therapy development and during the MA evaluation procedure and post-authorisation	• Discussion Paper: Use of patient registries for regulatory purposes(2018) • Inventory of Patient Registries (within the EnCePP Resources Database) • Reports on Qualification of two registry networks and reports from disease-specific workshops here
EJP for Rare Diseases	European Joint Programme Co-Fund for RD Research, Pillar 2, has a particular focus on Registries.	It will develop: • **A Centralized metadata repository** describing pre-existing resources (including catalogues, data repositories, tools and infrastructures) with rare disease-specific semantic standards and metadata which conforms to an ontological, machine-readable model.

		• **A federated ecosystem of FAIR-at-the-source resources**, in order to enable data discovery, sharing and analysis down to the record level
ERN Registry Grants (DG SANTE)	5 ERNs were funded to establish new/link existing registries in their field, back in 2018. A second call was launched for the other 19 in 2019. The main purpose of the 5 funded registries appears to be creating a tool to register *all* patients visiting the HCPs of which each ERN is composed, collecting well-defined datasets. These registries are building links to other existing disease registries	• Plans and priorities of the 5 funded ERN registry projects are available via their individual websites (you can find these here p51) • The call for registry-support for the other 19 Networks will close in September 2019. Collaboration across ERNs here, in terms of dataset selection and platform sharing, is being encouraged
RD-Connect	FP7 Initiative 2012-2018, establishing a platform to support RD research by linking data from biobanks, registries, databases and bioinformatics. Funding period expired	• Developed Registry ID Cards – designed to improve the accessibility and usability of existing RD registries by providing each with an ID card. Registries were enrolled to the RD-Connect Registry and Biobank Finder
PARENT Joint Action	Cross-border Patient Registries Initiative (PARENT JA) Funded via the 2nd Public Health Programme from May 2012 until November 2015 (funding period expired)	• Developed ***Methodological Guidelines and Recommendations for Efficient and Rational Governance of Patient Registries***, along with several other key outputs. • This output now exists as a Wiki (http://parent-wiki.nijz.si/index.php?title=Methodological_guidelines_and_recommendations_for_efficient_and_rational_governance_of_patient_registries) and was formally endorsed by the eHealth Network (eHN) in 2015

European Platform for Rare Disease Registration

In December 2013, the European Commission's Joint Research Centre, in collaboration with DG SANTE, initiated development of the European Platform on Rare Diseases Registration (EU RD Platform) to address the serious fragmentation of rare disease patient data contained in hundreds of registries across Europe. The services and tools to be offered by this Platform have become much more clear and concrete in recent years, and a high-level summary is therefore presented below (see further https://eu-rd-platform.jrc.ec.europa.eu/)



(Image courtesy of JRC: as utilised in the Overview Report for the State of the Art of Rare Disease Activities in Europe)

The Platform has two main functions, as above: Interoperability and Data Repository

1. Searchable, queryable and findable RD patient data across RD patient registries (Interoperability)
This achievement, requested for many years by the RD community, is based on the development of the European RD Registry Infrastructure (ERDRI), which contains the following main components:

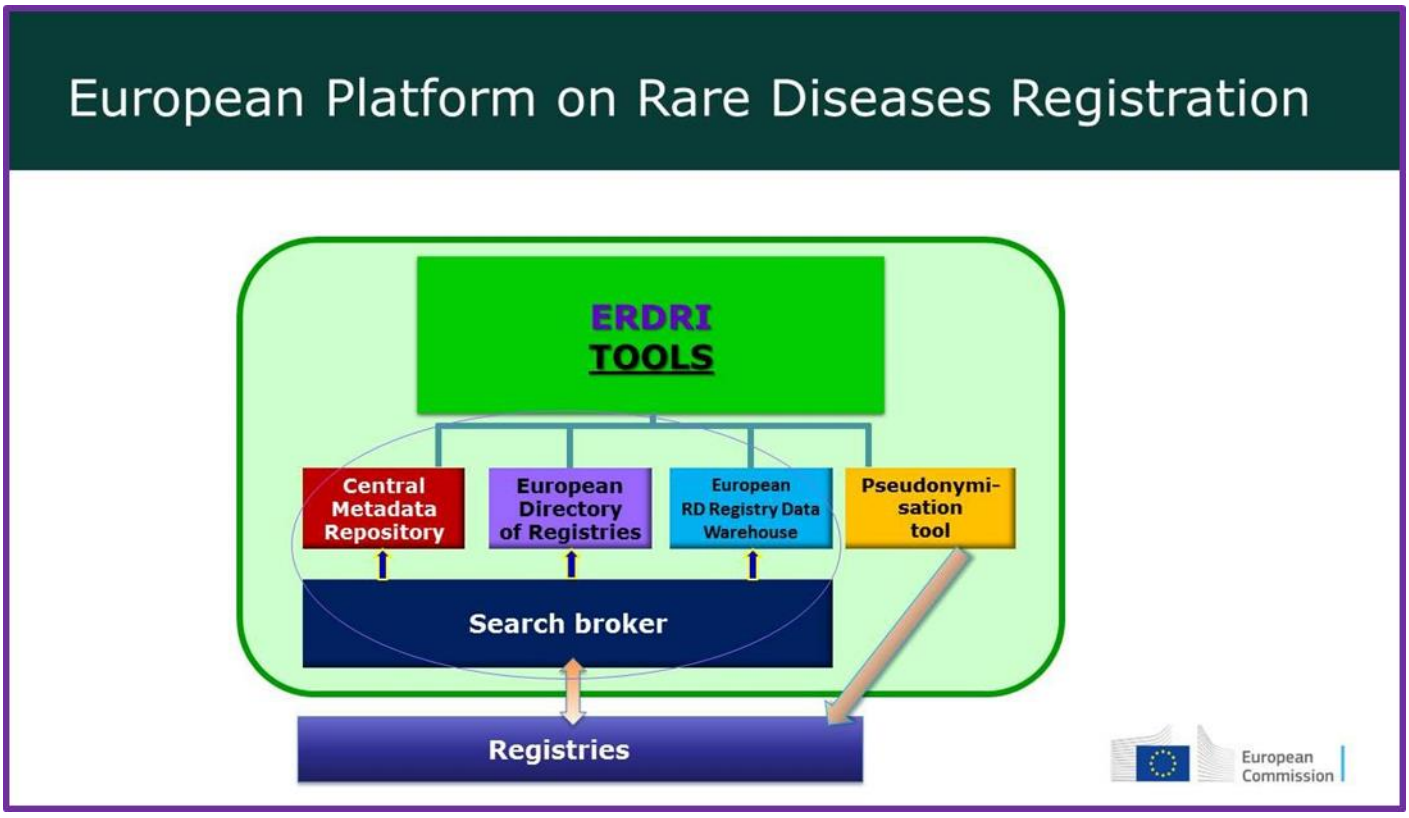
- the European Directory of Registries (ERDRI.dor) which gives an overview of the RD registries joining the Platform, with their main characteristics and description;
- the Central Metadata Repository (ERDRI.mdr) which ensures semantic interoperability between RD registries;
- the Pseudonymisation Tool (EUPID) providing pseudonyms to participating registries;
- a Search broker helping to retrieve data of interest

The European Commission's JRC also offers training on the tools and functions provided

2. Data Repository

The EU RD Platform provides:

- the European RD Registry Data Warehouse (data repository), which will contain aggregated data from the RD registries. This is facilitated by the promotion of a single set of **common data elements** (see table above)
- the central data repositories (and function of Central Registries) for two long-established surveillance networks: EUROCAT (congenital anomalies) and SCPE (cerebral palsy in children and young people). This activity involves more than 40 registries for EUROCAT and more than 20 for SCPE; therefore, establishing these repositories and central registries was a complex legal and organisational process.



(Image courtesy of JRC: as utilised in the Overview Report for the State of the Art of Rare Disease Activities in Europe)

Drive towards interoperability and reuse of rare disease data

Significant emphasis has been placed in recent years -via a number of cross-cutting disease -agnostic projects (e.g. EU Joint Actions for Rare Diseases, RD-Connect) on capturing data about RD patients in a standardised way, to allow some degree of pooling/sharing/querying of that data. An important step forwards, in terms of clarifying the best standards and approaches (e.g identifying the most appropriate ontologies) has been the emergence and greater visibility of the **FAIR data principles**.

The FAIR principles originated outside of the RD field but are especially pertinent in domains which necessitate a significant level of data 'sharing'. FAIR is an acronym, standing for Findable, Accessible, Interoperable, Reusable. The concept was developed by a team of scientists and data experts led by Prof. Barend Mons and has –particularly since publication of a key 2016 paper - gained traction globally: organisations which endorse FAIR data principles include ELIXIR, BBMRI, the European Open Science Cloud, FORCE11, NIH through its 'commons' program, and the G20. The FAIR principles acknowledge that actually *exchanging* data between centres and certainly between jurisdictions is challenging. Instead, 'FAIR' promotes the concept of making data *queryable*, which is an efficient -and far more achievable- goal. A key publication is http://www.nature.com/articles/sdata201618 and there is a useful introduction to using FAIR concepts here.

In 2017, a number of fields established **GO-FAIR Implementation Networks**, designed to unite stakeholders interested in promoting the spread of FAIR principles in their particular domain, working towards an ecosystem of FAIR data services. In 2018 a GO-FAIR Implementation Network for Rare Diseases was established, seeking to anchor together the individual 'FAIRification' efforts in the RD field.

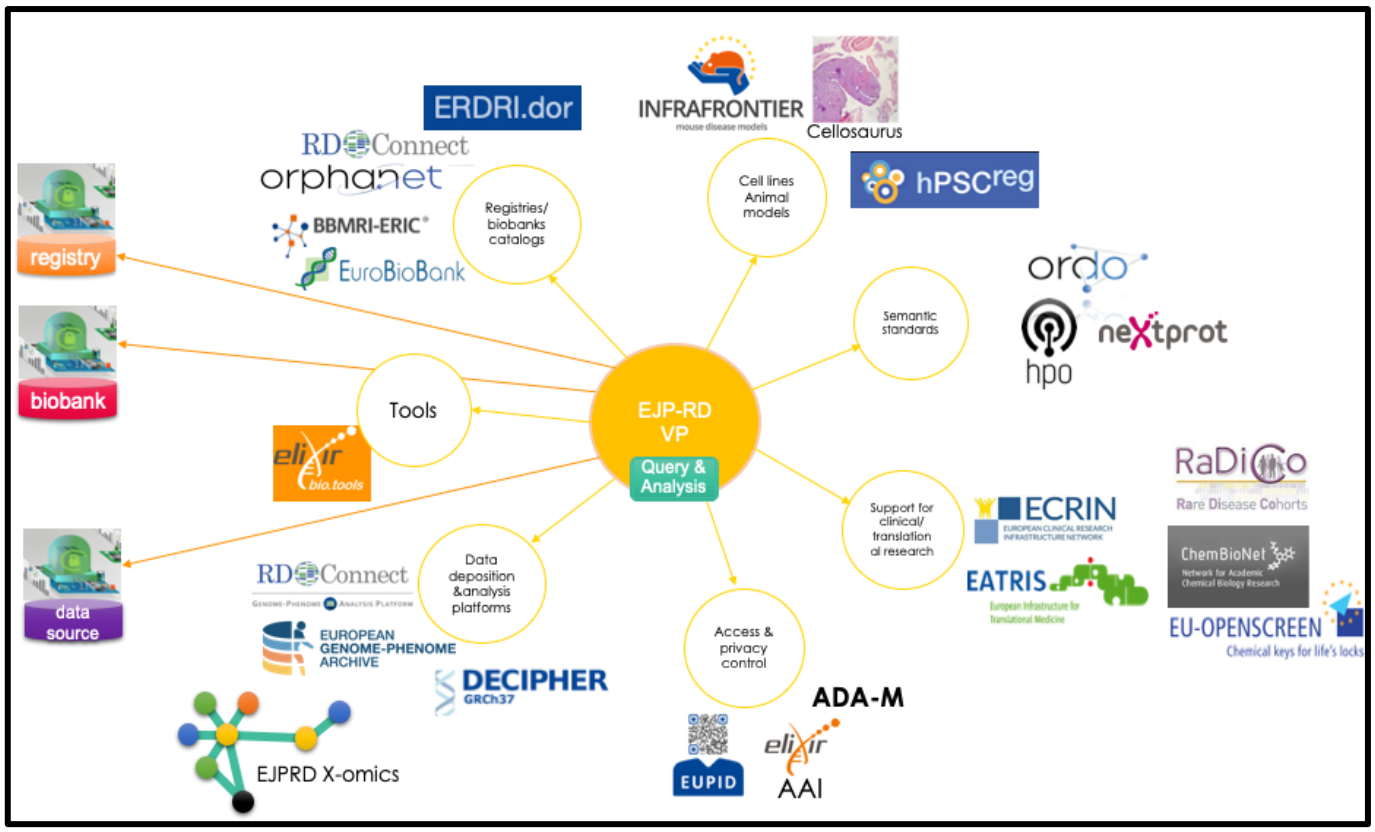
Particular emphasis is placed upon supporting the ERN community to make their data FAIR, given the unique opportunities and economies of scale offered by these new Networks. For instance, the GO-FAIR Network is an opportunity to advance the actions espoused by the '*RD-ACTION Recommended Practices on Standardising Data in the context of the operation of ERNs*' relating to FAIR data in the ERN framework.

An important component of making data FAIR is the use of appropriate and agreed ontologies to enhance the visibility of rare disease cases in national health systems and research resources, and to allow the exchange and understanding of such data through (increasingly) electronic formats (see below)

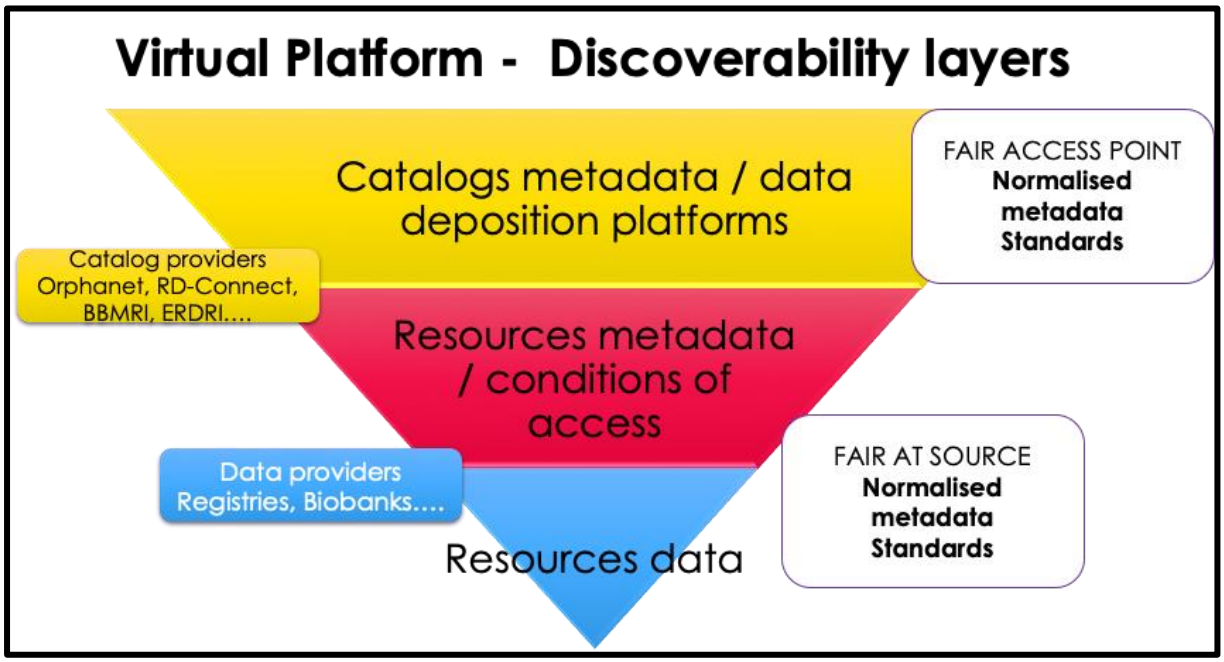
EJP-RD Pillar 2

The European Joint Co-fund Progamme for RD (EJP-RD) will promote and facilitate the implementation of FAIR principles in RD data sources, with a special focus in RD registries. This will be achieved by providing data stewardship support to ERN's registries and providing training on FAIRification.

The main aim of the collaborative work in Pillar 2 is geared towards decreasing fragmentation and maximizing European capacity to enable better and more efficient research on RD by bringing together the interdisciplinary key players, their assets and know-how, to provide coordinated access to resources and data through a common Virtual Platform (VP). These resources either exist already or will be created over time; for instance, RD multi-omics pathways data will be generated and made available, and ERNs registries data will be made discoverable and queryable as these registries are established. The following schema seeks to illustrate the range of resources and actors Pillar 2 of the EJP will unite:



The Virtual Platform main concept can be schematised as follows:



Besides the RD-specific endeavours, many initiatives are exploring the potential for 'big data' (coupled with enhanced interoperability and data management capabilities) to revolutionise health and research. Several of these are poised to impact on the rare disease community, for instance:

- The Global Alliance for Genomics and Health (GA4GH) which seeks to advance genomic data sharing (see further the Diagnostics subgroup Summary)
- The Joint HMA (Heads of Medicines Agencies) and EMA (European Medicines Agency) Task Force on Big Data . The TF is mapping relevant sources of big data for regulatory activities, identifying the various applications of big data, exploring challenges and opportunities, defining a big data roadmap, etc.

Codification of Rare Diseases and Capture of Phenotypic Features

In line with the Council Recommendation of 2009 (see above, p1-2), significant progress has been made to increase the visibility of rare diseases in health systems and in research data collections, through use of appropriate nomenclatures and ontologies. Orphanet produces a nomenclature and classification specific for RD http://www.orphadata.org/cgi-bin/rare_free.html, in which each RD has a unique identifier, **the ORPHAcode**. The Orphanet nomenclature is interoperable with other medical terminologies in use (ICD10 and 11, SNOMED-CT, OMIM, MeSH, MedDRA, GARD) and is the backbone of a network of relationships with other data such as genes, phenotypes, functional consequences, epidemiology, related to RD. This network is delivered as an ontology of RD, ORDO.

The ORPHAcode was recently promoted as a best practice by the Commission Steering Group on Promotion of Health and Prevention of chronic non-communicable diseases (SGPP), which resulted in a EU-funded project, **RD-Code** (2019-2021) aiming at implementing the ORPHAcodes in 4 EU countries (Czech Republic, Malta, Spain and Romania) following the guidance and recommendations for codification of rare diseases produced by RD-Action (2015-2018).

Indeed, ORPHAcodes are already being used by the majority of Member States, albeit via diverse implementation models (in centres of expertise, in national registries, in hospitals or in the national codification system). Generalisation of the ORPHAcodes will ultimately allow for improvement of RD patients' visibility and traceability in health systems, and for a better epidemiological knowledge across Europe.

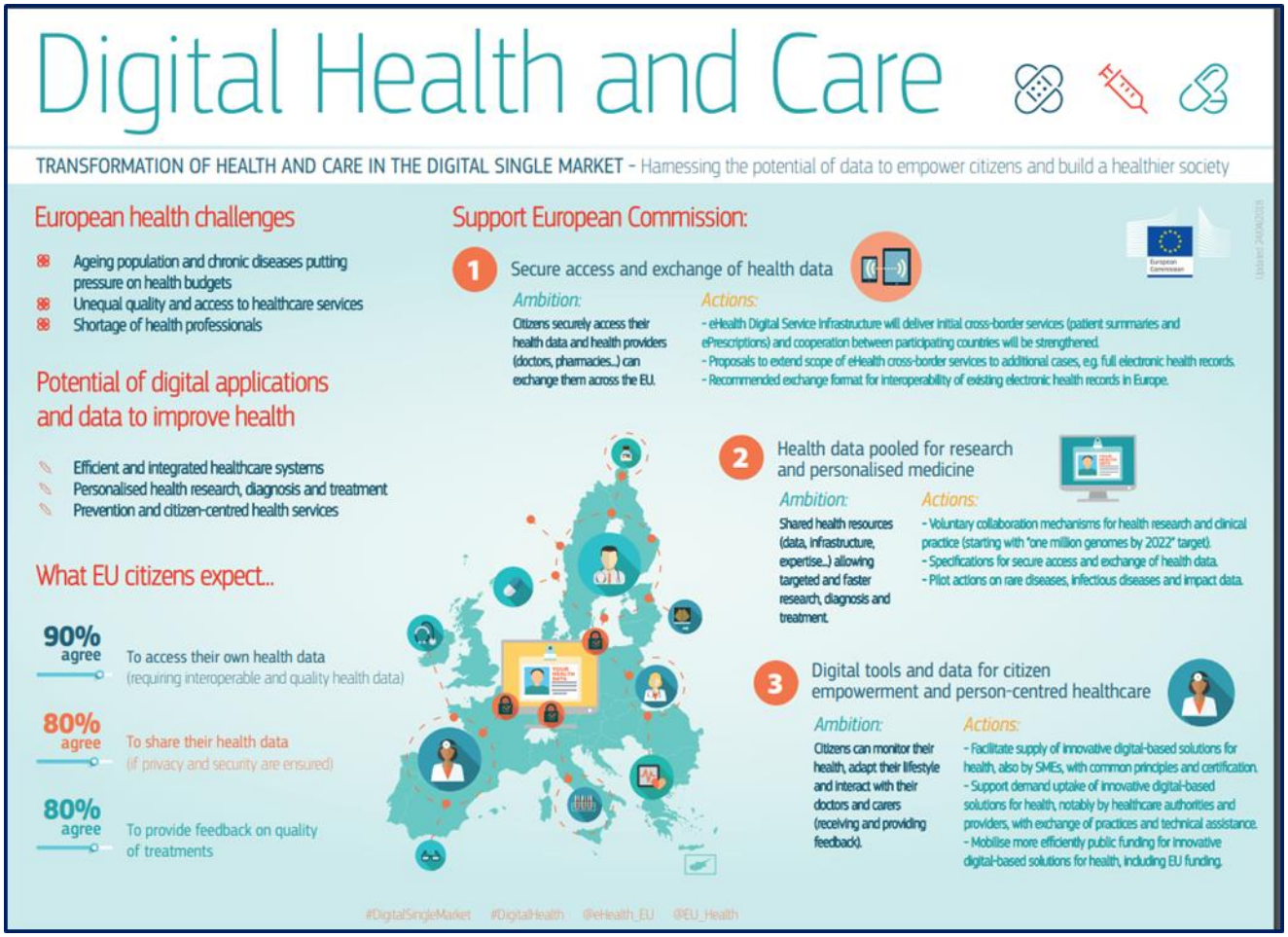
Further to the recognition of a rare disease diagnosis in health systems and registries, a standardised characterization of the clinical *manifestations* (phenotypes) of rare diseases is crucial to improve recognition of conditions by doctors and for RD patient match-making and genomics interpretation. **The Human Phenotype Ontology (HPO) is now the standard terminology and ontology for RD phenotyping (and indeed has secured the status of 'IRDiRC-Recognised Resource'). HPO was developed at the Charité (Berlin, Germany)** and it is now run by the Jackson Institute (USA). HPO and ORDO are usable together as an ontological ecosystem, HOOM (HPO-ORDO ontology module). This was made possible through an eRARE-funded project, HIPBI-RD.

Electronic Health Records: the European status quo

As Europe moves increasingly to electronic (as opposed to paper) health records, exciting opportunities await in terms of the potential to link the health records of patients living with a rare disease, resulting in such benefits as

a. reduced need to explain health histories time and again when meeting any new professional; and
b. more streamlined approaches to integrated care, with all relevant encounters (ideally across the health and social spheres) amalgamated to one EHR.

A particular benefit, for time-short data entry teams, would be the capacity to populate at least sections of complimentary real-world evidence resources such as registries by automatically extracting relevant data from EHRs. Enriched and well-designed EHRs could also potentially support activities such as feasibility studies and recruitment to clinical trials. Many barriers stand in the way of a seamless integration of EHRs both between geographical jurisdictions (sometimes within) and indeed between EHRs and other complimentary data resources.



(Infographic taken from https://ec.europa.eu/digital-single-market/en/news/infographic-digital-health-and-care-eu)

Not least amongst these is the fact that European countries are developing their own systems for electronic data capture in the health sphere. An important step to address this fragmentation was the publication in 2018 of the *Commission Communication on enabling the digital transformation of health and care in the Digital Single Market; empowering citizens and building a healthier society*. This document sets out the Commission strategy to transform healthcare under the Digital Single Market, and sets out a number of specific proposals, geared around 3 areas:

1. **Citizens' secure access to their health data, also across borders**- enabling citizens to access their health data across the EU;
2. **Personalised medicine through shared European data infrastructure** - allowing researchers and other professionals to pool resources (data, expertise, computing processing and storage capacities) across the EU;
3. **Citizen empowerment with digital tools for user feedback and person-centred care** - using digital tools to empower people to look after their health, stimulate prevention and enable feedback and interaction between users and healthcare providers.

An important step forwards, in terms of enabling the exchange of health data across borders, is the European Commission drive to **prototype a European interoperable EHT exchange .**

Exchanging data across borders

Once one accepts the need to be able to pool/share/query data held in different national jurisdictions, it is necessary to agree and implement mechanisms (with accompanying legal and social governance frameworks) to enable this. There have been numerous efforts to exchange health-related data across borders: two examples are briefly highlighted below:

European Reference Networks: A key pillar upon which the ERN concept is based is the mantra that wherever possible, data should travel, rather than patients themselves. In reality, this meant the creation of a robust, secure platform to exchange data between HCPs based in different EU MS/EEA countries. The European Commission supported the provision of a suitable platform, which is today known as the CPMS (Clinical Patient Management System). Before, during, and after the creation of this Platform, efforts were made to ensure data was captured in such a way as to extend the 'life' of that data for secondary purposes, beyond the immediate goal (i.e. the virtual referral to a panel of experts, on diagnostic advice, suitability for specialised procedures, treatment options, etc). For instance, see the *RD-ACTION Recommended Practices for Data Standardisation in the Context of the Operations of ERNs*.

CPMS in numbers:

- **As of May 2019, 1268 active users are registered in the CPMS (an 'active user' is an individual who has logged in at least once);**
- **623 panels have been opened at some stage**
- **245 panels have been closed and archived.**

An important step in this process was the creation of a common pan-ERN Informed Consent template and information sheet, to authorise the exchange of data for care (and possible additional uses). The Networks are being encouraged to personalise core datasets specific to diseases or groups of diseases

addressed by their network, and to implement these datasets with reference to particular ontologies (e.g. the Human Phenotype Ontology or HPO), to increase the interoperability of that data (for a variety of possible future purposes).

eHealth Network: To support the exchange of patient data across borders, the CrossBorder healthcare Directive established (via Art.14) a voluntary body known as the eHealth Network (eHN). The eHN oversaw the creation and evolution of a number of eHealth Digital Service Infrastructures or eHealth DSIs. This work has been funded within the framework of the Digital Europe Programme and can, in some sense, be considered to stem from (or at least was largely driven by) the epSOS initiative. Ending in 2014, epSOS ("Smart Open Services for European Patients") was a European large-scale pilot testing the cross-border sharing of

a) a patient's most important health data summary, intended for use in an unplanned (e.g. emergency) care situation when travelling or working abroad; and
b) b) an electronic prescription (ePrescription).

A small TaskForce initiated under the EU Joint Actions for Rare Diseases has undertaken initial work with eHealth initiatives to highlight the need to consider rare disease patient needs in these two Digital Service Infrastructures. Caring for a person living with a rare disease presents certain specificities that merit the inclusion of additional data elements in the patient summaries to support emergency care or planned cross-border healthcare.

Ethical Data management and Data protection

Collection and use of patient health-related data is, naturally, subject to strict regulations. In Europe, the EU General Data Protection Regulation (Regulation (EU) 2016/679) (GDPR), effective on May 25, 2018, is directly applicable in each EU Member State. The GDPR introduces a single legal framework across EU Member States, but it includes several open provisions that allow each country to restrict, specify or expand the requirements of the GDPR. This is the case with regards to the processing of genetic data, biometric data and data concerning health where Member States may maintain or introduce further limitations to the processing of these types of data.

Organisations must have a valid, legal reason to process personal data. This is called a 'legal basis' and there are six available legal basis described in Article 6. Under the GDPR, commercial companies and charitable research organisations will commonly use **'legitimate interests'** as their legal basis. However, public authorities, such as public research organisations or universities, when carrying out public tasks will use **'task in the public interest'** as their legal basis (https://ec.europa.eu/info/law/law-topic/data-protection/reform/rules-business-and-organisations/legal-grounds-processing-data/sensitive-data/under-what-conditions-can-my-company-organisation-process-sensitive-data_en)

In order to lawfully process special category data, such as genetic data, biometric data or data concerning health, organisations must identify both a lawful basis under Article 6 and a separate condition for processing special category data under Article 9 . There are ten conditions for processing

special category data in the GDPR itself, but Members States may introduce additional conditions and safeguards on the processing of genetic data, biometric data or data concerning health. Such flexibility means that any organisation processing this kind of data could be subject to different legal requirements in different countries.

Beyond these differences between Member States, there are other challenges linked more generally to the implementation of the GDPR that may have a direct impact on the processing of rare disease-related data captured in registries, biobanks, electronic health records and other databases. These include the following:

- Clarifying liability under the GDPR - who is responsible if a person figures out how to identify data that was pseudonymised in good faith?
- Operationalising the principles envisaged in the Regulation such as privacy by design and by default
- Developing standards for health data anonymization
- Clarifying the conditions to use broad consent under Recital 33 to process health data for research purposes

Patients' Perspectives on Data use and Re-Use

In recent years, research has been conducted to assess patients' perspectives on the use and reuse of their personal health-related research data. For instance, RD-Connect assembled a (disease-agnostic) panel of patient advocates, the PAC (Patient Advisory Committee). Data sharing was the topic of a recent Rare Barometer Voices survey (results to be released shortly). Such work has suggested that RD Patients are generally willing to share their health data and recognise that this is of vital importance to advance health research and healthcare, help other patients and ultimately benefit society. They have a greater incentive because data on each disease is usually very scarce and scattered, making research more challenging, and most conditions classed as rare have no cure (or even dedicated treatment). But at the same time, patients are deeply concern about privacy issues and security breaches.

Consultations and surveys suggest that RD Patients are willing to share their medical data for research as long as this is done respecting four core elements for responsible data sharing: respecting their preferences; protecting privacy and confidentiality; providing feedback on the results; and allowing patients to be part of defining the data governance and be involved in operating/managing these governance arrangements.

- **Consent is obtained respecting preferences.** Do patients have all the information they need to understand research objectives, who is going to access what data, for what purposes and under what conditions?
- **Privacy and confidentiality are protected and** mitigated through safeguards (such as ethical review, and IT solutions – privacy by design and default, security measures, data minimization, pseudonymisation…) while maintaining/respecting reasonable time frames
- **Resulting progress is communicated (feedback on the results)** Regular communication of outcomes to the patient community and the public at large should occur in a timely manner both at the aggregate and individual levels

- **Good and inclusive Health Data Governance frameworks:** In today's fast-evolving data-intensive research, while obtaining valid consent is necessary, it is not enough to restore the autonomy to individuals. Robust and transparent health data governance frameworks are required, involving patients/citizens across the data cycle and allowing them to participate actively in the collection and management of data. Clear accountability (who is responsible for misuse?) and a mechanism to redress harms should to be part of this governance framework:

Results of the literature review:

The emergence of a **new technological era** with the development of big data and the continuous sophistication of information and communication technologies has revolutionised many sectors, including health (Hong 2018; Belle 2015). It has both opened a field of new and **promising opportunities for the care and treatment of rare diseases, including personalised medicine,** as well as tremendous **challenges mainly linked to difficulties in finding, processing, and analysing the data and ethical issues regarding data protection.**

Firstly, a few trends can be observed when considering the process of collecting data. Our literature review identified that within the last decade, great progress has been made when looking at the number of data resources and ways of collecting data. Indeed, data for rare diseases can been found in the form of patient registries, population registries, electronic health records, as well as biobanks, each with its own characteristics and specific uses. Nevertheless, this tends to produce a situation in which these **resources multiply and divide indefinitely, creating a multitude of data silos**. Few links are made between resources and, as a result, very definite disease-specific (or disease sub-type) resources have developed, both in the public and private sector, often without a common data set (Taruscio et al. 2015; Lopes et al. 2015; Roos et al. 2017). National registries for rare diseases follow very different approaches, structures and purposes, even amongst similar and geographically proximate countries, such as European countries (Taruscio et al. 2015). This enhances the aforementioned **siloed data landscape** preventing many more general uses of the data and limiting research advances for rare diseases (Lopes et al. 2015; Roos et al. 2017).
When viewed within the context of health data, **rare disease data also tend to lack visibility in health information systems** which complicates efficient healthcare resource planning, patient management and follow-up (Choquet et al. 2015; Marx et al. 2017). Often, codes used to define a disease vary between countries, regions and sometimes hospitals, and many rare diseases were traditionally missing from coding terminologies. This **lack of standardisation** makes it difficult to identify rare diseases and complicates the combining of data on large geographic scales, an absolute necessity in the field of rare diseases, where patients are scattered all around the world (Lopes et al. 2015; Rath et al. 2012). It also leads to 'double entries' for patients, which further complicates the task of processing the data (Choquet et al. 2015; Marx et al. 2017).

Nonetheless, when analysing the trends regarding the exploitation of the data and the informatics and bioinformatics tools designed to make sense of this huge amount of information, one can perceive

efforts across borders and across disease areas. For instance, a **tendency towards harmonisation is appearing regarding coding practices**. Recommendations abound for routine double coding i.e. ICD-10 and Orphacodes (Marx et al. 2017) and the adoption of Common Data Elements, meaning the establishment of data elements commonly used in more than one dataset (Choquet et al. 2015; Roos et al. 2017). The overall goal of such initiatives is to break down national as well as discipline-specific barriers and easily identify patients affected by rare diseases in order to form a continuum of care across boundaries and expert centres. The general idea is to **enhance the interoperability of data and make the FAIR principles a reality**: rare diseases data should in the future be Findable, Accessible, Interoperable, Reusable (Gainotti et al. 2018; Lochmüller et al. 2018).

Another means of breaking silos observed in the literature is the use of new bioinformatics tools which allow for the combination of heterogeneous data resources and contribute to **innovative knowledge generation**. A perfect example is the l**ink made between omics and phenotypic data, creating genotype-phenotype relationships** which then enable more complete patient records and paves the way to personalised medicine (Lopes et al. 2015; Lochmüller et al. 2018). Other tools used to foster interoperability of datasets include the combinations of **semantic web, text-mining methods and ontologies** (Lopes et al. 2015).

Another significant trend in data collection is the importance and involvement of patient and family members. Patients are **solicited in their role as experts of their disease to provide data, evaluation and feedback on their experience** (Bambusch et al. 2019). This involvement prompts the emergence of **two-directional information pathways** where both patient/experiential knowledge and scientific or medical information are equally valued (Vicari and Cappai 2016). In this schema, patients become also **generators of knowledge and data,** informing research, clinical care and treatment. A direct manifestation of this trend is the development of **patient reported outcomes measures** (valuable data directly obtained from the patient about their health status or treatment without interpretation by an intermediary). These instruments help to make **patients' voices central to clinical decision-making** (Slade et al. 2018).

Finally, the collection, use and, most of all, sharing of personal and genomic data raises complex **ethical issues**. The stringent legislation of the General Data Protection Regulation implemented in May 2018, is probably the most striking example. Moreover, emphasis on the **responsibility of the data producer and user** is increasingly heightened and sanctions are currently drafted accordingly, adapting to the constant technological evolution (Takashima et al. 2018; Shabani 2016). For instance, IRDiRC partnered with the Global Alliance for Genomics and Health (GA4GH) to develop policy and guidelines around consent, data sharing and frameworks for ethical and secure data sharing, as well as promoting standards for nomenclature (Lochmüller et al. 2017).

Our literature review suggests a general promotion for the design and implementation of policies related to data protection, security and privacy with the **need to find a balance between data sharing and data protection** (Takashima et al. 2018) so as not to hinder scientific advances. The focus and importance on the **anonymisation of data** is a sign of such consideration (Oprisanu and De Cristofaro 2018). Furthermore, privacy seems to have become a central concern and **more attention is paid to patients' opinions and their perspectives on data and biomaterial sharing** (McCormack et al. 2016).

Finally, a quite novel trend which, among other things, could bring a solution to privacy concerns regarding data sharing, is the use of **blockchain technology**. This can be defined as an ever-growing list of records linked using cryptography and containing information that can be simultaneously used and shared within a large decentralized, publicly accessible network. Indeed, t**his system could ensure patients' ability to retain ownership on their data**, one of the core elements for the respect of privacy according to some experts (Angeletti et al. 2017; Terry and Terry 2011) and hence provides an **innovative way to improve the intelligence of healthcare systems while keeping patient data private** (Yue 2016).

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Knowledge Base Summary

Availability and accessibility of Orphan Medical Products (OMPs) and medical devices

Introduction to the Topic – the Policy context

The Regulation on Orphan Medicinal Products (Regulation (EC) No 141/2000) was adopted in December 1999 and came into force in the European Union in 2000, addressing the need to offer incentives for the development and marketing of medicines for rare conditions. The Regulation stipulated the definition for a rare disease in the European Union: for a medicinal product to be designated an *orphan* medicinal product, it must be intended for the treatment, prevention or diagnosis of a condition with a prevalence in the EU of no more than 5 in 10,000

This Regulation was followed by several further Regulations relevant the development and marketing of Orphan Medicinal Products (OMPs), including the following: Regulation (EC) No 847/2000 (established the implementation rules and provided definitions required for applications under Regulation 141/2000); Regulation (EC) No 726/2004 (provided the legal framework for the centralised authorisation and supervision of medicines and thus established the EMA); and **Regulation (EC) No 1901/2006** (concerning medicinal products for paediatric use, allowed OMPs to extend their exclusivity period to twelve years).

It has long been recognised, however, that the approval of an OMP does not automatically equal access for patients. Many policies and resources have a bearing on Health Technology Assessment and the availability of OMPs in national/regional health systems. Recent policies illustrate a growing shift towards pan-European collaboration here, for instance through the 2018 **Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on health technology assessment and amending Directive 2011/24/EU** (see below)

Thinking specifically about *rare disease* policies, the **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]** includes several 'chapters' on this topic:

5.3. Access to Orphan Drugs (the bold emphasis is not present in the original)

"There are specific bottlenecks in access to orphan drugs through the decision making process for pricing and reimbursement linked to rarity. ***The way forward is to increase collaboration at the European level for the scientific assessment of the (added) therapeutic value of Orphan Medicinal Products.*** *The Commission will set up a working party to exchange knowledge between Member States and European authorities on the scientific assessment of the clinical added value of orphan medicines. These collaborations could lead to* ***non-binding common clinical added value assessment reports with***

improved information that facilitate the national pricing and reimbursement decisions, without pre-empting respective roles of the authorities*. Furthermore, the involvement of the EMEA and existing international Health Technology Assessment networks as the Health Technology Assessment International (HTAi), the European Network for Health Technology Assessment (EUnetHTA) or the Medicines Evaluation Committee (MEDEV) should be considered."*

5.6. Incentives for Orphan Drug development

"Pharmaceutical companies invest heavily over a long period of time to discover, develop and bring to market treatments for rare diseases. They need to be able to show a return on investment. However, the ideal is that they are also able to reinvest that return on investment into discovering more treatments. With more than 45 treatments authorised in the EU – and some for the same conditions – there are still many conditions with no treatment. ***Exploring additional incentives at national or European level to strengthen research into rare diseases and development of orphan medicinal products, and Member State awareness with these products should be encouraged*** *in accordance with Article 9 of Regulation (EC) No 141/2000."*

(Specific chapters relating to **Compassionate Use programmes** and **Medical Devices** are included below). This theme of cooperation is also visible in the following year's **Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02.** The preface emphasises *"It is of utmost importance to ensure an active contribution of the Member States to the elaboration of some of the common instruments foreseen in the Commission communication on rare diseases: Europe's challenges of 11 November 2008 […]This could be also the case for the assessment reports on the therapeutic added value of orphan medicinal products, which could contribute to accelerating the price negotiation at national level, thereby reducing delays for access to orphan drugs for rare diseases patients."*

Further into the Recommendation, Member States (MS) are explicitly asked (in Section V: *GATHERING THE EXPERTISE ON RARE DISEASES AT EUROPEAN LEVEL*) to
"Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support: […]
(e) the sharing Member States' assessment reports on the therapeutic or clinical added value of orphan drugs at Community level where the relevant knowledge and expertise is gathered, in order to minimise delays in access to orphan drugs for rare disease patients."

EUCERD Recommendations on the CAVOMP Information Flow

With several policies therefore promoting greater cooperation between EU level authorities and MS to improve access to OMPs, in 2012 the European Union Committee of Experts on Rare Diseases (EUCERD) adopted a set of Recommendations addressed to the European Commission and Member States on ***Improving Informed Decisions Based on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow.***

The document highlights ways to facilitate scientific information exchange on OMPs, in order to support MS in making informed decisions as to the **scientific assessment of the clinical effectiveness** of an OMP. It encourages the creation of an 'Information Flow' between individual MS and between MS and the EU bodies, which would bridge knowledge gaps, especially those existing at the time of marketing authorisation. This information flow was designed to fit in to existing regulatory, clinical, Health Technology Assessment (HTA), pricing and reimbursement processes, while avoiding additional burdens. The CAVOMP information flow recommended by the EUCERD includes four time points:

- Timepoint 1: Early dialogue
- Timepoint 2: Compilation Report and evidence definition / Evidence Generation Plan (EGP)
- Timepoint 3: Follow-up of the EGP
- Timepoint 4: Assessment of relative effectiveness

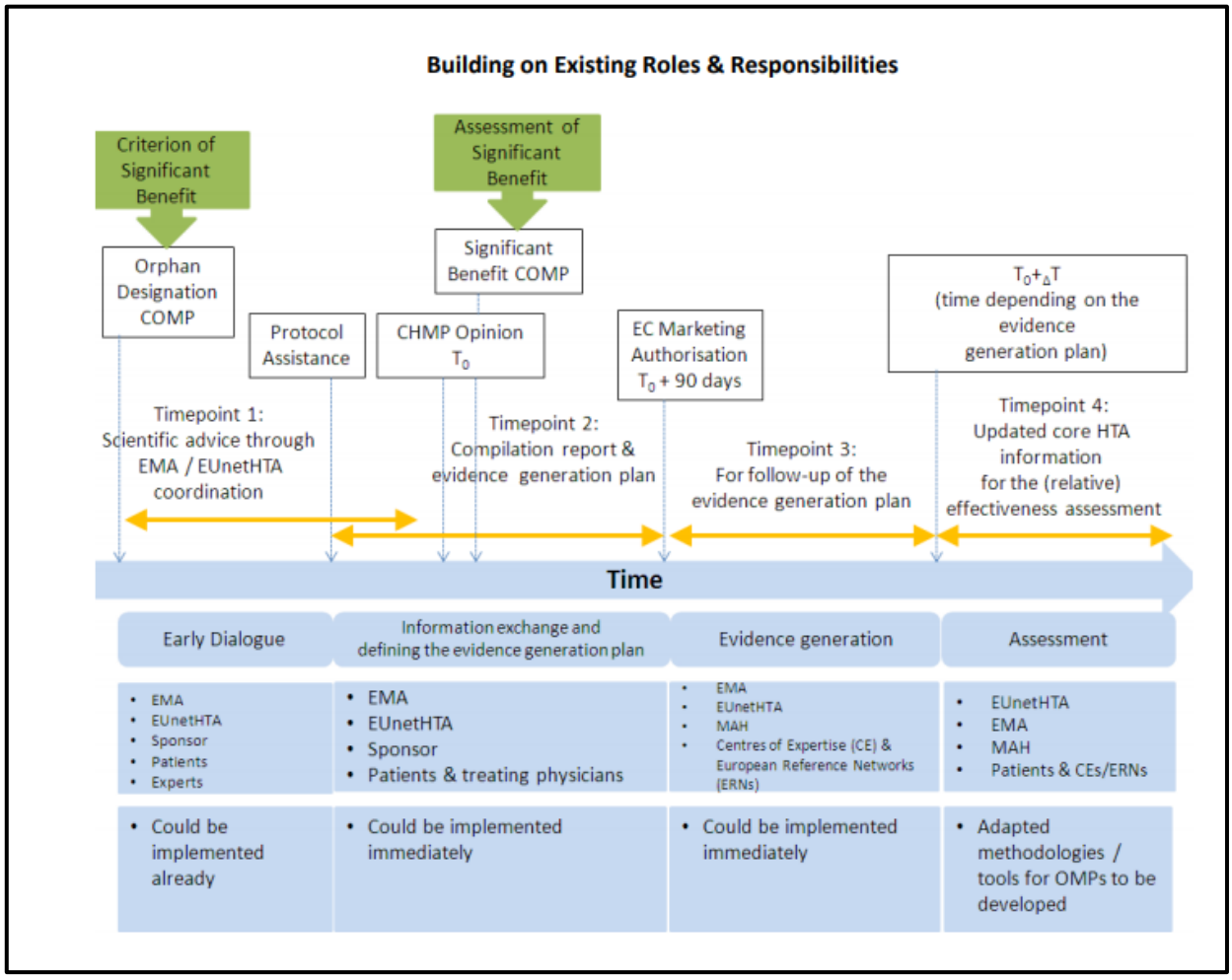


Image take from the EUCERD Recommendations on the CAVOMP-IF

Guiding Questions for Panel of Experts Discussion – to support the identification of trends and drivers of change

1. **How can we stimulate greater development and access to medical devices for people with rare diseases?**

2. **Is the current legislation affecting OMP access fit for purpose? Where could improvements be made?**

3. **What practical actions (at national and European level) would increase the accessibility and availability of OMPs?**

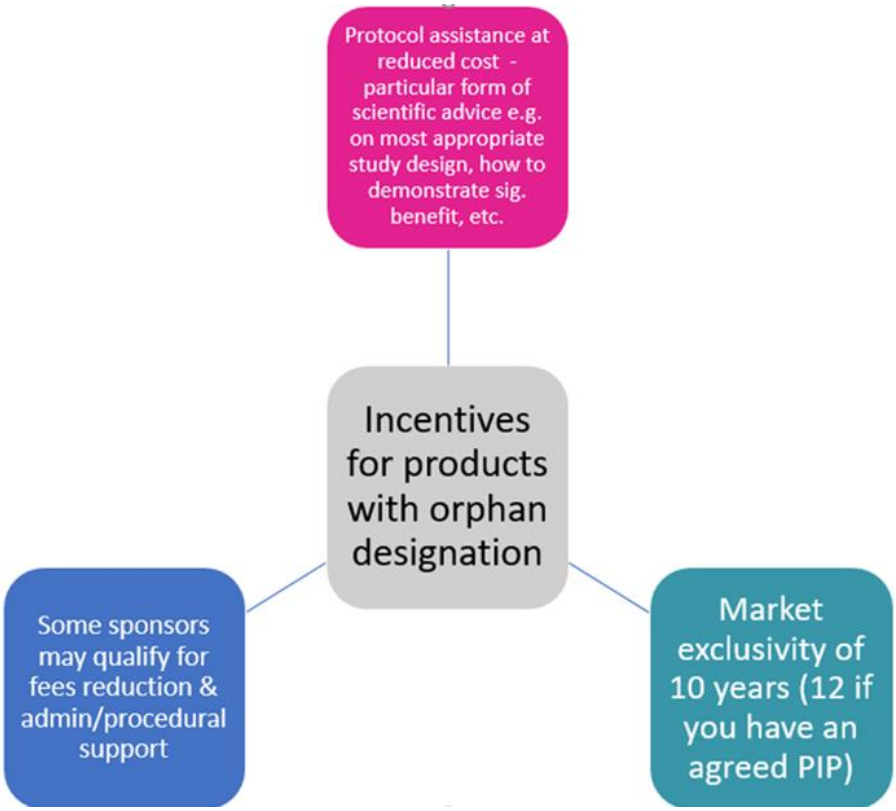
The Regulation on Orphan Medicinal Products (Regulation (EC) No 141/2000) addresses the need to offer incentives for the development and marketing of drugs to treat, prevent, or diagnose rare conditions; without such incentives, it is unlikely that products would be developed for rare diseases as the cost of developing and marketing products for these disorders would not be recovered by sales. The Regulation delineates the designation criteria, outlines the procedure for designation, and provides incentives for products receiving an orphan designation. The process by which a medicinal product enters the market as an orphan medicinal product (OMP) involves several stages:

- A sponsor submits an application to the European Medicines Agency (EMA), seeking orphan designation for their medicinal product
- The application is evaluated by the Committee for Orphan Medicinal Products (COMP) at the EMA (the COMP was established in 2000 via Regulation (EC) 141/2000. The COMP provides an Opinion on the application, which could be positive or negative: this Opinion is then conveyed to the European Commission
- The European Commission decides whether or not to bestow Orphan Designation

There are specific criteria which a medicinal product needs to fulfil, in order to qualify for this orphan designation:

- ✓ it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- ✓ the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- ✓ no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

Once ***orphan designation*** has been granted, the product attracts a range of incentives. For example:



Once a sponsor is ready to submit an application for **marketing authorisation** (MA), they are able to use a centralised procedure. The MA application itself will be assessed by the Committee for Medicinal Products for Human Use (CHMP), which will issue an opinion and convey this to the European Commission.

A set of FAQs has been issued by the EMA on the subject of orphan medicinal products and rare diseases:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2018/02/WC500244578.pdf

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Status Quo of OMP Designations and Authorisations in Europe

- ✓ **As of May 2019, there are currently 1643 products with active orphan designation in the EU (i.e. not withdrawn or expired)**
- ✓ **Between 2000-2018, 2121 orphan designations had been issued by the European Commission**
- ✓ **167 orphan medicinal products have received marketing authorisation**

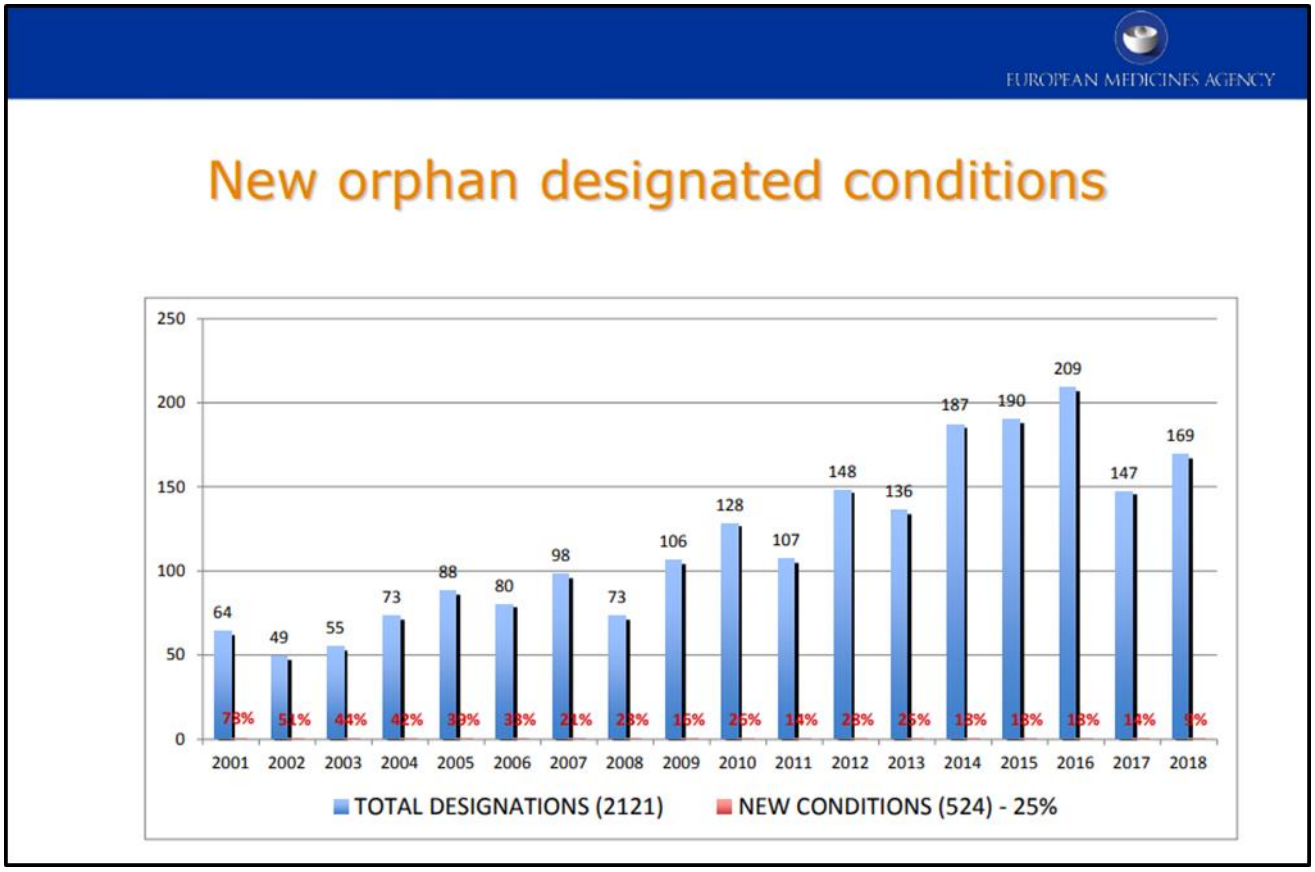
The following table from the EMA (COMP) annual report on OMPs shows the trajectory of orphan designations since 2000:

Applications for orphan medicinal product designation

	2000 2005	2006 2010	2011 2015	2016	2017	2018	**Total**
Applications submitted	548	686	1151	329	260	236	3210
Positive COMP Opinions	348	500	759	220	144	163	2134
Negative COMP Opinions	8	6	7	2	2	3	28
EC Designations	343	485	768	209	147	169	2121
Withdrawals after submission	150	144	313	77	100	92	876

EMA image: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf

The vast majority of new orphan designations, since 2003, have been for conditions which already have an indication. This table from the EMA (COMP) annual report illustrates the percentages of orphan designations each year awarded to new conditions

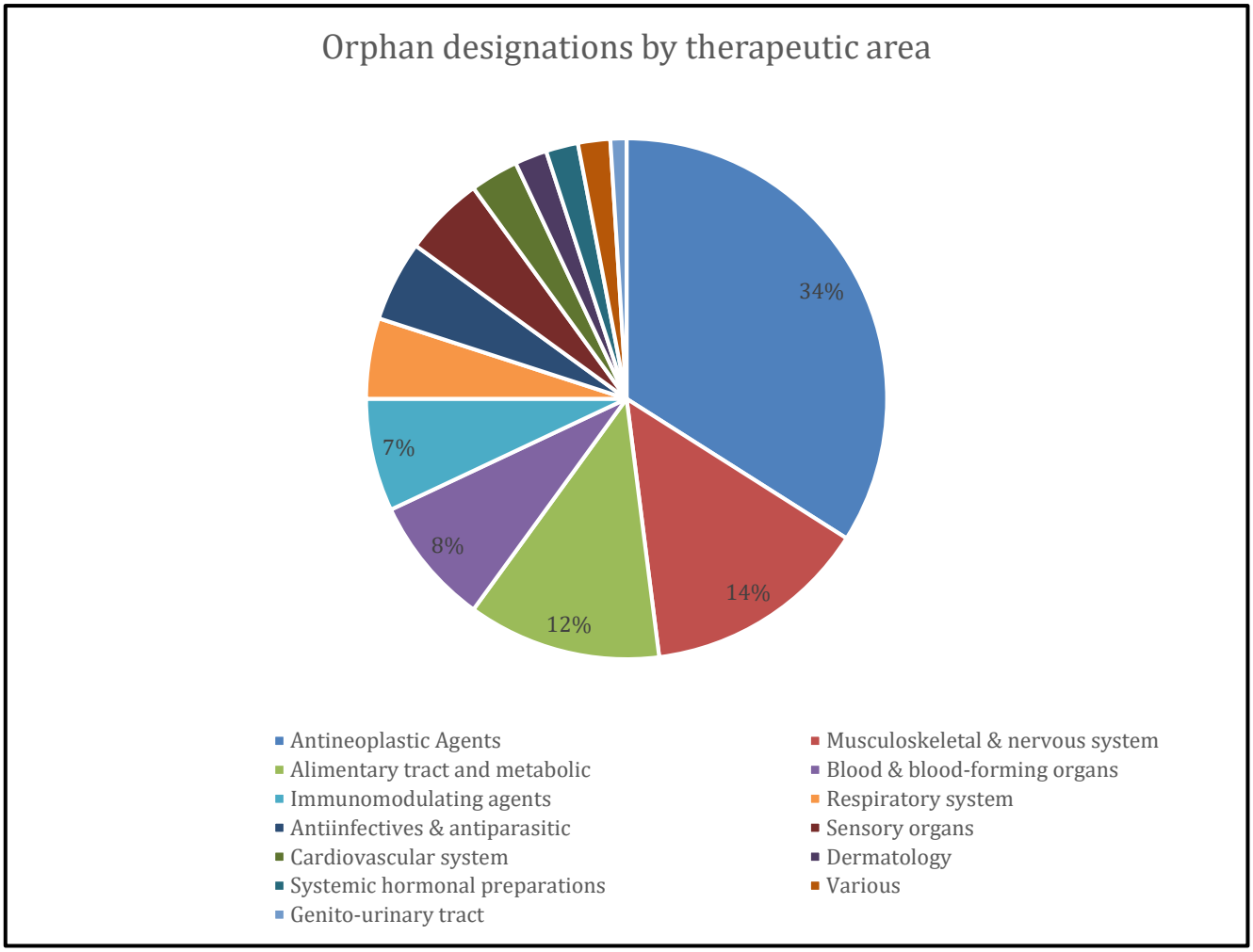


EMA image: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf

The majority of the 2121 orphan designations awarded by the end of 2018 tend to be for both **adult** and **paediatric** use (57 % according to EMA figures for 2018), with 31% for adults only and 12% for paediatrics only.

EMA statistics also illustrate that 44% of all Marketing Authorisations granted during the period 2000-2018 were for conditions with a **prevalence** of less than 1 per 10,000, meaning 56% are for those with a prevalence between 1 and 5 per 10,000. (source is https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf)

Orphan designations tend to be clustered around particular therapeutic areas, most prominently in the categories of oncology, musculoskeletal & nervous system, and alimentary tract & metabolic: the data in the pie chart below comes from the annual EMA (COMP) report on OMPs: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf



Does Marketing Authorisation equal Availability everywhere in Europe?

A major issue in the European rare disease field is that OMPs and innovative therapies which receive a central European Marketing Authorization are often *not* in fact available in all EU countries: each country determines for itself whether to make an authorised product available within the national territory, and whether to reimburse patients for using it.

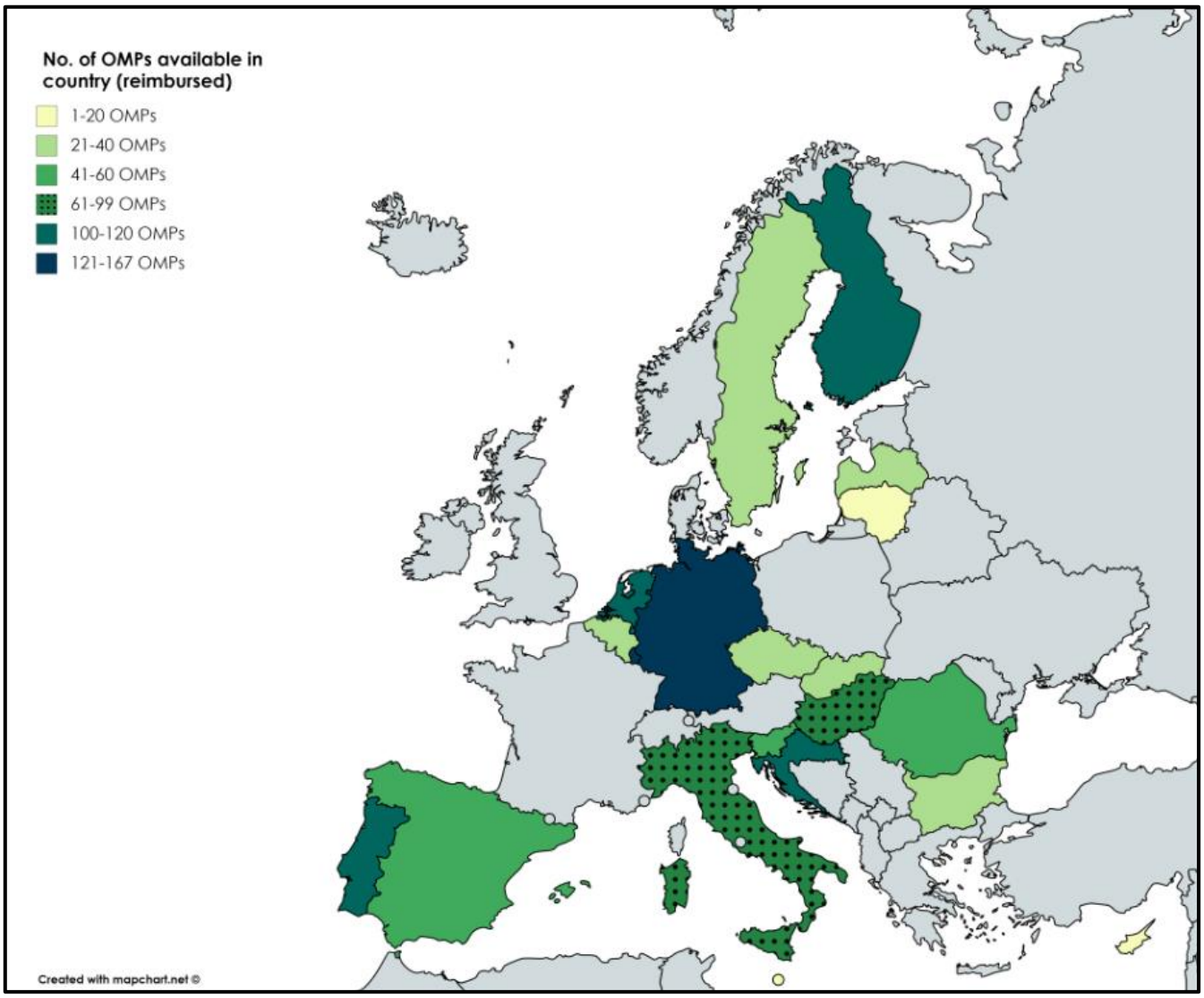
At Member State level, there is a great heterogeneity in the state of advancement of national policies, plans or strategies for rare diseases. This map shows the status quo as of May 2019.

The data in the map comes from the *Resource on the State of the Art of Rare Disease Activities in Europe*. Countries are asked to provide information on their national activities pertaining to rare diseases by responding to a structured survey. The questions in this survey are designed to enable countries to provide the data they pledged to submit when adopting the *EUCERD Recommendations on Core Indicators for Rare Disease National Plans and Strategies* in 2013.

Countries were asked *"How many OMPs with a European Union marketing authorisation are available in your country (i.e. are priced and reimbursed or directly provided by your country's health system)?"*

NB:

- Please note that data for a number of countries is still awaiting update; **therefore, these figures may change slightly in the coming months** (it is acknowledged that providing this information can be challenging).
- Clarifications will be sought from some MS.
- At present, **the MS depicted in grey** have not yet provided a response to this question.



'Alternative' routes to access OMPs and innovative therapies

It is sometimes possible for patients to access OMPs which have not yet received a marketing authorisation or which are not yet reimbursed in countries – an example is **'compassionate-use'**, sometimes called 'expanded access'. For instance, if a medicine is still working its way through the research and development stage, it may be accessible via this sort of programme for a patient (or group of patients) not eligible for/not included in the clinical trial.

- ✓ Compassionate use programmes are intended for cases when the medicine is expected to help patients with life-threatening, long-lasting or seriously debilitating illnesses, which cannot be treated satisfactorily with any currently authorised medicine.
- ✓ They can be intended for cohorts, or for individuals on a named-patient basis
- ✓ **Regulation (EC) No 726/2004** outlined the concept of Compassionate Use Programmes, emphasising that the product concerned must be working toward a Marketing Authorisation or else must be undergoing clinical trials. Member States are supposed to notify the EMA of Compassionate Use Programmes they employ.

The concept of compassionate use appeared in the 2008 Commission Communications on rare Diseases: Europe's Challenges (section 5.4) as follows: *"A better system for the provision of medicines to rare diseases patients before approval and/or reimbursement (so-called compassionate use) of new drugs is needed. Under the existing pharmaceutical legislation, the EMEA may issue opinions on the use of the product under compassionate use to ensure a common approach across the Community. The Commission will invite the EMEA to revise their existing guideline with a view to providing patient access to treatment."*

It is important to note that, although the EMA provides recommendations, countries make their own decisions on when to permit compassionate use. The efficiency of different national systems for Compassionate Use is variable. EURORDIS published a Position Paper on Compassionate Use in 2017, designed to raise awareness of this variation and to improve the status quo

Countries can also provide off-label access to medicines, for rare diseases and otherwise. (Off-label use is when a drug is used for an indication other than those specifically included in the labelling – this can be as significant as use for a different condition, or simply use at a different time of day).

Medicines Adaptive Pathways to Patients

The concept of Medicines Adaptive Pathways to Patients (MAPPs), or 'adaptive licensing' emerged from the realisation that there is a point after perhaps a decade of research and studies when a go or no-go decision is made concerning a marketing authorisation or a reimbursement. A 'No-Go' decision at this point, after years of financial, scientific, regulatory and emotional investment in a product, is regrettable for all parties. MAPPs represent a more flexible, non-traditional approach to bringing innovative drugs to market.

The key for many is 'early dialogue', to try to avoid products failing after so many years of development time, energy and cost. The essence of MAPPs is that alternative routes to availability should be permitted on the understanding that a greater collection of data will be collected in the post-marketing phase. (Usually, after marketing authorisation, there is a decline in data collection through observational studies and registries, as the number of patients taking the drug *without* surveillance increases significantly). For instance, under some adaptive licensing scenarios, an *Initial* License may be granted following clinical trials on a smaller number of patients, on the proviso that robust monitoring continues via studies and registry data collection until a point when the confidence is assured and *full* MA is awarded.

Evaluation of European regulations on medicines for rare diseases and paediatric populations

In recent years the Orphan Drug Regulation of 2000 has come under scrutiny. In 2016, **Commission notice 2016/C 424/03** facilitated the application of Articles 3 (criteria for designation), 5 (procedure for designation and removal from the register) and 7 (Union marketing authorisation).

In 2017, a 10-year evaluation report on the EU Paediatric Regulation was published. This report concluded that the Regulation had provided positive results overall in terms of paediatric product development, but that development for rare paediatric diseases, which is in many cases equally supported through the Orphan Regulation, often failed to materialise. Following this report, the European Commission announced a joint evaluation of the Paediatric and Orphan Regulations, due to take place in 2018-2019. The purpose of the evaluation is to provide an assessment of the strengths and weaknesses of the two Regulations, separately and combined, and to give insight in how the various incentives of the Regulations have been used and what the financial consequences have been. This information will be used to consider the possible need for future changes to the Regulations. The public consultation phase of this evaluation closed in early 2019, and a targeted consultation of stakeholders took place in June 2019. **The final report is due at the end of 2019.**

Health Technology Assessment for rare diseases

National (sometimes regional) Health Technology Assessment (HTA) bodies issue recommendations on health technologies to the healthcare system of a particular Member State or region. HTA is often associated with pharmacological products; however 'health technology' is actually a very broad term and includes medical and surgical interventions, medical devices, diagnostic tests, etc. HTA can include both clinical and non-clinical assessments of added-value.

In many EU countries, the decision on what to *do* with these assessments (e.g. determining whether to make a product available for reimbursement, and if so establishing the price) is usually made by payers; in other words, HTA is rooted in research and the scientific method, as opposed to price. A major cause of heterogeneity in levels of access to medicinal products is that generally speaking, the centralised European procedure ends with the marketing authorisation, whereas assessment of therapeutic value, pricing, and reimbursement decisions are handled by MS on an individual basis. There are many consequences to this, which each affect the availability of OMPs:

- For instance, when facing potentially 28 separate negotiations, Companies may prefer to first launch products in wealthier countries, establishing a benchmark too high for lower GDP countries to reach.
- National decisions on HTA are made very differently from country to country, even for the same product. A 2016 study (Kawalec et. al) analysed such decisions for the first 93 OMPs authorised in Europe: 23 of these had not been assessed in at least one of the countries.
- There appears to be ***no clear*** correlation between the assessment of value and the accessibility of the therapy through national reimbursement channels: the aforementioned study showed that despite a positive assessment in 50% of cases, the rate of reimbursement was significantly lower. In short, not all OMPs receiving positive assessments actually end-up

on reimbursement lists, whereas some negatively assessed products *will* be marked for reimbursement.

Many stakeholders have called for greater clarity and transparency in understanding the decision-making process around HTA in different countries.

European HTA Cooperation:

For many years, there have been calls to promote collaboration between countries on certain aspects of the HTA process.

- ✓ Art.15 of the 2011 Cross-border Healthcare Directive (2011/24/EU) called upon the EU to support and facilitate cooperation between national HTA bodies.
- ✓ The Health Technology Assessment Network was established (as a voluntary network) through an Implementing Decision in 2013, aimed at increasing scientific and technical cooperation.
- ✓ This network was supported by 3 successive EUnetHTA joint actions which have worked towards the piloting of joint assessments of relative effectiveness.
- ✓ In 2018 the European Commission published a **Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on health technology assessment and amending Directive 2011/24/EU**

The proposal for a new Regulation on HTA centres around common tools, methodologies and procedures across 4 areas:

1) Joint clinical assessments for innovative health technologies
2) Joint scientific consultations to enable developers to seek advice from HTA authorities
3) Horizon scanning/identification of emerging health technologies
4) Continuing voluntary cooperation in other areas.

Under the proposal, each individual country retains responsibility for the non-clinical aspects of HTA, and would continue to make all decisions pertaining to reimbursement and price. **The proposed Regulation would cover medicinal products but also certain medical devices**

The table below presents a VERY select overview of some past and ongoing initiatives, projects or resources with a particular relevance to this topic

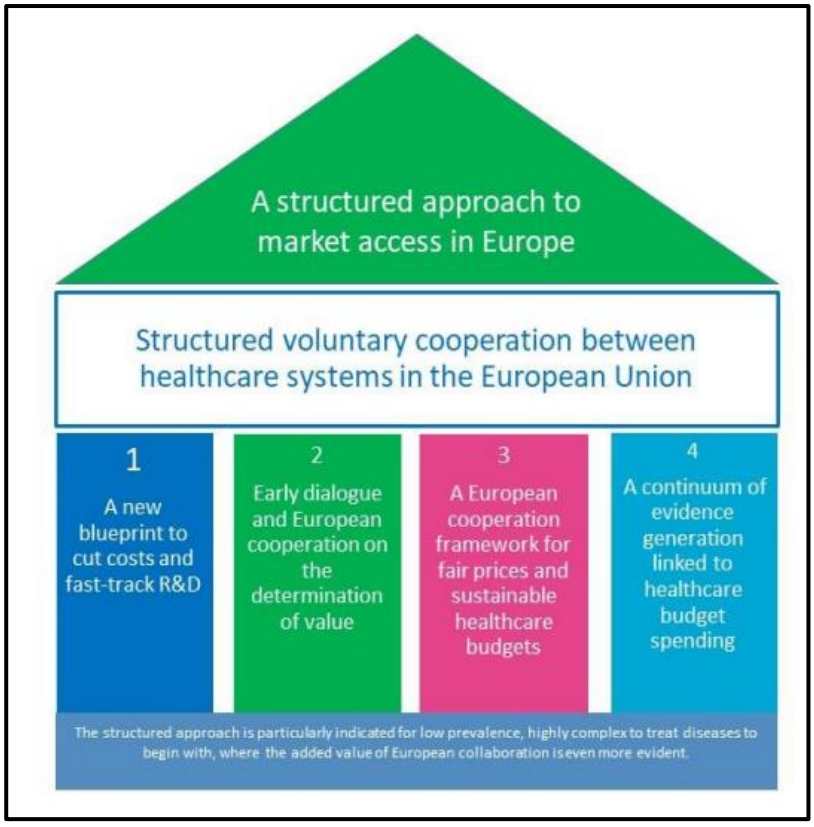
Initiative/Resource	Scope and Outputs
The Mechanism of Coordinated Access to OMPs (MoCA-OMP)	An initiative uniting patients, payers and companies. Created a tool called the 'European Transparent Value Framework', which is designed to structure discussions around the value of individual OMPs. MoCA was specifically focused on OMPs
'Breaking the Access Deadlock to Leave No One Behind'	A 2018 Position paper by EURORDIS and its members to propose possibilities for patients' full and equitable access to RD therapies in Europe. (see below)
EUCERD Recommendations on the CAVOMP-IF	As above – The Recommendations on ***Improving Informed Decisions Based on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow*** were adopted by the EUCERD in 2012.
'Early access to medicines in Europe: Compassionate use to become a reality'	A 2017 Position Paper on Compassionate Use from EURORDIS. Includes Recommendations to Industry; to national and European authorities; and to patients' organisations and healthcare authorities
European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL)	ORPH-VAL was a collaboration between rare disease experts, patient representatives, academics, health technology assessment (HTA) practitioners, politicians and industry representatives. It produced Recommendations in 2017 on 4 areas: OMP decision criteria; OMP decision process; OMP sustainable funding systems; and European co-ordination
The European Network for Health Technology Assessment (EUnetHTA)	EUnetHTA as an entity was formed in 2006. Since 2010 it has been supported as three successive European Joint Actions (the 3rd will end in 2020). EUNetHTA was established to harness synergies between regulatory evaluation and HTA along the lifecycle of a medicine. Outputs include shared tools such as the HTA Core Model®, a methodological framework for production and sharing of HTA information. EUnetHTA is not specific to rare diseases.
Health Technology Assessment Network	The HTA Network was established in 2013 answer to Art. 15 of the Cross-Border Healthcare Directive (2011/24/EU). All EU countries are represented. The goal is to provide strategic and political guidance to the scientific and technical cooperation of HTA at EU level.
ADAPT-SMART	This project –funded by the Innovative Medicines Initiative, from July 2015 to April 2018- investigated MAPPs tools and methodologies, engaging in dialogue with all relevant stakeholders to prove and develop MAPP concepts. ADAPT-SMART was not specific to RD but has a clear relevance to this community. Results are available here
PRIME	PRIME is an EMA initiative to enhance support for the development of medicines that target an unmet medical need. The scheme is voluntary and centres upon early dialogue and stronger interactions with developers, through scientific advice. It seeks to improve trial design to generate better data more suited to the MA application. PRIME is not specific to OMPS but includes medicines for RD

2018 EURORDIS Position Paper

In 2018, EURORDIS and members issued a position paper 'Breaking the Access Deadlock to Leave No One Behind'. The paper is designed to address the issues around availability and accessibility to OMPs, as part of EURORDIS' ambition to have 3 to 5 times more new rare disease therapies approved per year, 3-5 times cheaper, by 2025.

The position paper outlines a framework composed of 4 pillars.

It concludes with a number of key recommendations to 'break the deadlock':



(Image from the 2018 EURORDIS position paper)

- All EU Member States already engaged in multi-country cooperation platforms should accept to join voluntarily to establish the "European Table of Negotiation". If not all EU27, a significant number will create a population critical mass enabling to address the challenge of rarity, hence immediately becoming the pivotal partner for negotiations and launching a dynamic.
- All EU Member States on board the "European Table of Negotiation" should commit to examining, in an open multi-stakeholder format, the innovative approach to lay out a more transparent pathway to the construction of prices (based on costs, compounded by a determination of the value of the product, and adjusted by premiums and discounts as relevant).
- All EU Member States on board the "European Table of Negotiation" should commit to entering into Joint Price Negotiations or Joint Purchasing as the next step – if only for orphan medicines at the beginning – and to formalising the outcomes of these negotiations into Managed Entry Agreements with manufacturers.
- All EU Member States on board the "European Table of Negotiation" should commit to exploring much further the feasibility of applying differential pricing mechanisms to the agreed "European Transactional Price", as a means to tailor the said price to their respective levels of purchasing power and domestic wealth.
- All EU Member States on board the "European Table of Negotiation" should commit to considering discounts for uncertainties, payments based on outcomes, formative HTA assessments and all other appropriate modalities or techniques so as to provide early patient access to medicines approved under exceptional circumstances, under conditional approval, at the end of stage 2, or in any other situation when uncertainties are high or significant

Global legislation around OMPs

In the US, the Orphan Drug Act has been in place since 1983. It provides orphan drug designation for medicines, biologics, or medical foods intended for the safe and effective treatment, diagnosis, or prevention of rare diseases/disorders which affect fewer than 200,000 people in the US, or which affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug. There are currently more than 3500 products with active orphan designation in the US (i.e. not withdrawn). As of the end of 2018, over 600 orphan drugs had been approved. A search of the FDA site shows over 800 instances authorisations (including some instances of the same product authorised for new indications) (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/)

Following the success of the US Orphan Drug Act, a number of other countries (outside of Europe) have also implemented orphan drug policies, including Singapore (1991), Japan (1993, update of earlier RD legislation), Australia (1997), and Taiwan (2000) (for further details see the 2018 Overview Report from the Resource on the State of the Art of Rare Disease Activities in Europe, p23 onwards)

Medical Devices for Rare Diseases

'Medical Devices' as a term, is incredibly broad. Over 500,000 devices are on the market in Europe, including medical software. The first legislation in Europe for Medical Devices emerged only in the 1990s, and began operating via the existing system of 'notified' bodies ('Notified' bodies are national bodies recognised and authorised to perform assessments of products – countries 'notify' the EC 'of these bodies, which are then added to the NANDO database (which contains hundreds of such bodies).

Medical Devices are very important for people with rare diseases, an importance which is arguably *heightened* by the absence of a dedicated medicinal treatment for 95% of the conditions classed as rare. Specialised devices can make a huge difference to the diagnosis, treatment, care and quality of life of this population; however, the cost of (particularly customised) devices can be prohibitive and, as is the case for OMPs, they may not be included in an appropriate reimbursement system.

The topic was incorporated to the **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]** as follows:

5.5 Medical devices: *"The Orphan Medicinal Product regulation does not cover the field of medical devices. The limited size of the market and the limited potential return on investment is a disincentive. The Commission will assess whether there is a need for measures to overcome this situation, possibly in the context of the forthcoming revision of the Medical Devices Directives."*

In April 2017, two new regulations for Devices were adopted:

- Regulation (EU) 2017/745 on medical devices;
- Regulation (EU) 2017/746 on in vitro diagnostic medical devices

Entering into force in May 2017, these Regulations replace the previous Directive (Directive 93/42/EEC concerning medical devices) meaning their contents are directly applicable at national level without requiring transposition through specific national legislation. One of the main strengths of the new

legislation is **greater emphasis on greater clinical evidence**, as opposed to only safety and risk/benefit ratio. There is also stronger emphasis on post-marketing surveillance for devices. However, issues remain; for instance, notified bodies do not need to publish their clinical evaluation assessments, meaning there is a lack of transparency. Most European countries treat pharmaceuticals and devices desperately, through entirely different agencies and units, in fact.

Despite the improvements offered by Regulation (EU) 2017/745, there is no European agency for medical devices – i.e. no equivalent of the EMA – to perform centralised reviews and authorisations. The EU is supposed to support the process; however, the main activity here will likely be the launch of the second generation of the EUDAMED (European database on medical devices) database, expected in 2020. There is also no European process for the conditional approval of devices: notified bodies are able to grant this, but supposedly only upon assurance of a robust data-collection strategy and data submission after 12 months, which may not in fact materialise.

Unlike in the case of OMPs, there are no incentives in the existing European legislation for the development of medical devices intended specifically for rare diseases. The United States, by comparison, has a 'Humanitarian Use Device' exemption for devices intended for conditions affecting/manifesting in no more than 4000 people in the US each year.

The 2018 **Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on health technology assessment and amending Directive 2011/24/EU** which aims at supporting a European approach to HTA clinical assessments includes a selection of Class II, IIIb, and In-vitro diagnostics Devices.

Repurposing of Medicines

Drug repurposing is a good example of innovation in research and care – it centres upon the use of a rigorous scientific process to find new ways to make use of existing medicinal products. Greater understanding of the underlying causes and biochemical pathways responsible for rare diseases opens up opportunities to use existing medicines to address impairments and errors. Drug screening and data mining approaches can identify promising candidates. Repurposed medicines carry the advantage of a strong safety profile, and although preclinical and clinical studies may still need to be performed in the newly-intended community, the extent and therefore the costs of such activities are often lower than developing a brand new medicine from scratch (there will usually be robust data on the pharmacokinetic performance, for instance).

Groups such as Findacure are raising awareness of repurposing opportunities in the rare disease community (and indeed are accelerating these). At European Level, the Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) is currently focusing on the potential of repurposing

Results of the Rare2030 literature review

As a consequence of the commercial unattractiveness of orphan medicinal products, one can observe a diversity **of incentive policies**, most notably in Europe or the United States, in order to guarantee the availability of orphan medicinal products (Annemans et al. 2017; Gong and Jin 2012). Indeed, the nature of rare diseases, affecting few and scattered patients, induces high costs for orphan medicinal products and is often viewed as a serious burden for healthcare systems. In addition, the current economic crisis and tendency to reduce public spending strengthen the hurdles for their development. The small population concerned as well as the substantial research costs associated with orphan medicinal products are also great impediments to research in the field of rare diseases (Gammie et al. 2015).

Two types of incentives can be distinguished: push and pull incentives. Push factors comprise various mechanisms such as the allocation of subsidies for research, tax credits, intellectual property rights, patent buyouts, public innovation funding and grants and fast-track procedures. Pull incentives include mainly long market exclusivity and authorisation criteria. Most of these are present in Europe and the United States and some are also applied in China, demonstrating the global characteristic of this trend (Gong and Jin 2012; Patel and Miller Needleman 2019).

Moreover, as a means to regulate the availability of orphan drugs and the orphan drug market, countries tend to establish regulatory agencies such as the Committee for Orphan Medicinal Products or the US Food and Drug Administration, which offer a framework for and facilitate research on treatments for rare disease (Gammie et al. 2015). Pieces of legislation are gradually drafted and implemented - cf. Regulation (CE) N°141/2000 for the European Union and the 1983 Orphan Drug Act for the United States - to enhance orphan drug research, development and marketing (Gammie et al. 2015; Wellman-Labadie and Zhou 2010) .

Besides the public efforts to incentivise the production of new orphan drugs, the **state of the market and the technological advances** can also act as drivers attracting certain pharmaceutical companies towards rare diseases (Mingorance 2018). In fact, the unfavorable and competitive market conditions, specificities of rare diseases combining the absence of drugs and high clinical unmet needs, and technological innovations in genomics, push small, technology-focused companies to invest in orphan drug development, pushing them away from the canonical “blockbusters” research programmes (Attwood et al. 2018; Mingorance 2018). Nonetheless, the **maturity of the drug pipeline also needs to be taken into account** when examining the attractiveness of rare diseases (Mingorance 2018).

As a whole, the more general trend which emerges out of the association of all these phenomena is a **reasonable availability rate of orphan drugs, at least in Western and economically influential regions of the world, but at a very high price** (Hughes-Wilson et al. 2012).

This creates an issue in terms of **real accessibility of such treatments which is utterly different from their availability** (Blankart et al. 2013) **and is particularly heterogeneous**. Indeed, reimbursement policies vary across Europe regarding the share of reimbursed orphan drugs and the possibility of direct provision by healthcare systems. A schism exists between countries of Western and Eastern Europe but also among European countries and within the same country (Bourdoncle et al. 2019;

Deticek et al. 2018; Korchagina et al. 2017; Pejcic et al. 2018; Szegedi et al. 2018). As a result, a trend pushing for **harmonisation of orphan drug reimbursement and prices in Europe** can be observed. As a matter of fact, market exclusivity is an effective measure to foster drug availability but can be detrimental to patient access when pharmaceutical companies benefit from this exclusivity to maintain a high price when the costs of development have already been compensated (Blankart et al. 2013; Waxman et al. 2019). Indeed, as the spending on orphan medicinal products as a proportion of GDP and healthcare expenditure is similar between lower and higher income countries, those with fewer resources cannot guarantee the same level of accessibility to these products (Szegedi et al. 2018). As such, one can distinguish a trend challenging the efficacy of legislation around orphan medicinal products as some practices of companies are seen as abuses of dominant position and generate inequity in patient access (Blankart et al. 2013; Waxman et al. 2019; Wellman-Labadie and Zhou 2010).

The variation in reimbursement rates and policies therefore suggests the need and prompts a call for **new assessment methods** and a different prioritisation of criteria for reimbursement. Our literature review showed a trend towards a re-evaluation of the standards in place **challenging the most common cost-effectiveness threshold test**, a gradual **incorporation of social preferences**, an **acknowledgement of the importance of disease and socio-economic burden for decision-making** as well as a desire to **tailor health technology assessments to the specificities of orphan drugs** (Annemans et al. 2017; Hughes-Wilson et al. 2018; Iskrov et al. 2016; Nicod et al. 2017; Rizzardo et al. 2019). Others also describe the l**ack of mutual understanding between payers and manufacturers** and **lack of transparency for orphan drug prices** (Annemans et al. 2017; Waxman et al. 2019).

Furthermore, the high cost of orphan drugs and their impact on the public budget creates a problem of potential shortages of orphan drugs and a serious challenge to patient care (Jaroslawski et al. 2016). Our horizon scanning regarding this issue indicates that some alternatives are being explored to limit the risks of shortages and increase the number of treatments and therapies. For instance, some researchers study the possibility of **drug repurposing, generic substitution, off-label use and early-access and advanced therapy medicinal products are being incentivised by a specific regulation implemented by the Committee for Orphan Medicinal Products** (Balasubramanian et al. 2016; Di Paolo and Arrigoni 2018; Dooms 2016).

Finally, the last trend detected concerns the **involvement of patients for drug development.** Studies show that they would appreciate the **incorporation of patient experiences for coverage decision-making** and to improve care and raise awareness of rare diseases, which is currently used as a means to reduce uncertainties in clinical benefit (Menon et al. 2015; Young et al. 2018).

***Possible* trends emerging from the Literature Review:**

- public incentives
- establishment of regulatory bodies and legislation
- market changes and technological innovations
- inequity and heterogeneity of patient access
- questioning of the efficacy of OMP legislation - commercial abuses
- call for new assessment methods and prioritisation for reimbursement decision-making

- involvement of patients in drug development processes

Possible **drivers of change emerging from the Literature Review:**

- market/economic conditions
- technological innovation

References from the rare disease literature review

Full list of articles/publications found in the literature review:
https://docs.google.com/spreadsheets/d/1SRXASsFiD9sdQz286SVo860XdTpGaOIncyjIhGphULI/edit#gid=364400914

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Knowledge Base Summary

Basic, Clinical, Translational and Social Research for Rare Diseases

Introduction to the Topic

The boundary between research and care is often somewhat blurred in the rare disease field. The lack of treatment options for so many conditions (ca. 95%) necessitates a reliance on research to give patients their best chance for appropriate diagnosis, treatment and care. Naturally, 'research' as a topic is vast. This document seeks to highlight just a few fundamental activities of relevance to the rare disease research status quo, from a policy perspective. Arguably, much of the potential of the European Reference Networks, launched in 2017, stems from the fact that aside from being the first pan-European structures dedicated to care, the networks also have a strong research focus, hence the document highlights this added-value. Global and international developments in research are summarised. Approaches to optimise the use and reusability of rare disease data have a strong potential to drive forwards research. Patient partnerships, at all levels, are increasingly recognised as essential to the integrity and success of research. A few select statistics concerning research into new OMPs and Medical Devices are incorporated, as is the status quo regarding research into the social and socio-economic impact of rare diseases. Finally, the Research Infrastructure landscape provides a rich backdrop to support and streamline rare disease research, and thus is also is featured here.

As research is so cross-cutting, many topics in the 'foundational' European policy documents are relevant here. For instance, RD research requires an agreement on definitions of what constitutes a rare disease; capacity entails the visibility and recognition of expertise and where it lies, via well-designed centres of expertise for rare diseases which network effectively. Research entails an understanding of the natural history of rare diseases, which typically comes from longitudinal natural history studies, for instance based upon registries (if sufficiently 'open' to allow for the uncovering of unknowns) or by 'mining' clinical care records.

Beginning with the **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final],** particular chapters relate to Medical Devices (see below). Section **5.6** concerns **Incentives for Orphan Drug development**:

"Pharmaceutical companies invest heavily over a long period of time to discover, develop and bring to market treatments for rare diseases. They need to be able to show a return on investment. However, the ideal is that they are also able to reinvest that return on investment into discovering more treatments. With more than 45 treatments authorised in the EU – and some for the same conditions – there are still many conditions with no treatment. ***Exploring additional incentives at national or European level to strengthen research into rare diseases and development of orphan medicinal***

products, and Member State awareness with these products should be encouraged in accordance with Article 9 of Regulation (EC) No 141/2000."

Section 5.11. Registries and databases reads as follows: "*Registries and databases constitute key instruments to increase knowledge on rare diseases and develop clinical research. They are the only way to pool data in order to achieve a sufficient sample size* ***for epidemiological research and/or clinical research.*** *Collaborative efforts to establish data collection and maintain them will be considered, provided that these resources are open and accessible. A key issue will also be to ensure the long-term sustainability of such systems, rather than having them funded on the basis of inherently precarious project funding.*

Section 5.12 is entirely dedicated to **Research and Development**

"For most severe rare diseases that would potentially be treatable, there is simply no current specific treatment. The development of therapies faces three hurdles: the lack of understanding of underlying pathophysiological mechanisms, the lack of support of early phases of clinical development and the lack of opportunity/cost perception from the pharmaceutical industry. Indeed, the high cost of drug development, together with the estimated low return on investment (due to very small patient populations), has usually discouraged the pharmaceutical industry from developing drugs for rare diseases, despite the huge medical need. A process of early dialogue regarding medicines under development should be established between these companies and authorities funding medicines. This will give the sponsoring company more certainty on its potential future return and will give authorities more knowledge and trust in the value of medicines it will be requested to assess and fund. Rare diseases research projects have been supported for more than two decades through the European Community Framework Programmes.[…] Coordination projects aimed at an optimal use of the limited resources dedicated to research on rare diseases should be encouraged. As an example, the EU FP6-supported ERANet project (E-Rare) currently coordinating the research funding policies for rare diseases of seven countries contributes to tackling the fragmentation of research efforts. Such approaches should be given due consideration."

The **Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02** highlighted the EC commitment to rare disease research (Preface 6): "*Rare diseases were one of the priorities of the Community's sixth framework programme for research and development and continue to be a priority for action in its seventh framework programme for research and development,* ***as developing new diagnostics and treatments for rare disorders, as well as performing epidemiological research on those disorders, require multi-country approaches*** *in order to increase the number of patients for each study."*

It also emphasised the need for **sustainability** of research enterprises: (Preface 22) *"The* ***development of research and healthcare infrastructures in the field of rare diseases requires longlasting projects and therefore an appropriate financial effort to ensure their sustainability in the long term****…"*

Moving on to the 'Recommendations to Member States', an entire section is dedicated to RESEARCH ON RARE DISEASES (section III), with the following requests:

- "6. Identify ongoing research and research resources in the national and Community frameworks in order to establish the state of the art, assess the research landscape in the area of rare diseases, and improve the coordination of Community, national and regional programmes for rare diseases research.
- 7. Identify needs and priorities for basic, clinical, translational and social research in the field of rare diseases and modes of fostering them, and promote interdisciplinary cooperative

approaches to be complementarily addressed through national and Community programmes.

- 8. Foster the participation of national researchers in research projects on rare diseases funded at all appropriate levels, including the Community level.
- 9. Include in their plans or strategies provisions aimed at fostering research in the field of rare diseases.
- 10. Facilitate, together with the Commission, the development of research cooperation with third countries active in research on rare diseases and more generally with regard to the exchange of information and the sharing of expertise."

Guiding Questions for Panel of Experts Discussion – to support the identification of trends and drivers of change

1. **How far have EU countries addressed the requests in the *2009 Council Recommendation on an action in the field of rare diseases* (as above)**
2. **How do we accelerate the rate of progress for basic, clinical, translational, and/or social research?**
3. **What would be a 'game-changer' for rare disease research?**

The International Rare Disease Research Consortium (IRDiRC)

To achieve its goals, IRDiRC has undertaken numerous dedicated actions to increase access to harmonized data and samples, enhance the molecular and clinical characterization of rare diseases, support translational, preclinical and clinical research, and streamline ethical and regulatory procedures. IRDIRC organised itself into:

- 3 constituent committees (dedicated to funders, companies, and patient advocates respectively); and
- 3 scientific committees (Therapeutics, Diagnostics, and Interdisciplinary).

Under each of these sits a number of dedicated Task Forces:

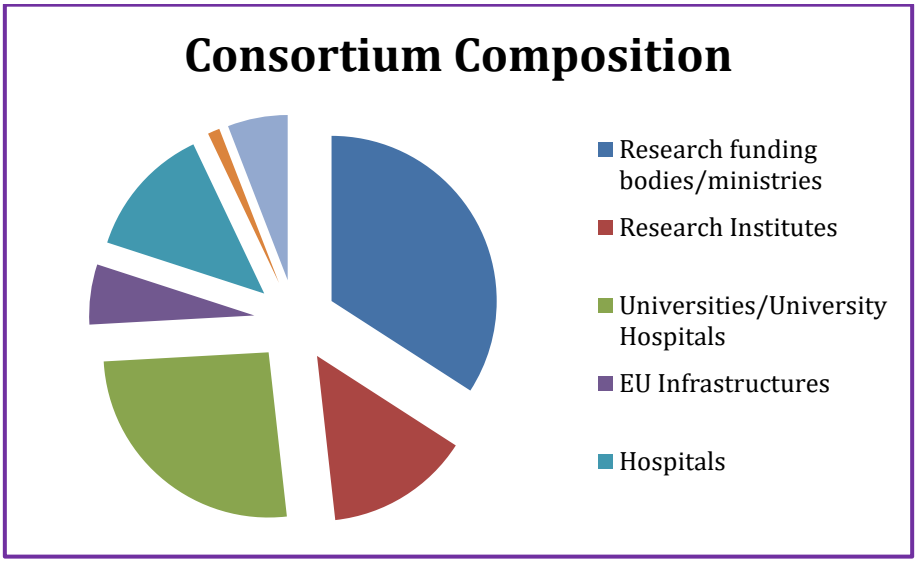
- Automatable Discovery and Access
- Data Mining and Repurposing
- International Consortium of Human Phenotype Terminologies
- Matchmaker Exchange
- Model Consent Clauses for Rare Disease Research
- Patient Centred Outcome Measures
- Privacy-Preserving Record Linkage
- Small Population Clinical Trials
- Solving the Unsolved

European Joint Programme for Rare Disease Research

The European Rare Disease research field is currently in the first year of a European Joint Programme Co-Fund for rare disease research. A European Joint Programme (EJP) is an instrument allowing high-level strategic organization and performance of research activities in an organized and transversal manner. It is operated by Programme Owners (typically ministries) and Programme Managers (Research Funding and Research Performing organizations) in conjunction with other relevant stakeholders (e.g. patients' organisations, regulatory bodies and the private sector).

The 2018 Work Programme of H2020 included a very important call, to establish an EJP in the field of rare disease research (SC1-BHC-04-2018) for 5 years (2019-2023). The total budget of the entire EJP is expected to exceed €110 million (€55 million directly from the EC, supplemented with substantial national and in-kind contributions).

33 countries are currently participating in total, from 25 EU Members States, 8 Associated Countries, and one Third Country (Canada).



Part of the EJP mission is to continue the successes of E-RARE 3 , which covers the period 2015-2019. E-RARE 3 involves 25 partners (public bodies, ministries and research funding organizations) in 17 countries. A major focus has been the transnational calls (in which each Country funds the participation of its own RD researchers). E-Rare3 follows two very successful ERA-NETs - E-Rare-1 (2006-2010) and E-Rare-2 (2010-2014): in seven years, 56.4 Million Euros were invested to fund 79 research projects involving 347 research teams.

The main goals of the EJP RD are as follows:

- 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

The EJP operates through 4 interconnected pillars:

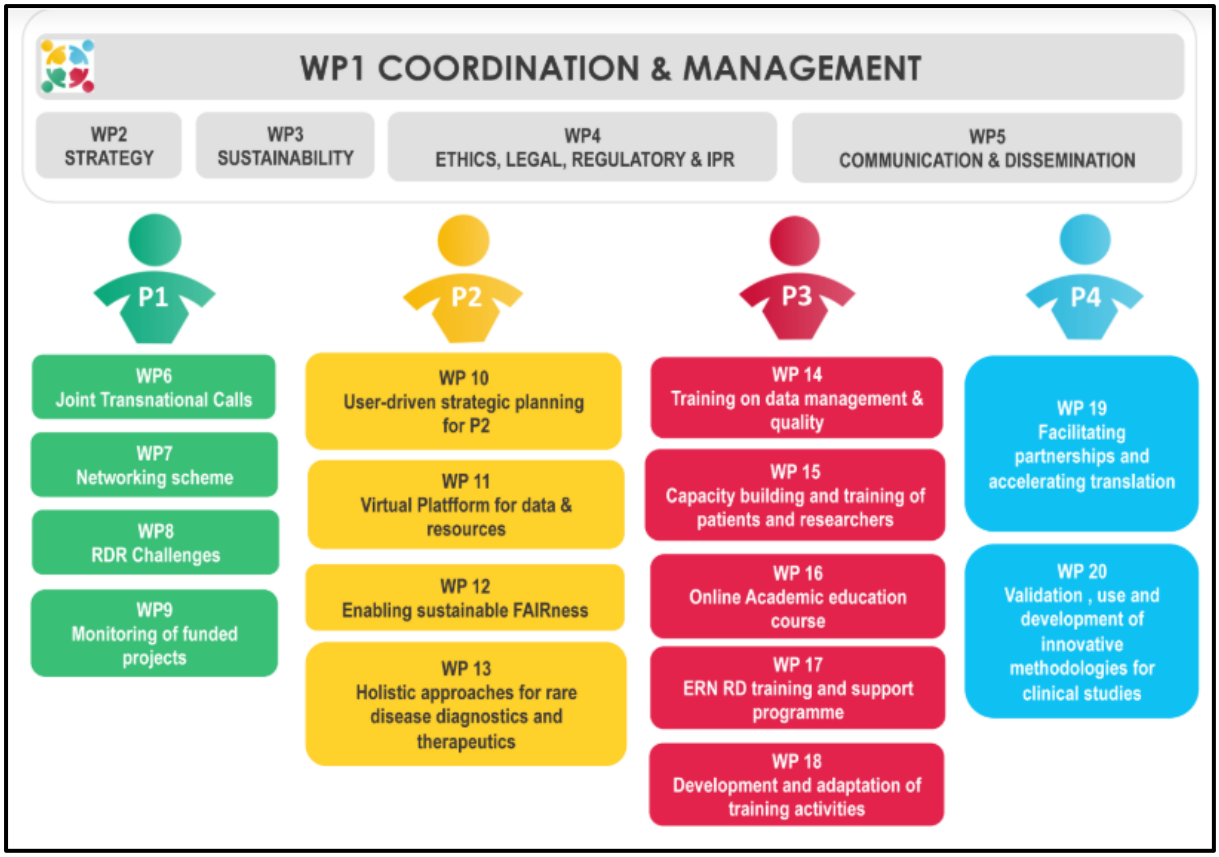


Image from EJP-RD website

Building a better data ecosystem for rare disease research

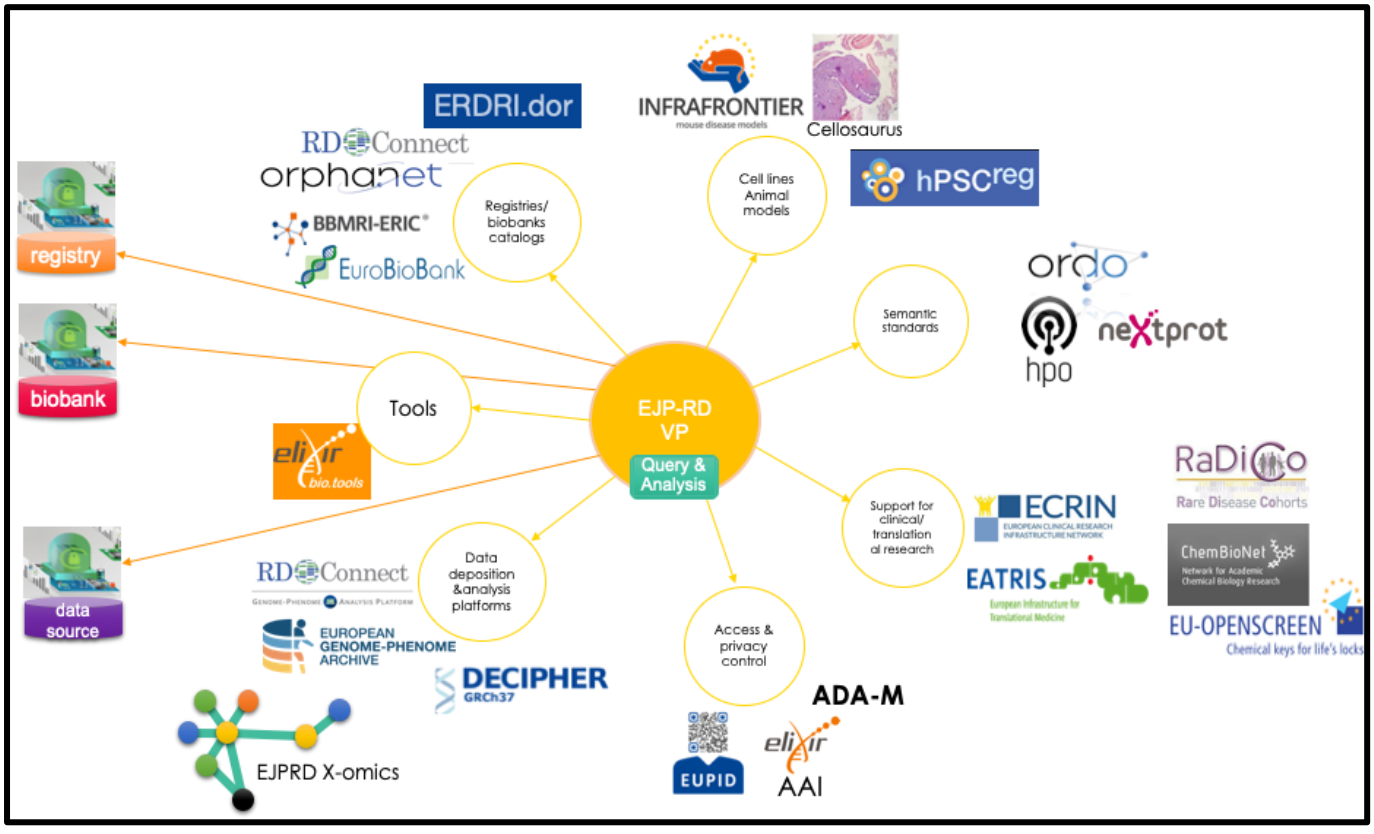
In recent years, rare disease research has increasingly emphasised the importance of linking and somehow sharing or federating precious data relating to rare disease patients, which traditionally is fragmented and siloed. RD-Connect, for instance, initiated several major drives to increase the usability and reusability of data from registries, databases, biobanks and bioinformatics. The main output of RD-Connect, the Genome-Phenome Analysis platform was intended to be piloted using real genomic and phenotypic data from two linked projects: EURenOmics, dedicated to the molecular characterisation of rare kidney diseases; NeurOmics, dedicated to the molecular characterisation of rare neuromuscular and neurodegenerative diseases.

Some of this work involved developing use cases to link data from different sources, and the use of agreed ontologies became increasingly important if RD data was ever going to become interoperable between systems and countries. The IRDiRC gave two such ontologies its 'IRDiRC Recognised Resources' label: the Orphanet Rare Disease Ontology (the ontological form of the OrphaCode) and the Human Phenotype Ontology. These are now considered by many to be the most appropriate and sensitive (in terms of granularity) ontologies for capturing diagnoses and giving visibility to individual RD, and for capturing the 'deep' phenotypic data so important for diagnostics and in understanding the natural history of a condition. The ability to link/query data from distinct but searchable sources embraces the spirit of the FAIR data principles, which originated outside of the RD field but are especially pertinent in domains which necessitate a significant level of data 'sharing'. FAIR is an

acronym, standing for Findable, Accessible, Interoperable, Reusable. The concept was developed by a team of scientists and data experts led by Prof. Barend Mons and has –particularly since publication of a key 2016 paper - gained traction globally: organisations which endorse FAIR data principles include ELIXIR, BBMRI, the European Open Science Cloud, FORCE11, NIH through its 'commons' program, and the G20.

The FAIR principles acknowledge that actually *exchanging* data between centres and certainly between jurisdictions is challenging. Instead, 'FAIR' promotes the concept of making data *queryable*, which is an efficient -and far more achievable- goal. A key publication is http://www.nature.com/articles/sdata201618 and there is a useful introduction to using FAIR concepts here. In 2017, a number of fields established **GO-FAIR Implementation Networks**, designed to unite stakeholders interested in promoting the spread of FAIR principles in their particular domain, working towards an ecosystem of FAIR data services. In 2018 a GO-FAIR Implementation Network for Rare Diseases was established, seeking to anchor together the individual 'FAIRification' efforts in the RD field.

Pillar 2 of the EJP is going to develop a **federated ecosystem of FAIR-at-the-source resources**, as part of its Virtual Platform (VP in the image below) in order to enable data discovery, sharing and analysis down to the record level:



Patient partnerships in rare disease research

By providing training, patient advocacy groups empower patients and ensure they have the confidence and knowledge needed to bring their expertise to discussions on **leadership, digital health, health care, research and medicines development** with policy makers, industry and scientists. Examples of such trainings at the European and International level include:

1. EURORDIS - Rare Diseases Europe Open Academy
2. European Patients Academy (EUPATI)
3. Patient Centred Outcomes Research Institute (PCORI) Training for Rare Disease Patient Advocates
4. Numerous patient trainings by national or disease-specific patient organisations

EURORDIS identifies and supports rare disease patient representatives for participation in:

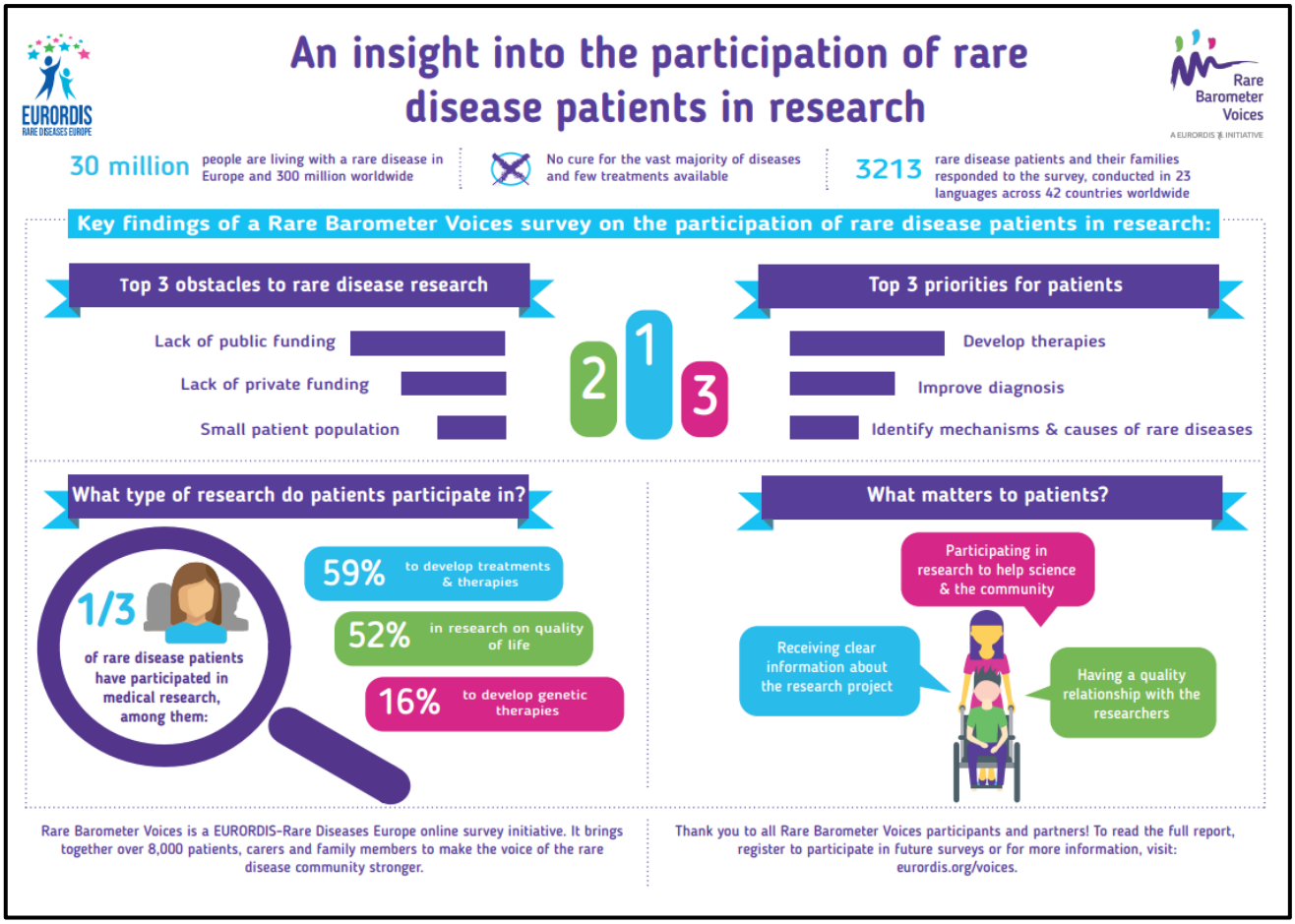
- Patients' representatives involved in EMA scientific committees and working parties
- Protocol assistance
- Scientific Advisory Groups (SAG) at the Committee for Human Medicinal Products
- Other meetings such as discussions on guidelines and risk management programmes

EURORDIS also provides the link between its trained alumni and research, regulatory and healthcare provision by:

- nominating patient representatives to the European Medicines Agency (EMA), where trained patients actively engage in scientific committees and working parties, protocol assistance, Scientific Advisory Groups (SAG) at the Committee for Human Medicinal Products, other meetings such as discussions on guidelines and risk management programmes
- creating the European Patient Advocacy Groups (ePAGs) in every European Reference Network to promote a patient-centric approach in both delivery of clinical care, service improvement and strategic development and decision-making
- representing patient needs alongside 13 international organisations on the International Rare Disease Research Consortium (IRDiRC) Patient Advocates Constituent Committee (PACC)

With the growing recognition that patients can and should be more involved in the medicines development process, a multistakeholder effort to develop a framework for structured, effective, meaningful and ethical patient engagement supporting the integration of patient perspectives into drug development is underway via the landmark PARADIGM IMI project.

In 2018, the results of a large-scale European survey of over 3000 rare disease patients were released. Respondents to the Rare Barometer Voices survey were asked about obstacles to research, priorities for patients, what *matters* to patients, and what type of research patients wish to participate in. The full report is available here and the following infographic was created to highlight the key findings.



(Infographic courtesy of Rare Barometer Voices)

ERNs and Research:

In Summer 2018, a workshop on the topic of 'How ERNs can provide added value in the area of clinical research' took place at the EMA, co-organised by RD-ACTION & DG-SANTE. The workshop highlighted some of the specific advantages of the ERN model (see the full output, on Conclusions and Next Steps, here):

- **Permanence:** ERNs are permanent structures– they are not time-bound projects but should, assuming the 5 year evaluations are positive, become sustained structures sitting alongside and complimenting existing national channels and entities.

- **Proximity of Research and Clinical Spheres:** The Legal Acts upon which ERNs are based mandate the unity of clinical and research expertise. This offers the opportunity for ERNs to make significant strides in translational research.

- **Comprehensive Disease Coverage:** ERNs have a mandate to, in time, address all rare diseases under their 'Thematic Grouping'. The *EUCERD Recommendations on RD ERNs* proposed that such a development should logically be stepwise, For the first time, conditions will all have 'a home' in theory, under at least one of the Networks (sometimes more than one). This could foreseeably lead to research attention and activity in hitherto unexplored/untapped disease

areas, which perhaps have not been the recipients of specific funding to date, and which do not have resources to stimulate clinical research.

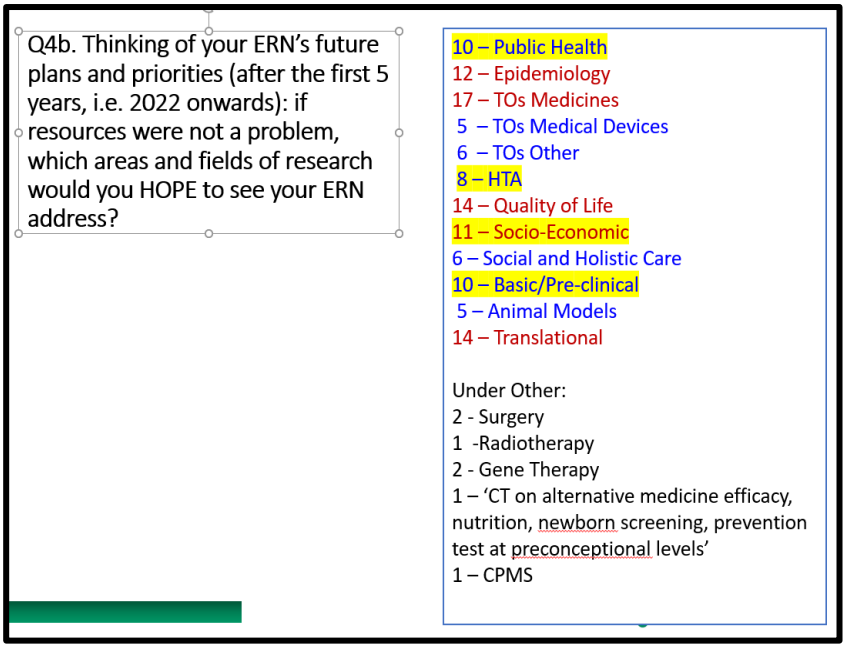
- **Data Generation/Linkage Opportunities:** ERNs provide unprecedented opportunities to collect good quality, relevant, and interoperable data which can be used effectively for a specific purpose at hand (e.g. a clinical consultation through the CPMS, or to elucidate genome-phenome associations through inclusion in an appropriate registry) but can also be *re*-used, for a number of essential purposes. ERNs are based upon centres which have demonstrable expertise in particular areas, but the Networking tools which connect these well-established centres are being created -or at least delivered- anew. This offers exciting opportunities for the almost 1000 individual HCPs across Europe to subscribe to best practices around collecting and pooling precious RD data which would support the provision of highly specialised care. ERNs are very well positioned to build platforms and infrastructure -especially perhaps registries- for collaborative research with a standardized approach and broader focus (beyond a single disease). They can be perfect curators to collect real word evidence (RWE) and conduct natural history studies. There is a chance here to establish data collection infrastructure (e.g. CPMS, registries, etc.) 'optimally' from the start, and apply good practices to data collection, standardisation and sharing.

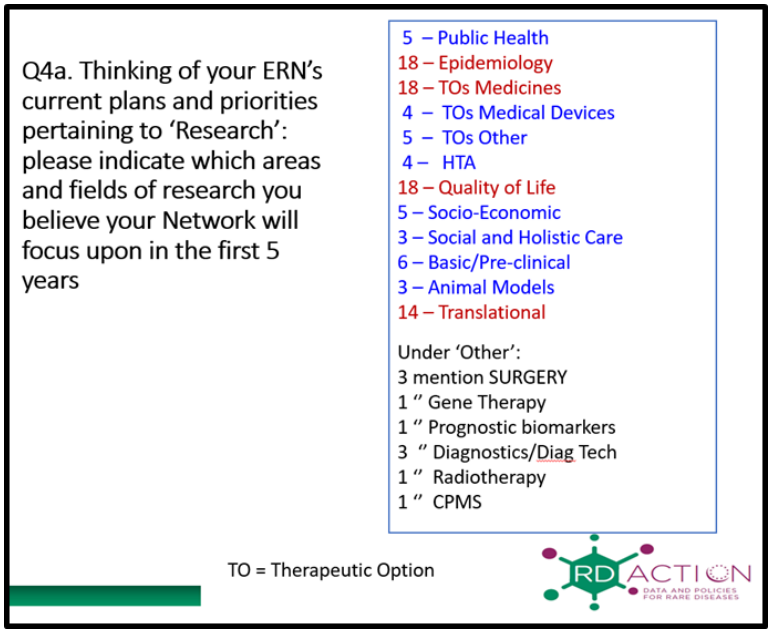
- **Cross-fertilisation of Expertise:** Several survey respondents *and* workshop participants emphasised the added-value of the ERN structure. As above, broad disease groups are brought together under a single heading, and compartmentalised into subdomains. Groups attested the advantage of working and liaising with colleagues in different sub-domains, in terms of forging new collaborations, elucidating characteristics of the diseases they work on, sharing proposals for new research and therapy development etc., presumably none of which would have happened in the pre-ERN environment.

- **Patient Involvement:** Patients sit at the heart of the ERN concept (indeed the concept *emerged* largely from the patient community in Europe). The Addendum to the EUCERD Recommendations stipulated that Patients should have a meaningful role in all levels of ERN activity, governance included. Also, by simplifying and streamlining recruitment of patients for trials, ERNs could contribute to bring the trials to the patients, rather than the other way around as is currently the case.

- **Reputational Excellence**: ERNs have strong potential to represent a certain 'seal of approval'. On the one hand, it is important that ERNs are not viewed as an exclusive club: not all centres with expertise in rare and complex diseases will be part of these Networks formally, and indeed this was never the concept of an ERN. On the other hand, the ERNs should absolutely be viewed as something unique, as a concentration of the expertise which exists in Europe. The combined expertise of an ERN and its composite centres/tools/resources should enjoy a certain reputation in the field, with the ERN logo signifying a 'trusted' badge of quality conveying reputational status for research activities.

In preparation for this workshop a survey was completed by 21 of the 24 ERNs. Networks were asked which sorts of research they planned to focus on across the first 5 years of operations. The results showed that research on epidemiology, therapeutic options, Quality of Life, and Translational research were the most highly prioritised (ERNs were free to select all options that applied).



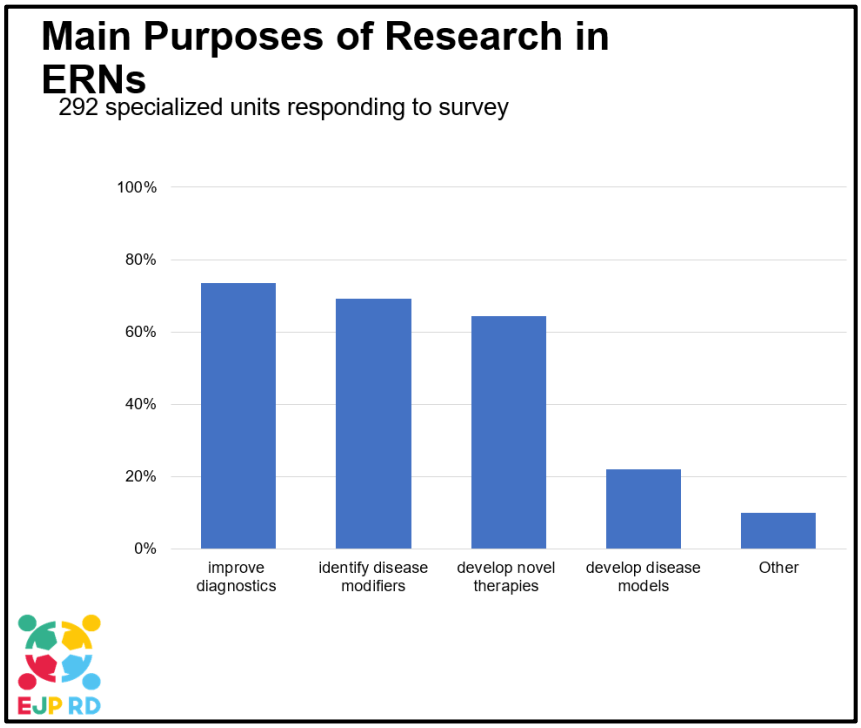


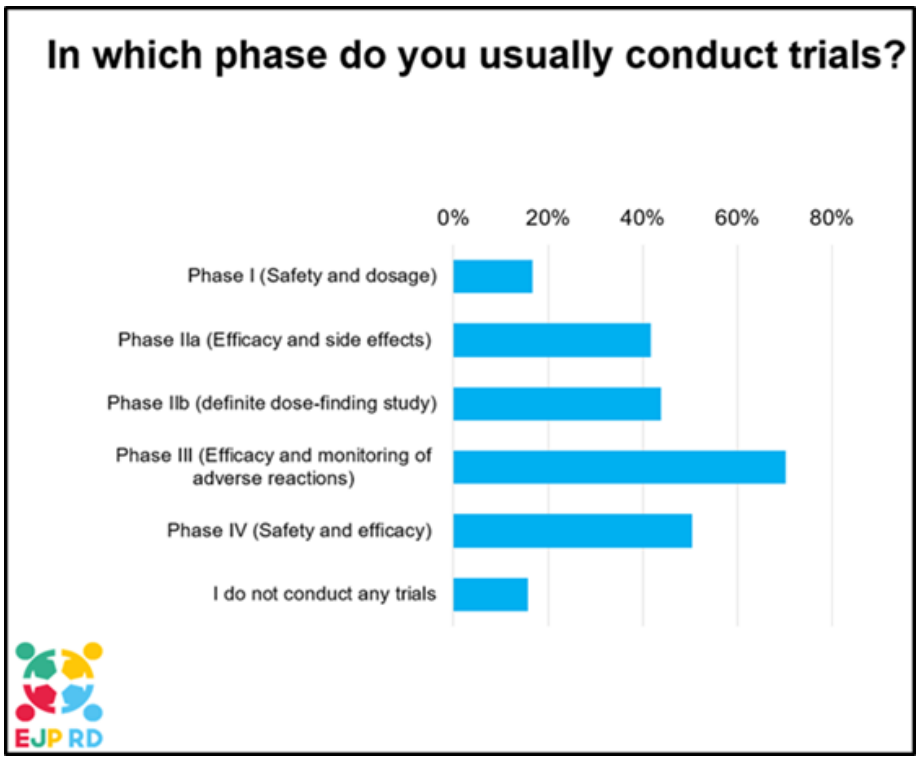
When asked about research priorities beyond 5 years, a number of additional types of research gained popularity (as highlighted in yellow)

In March 2019, the **EJP-RD** conducted a survey intended to clarify the research activities and intentions of ERNs.

292 specialised units responded.

Notable results included the following:





Stimulating Development of Medicinal Products and Medical Devices for Rare Diseases

In Europe, the legislation which initiated the provision of incentives to companies for research was of course Regulation (EC) 141/2000. To assess the success of basic and clinical research to-date, one should perhaps consider the status quo in terms of orphan medicinal products (OMPs) making it through the R&D pipeline to secure marketing authorisation (see further the Knowledge Base Summary on Accessibility and Availability of OMPs and Medical Devices)

- ✓ **As of May 2019, there are currently 1643 products with active orphan designation in the EU (i.e. not withdrawn or expired)**
- ✓ **Between 2000-2018, 2121 orphan designations had been issued by the European Commission**
- ✓ **167 orphan medicinal products have received marketing authorisation**

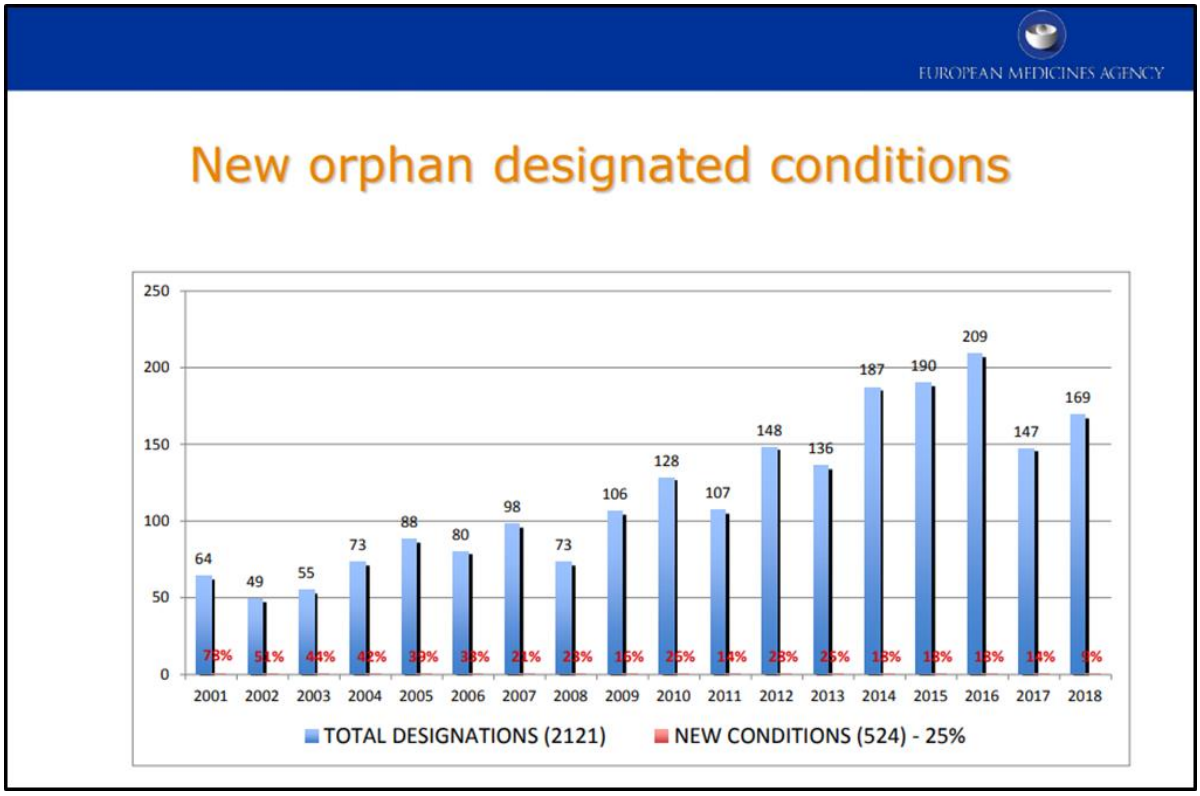
The following table from the EMA (COMP) annual report on OMPs shows the trajectory of orphan designations since 2000:

Applications for orphan medicinal product designation

	2000 2005	2006 2010	2011 2015	2016	2017	2018	**Total**
Applications submitted	548	686	1151	329	260	236	3210
Positive COMP Opinions	348	500	759	220	144	163	2134
Negative COMP Opinions	8	6	7	2	2	3	28
EC Designations	343	485	768	209	147	169	2121
Withdrawals after submission	150	144	313	77	100	92	876

EMA image: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf

The vast majority of new orphan designations, since 2003, have been for conditions which already have an indication. This table from the EMA (COMP) annual report illustrates the percentages of orphan designations each year awarded to new conditions

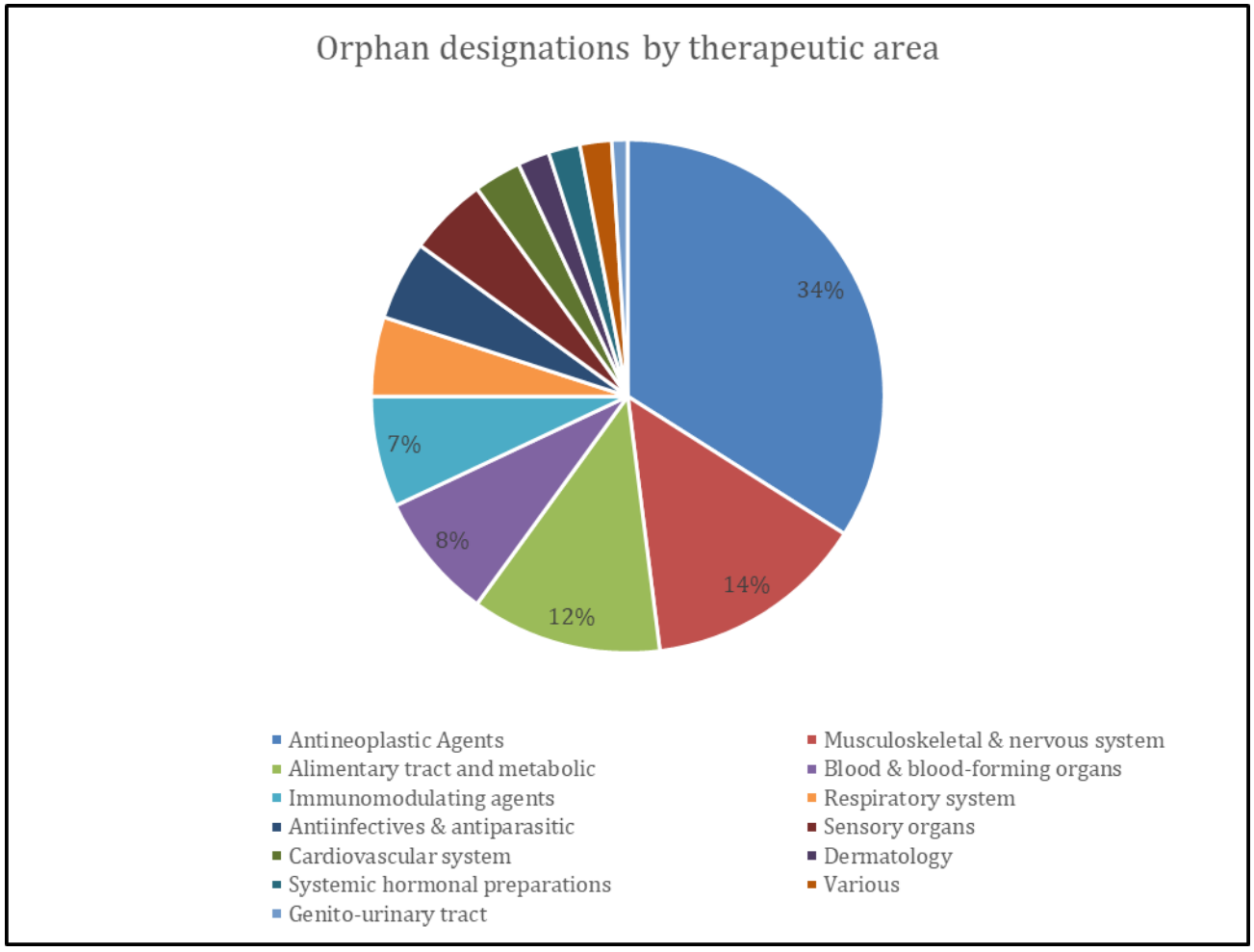


EMA image: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf

The majority of the 2121 orphan designations awarded by the end of 2018 tend to be for both **adult** and **paediatric** use (57 % according to EMA figures for 2018), with 31% for adults only and 12% for paediatrics only.

EMA statistics also illustrate that 44% of all Marketing Authorisations granted during the period 2000-2018 were for conditions with a **prevalence** of less than 1 per 10,000, meaning 56% are for those with a prevalence between 1 and 5 per 10,000. (source is https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf)

Orphan designations tend to be clustered around particular therapeutic areas, most prominently in the categories of oncology, musculoskeletal & nervous system, and alimentary tract & metabolic: the data in the pie chart below comes from the annual EMA (COMP) report on OMPs: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf



Medical Devices for Rare Diseases

'Medical Devices' as a term, is incredibly broad. Over 500,000 devices are on the market in Europe, including medical software. Medical Devices are very important for people with rare diseases, an importance which is arguably *heightened* by the absence of a dedicated medicinal treatment for 95% of the conditions classed as rare. Specialised devices can make a huge difference to the diagnosis, treatment, care and quality of life of this population; however, the cost of (particularly customised) devices can be prohibitive and, as is the case for OMPs, they may not be included in an appropriate reimbursement system. The topic was incorporated to the **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]** as follows:

5.5 Medical devices: *"The Orphan Medicinal Product regulation does not cover the field of medical devices. The limited size of the market and the limited potential return on investment is a disincentive. The Commission will assess whether there is a need for measures to overcome this situation, possibly in the context of the forthcoming revision of the Medical Devices Directives."*

In April 2017, two new regulations for Devices were adopted:

- Regulation (EU) 2017/745 on medical devices;
- Regulation (EU) 2017/746 on in vitro diagnostic medical devices

Despite the improvements offered by Regulation (EU) 2017/745, there is no European agency for medical devices – i.e. no equivalent of the EMA – to perform centralised reviews and authorisations. And unlike OMPs, there are no incentives in the existing European legislation for the development of medical devices intended specifically for rare diseases. The United States, by comparison, has a 'Humanitarian Use Device' exemption for devices intended for conditions affecting/manifesting in no more than 4000 people in the US each year.

Repurposing of Medicines

One form of research often highlighted as promising (and perhaps particularly appealing as a focus for academic-led trials) is the repurposing of medicines for rare indications. Drug repurposing centres upon the use of a rigorous scientific process to find new ways to make use of existing medicinal products. Greater understanding of the underlying causes and biochemical pathways responsible for rare diseases opens up opportunities to use existing medicines to address impairments and errors. Drug screening and data mining approaches can identify promising candidates. Repurposed medicines carry the advantage of a strong safety profile, and although preclinical and clinical studies may still need to be performed in the newly-intended community, the extent and therefore the costs of such activities are often lower than developing a brand new medicine from scratch (there will usually be robust data on the pharmacokinetic performance, for instance).

Groups such as Findacure are raising awareness of repurposing opportunities in the rare disease community (and indeed are accelerating these). At European Level, the Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) is currently focusing on the potential of repurposing

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Research on the socio-economic burden posed by rare diseases

Few projects to-date have sought to estimate the full socio-economic burden of rare diseases. Individual disease communities may have conducted research in this area: some seeking to demonstrate the benefits of truly multidisciplinary care approaches, as delivered by genuine expert centres able to unite all necessary specialists across not only medical but also psychological, social, and educational actors. However, research on the full impact of rare diseases to society at large seems scarce and fragmented: the field is missing broad studies assessing, for instance, the costs of disjointed medical and social care for patients and health systems, and the economic impact (to patients and families and to society at large) of patients/family members being forced to abandon or reduce employment due to affliction with the disease or the need to act as -potentially unpaid- carers.
A 2010-2013 project, BURQOL-RD, was funded by the 2nd Public Health Programme. The project set out to conduct the first comprehensive analysis on this scale in the rare disease field, by employing a single methodology to assess both direct costs and indirect costs of rare diseases across numerous health systems. The team assessed the socio-economic burden for 10 different rare diseases, using what they termed the *BURQOL-Metre*, and also proposed a methodological framework to measure the health-related quality of life (HRQOL) of patients and their caregivers (see http://burqol-rd.eu/pag/publications.html for publications).

However, there has been limited activity in this sphere since the end of this project, despite the fact that the Commission Expert Group on Rare Diseases *Recommendations to support the incorporation of rare diseases to social policies and services (2016)* explicitly call for a renewed focus:

"Recommendation 10. Socio-economic research in the field of RD care provision/organisation should be supported both at MS level and at European Union level. Support should be provided for research on the following topics:

- Socio-economic burden of RD;
- Accessibility and appropriateness of healthcare services, including social services, for people living with a RD and their families;
- Effectiveness and cost-effectiveness of social services and support, as well as rehabilitation and assistive technologies for people with a RD;
- Innovative care practices in health and social services and their impact on the quality of life of people living with RD".

European Strategy Forum of Research Infrastructures (ESFRI)

The ESFRI is a coordinating body of sorts, for the various Research Infrastructures (RIs) across Europe. It is composed of national delegates nominated by research ministers of EU countries and countries associated with Horizon 2020, along with a European Commission representative. RIs exist to foster collaboration across borders and address ambitious topics and activities which would either be impossible or at least impractical for countries in Europe to tackle alone. In the biomedical science domain, RIs are working to improve human health and wellbeing. The following RIs –BBMRI, EATRIS, ECRIN, ELIXIR, EU-OPENSCREEN, INFRAFRONTIER- cover the translational pipeline incorporating

- Capturing and pooling of data for patient diagnosis
- Use of data analytics for target identification
- The implementation of chemical libraries and high-throughput screening,
- Animal model optimisation,
- Translational research,

- Biobanking
- Clinical trials

… and much more. They are therefore well-placed to address some of the challenges of the RD community. Increasing linkage of the biomedical RIs has been an emphasis of the ESFRI roadmap over the last few years, and through various grants and funded projects, collaborations between *rare disease* researchers and the RIs is increasing.

Results of the literature review

The first trend regarding research is linked to the emergence of a **new technological era** with the development of **big data and the continuous sophistication of information and communication technologies** which has revolutionised many sectors, including health (Hong 2018; Belle 2015). Indeed, a "**data revolution**" has taken place, transforming research processes and opening a field of new and promising opportunities. Great progress has been made when looking at the number of data resources and ways of collecting data. Indeed, data for rare diseases can been found in the form of patient registries, population registries, electronic health records, as well as biobanks, each with its own characteristics and therefore specific use for research. This trend of **data-driven research** is accompanied by challenges as regards the profusion of data which needs to be organised and analysed. New tools are constantly being designed in order to make sense of this profusion of data, as well as cross data resources in order to generate the richest knowledge for the advancement of rare disease research (Lopes et al. 2015; Lochmüller et al. 2018). For instance, data from biobanks and registries can be linked in order to facilitate rare disease research. It represents an impactful and cost-effective solution to improve treatment and care of rare diseases (Garcia et al. 2018).

New technologies have a striking impact on research processes and outcomes and this has brought radical changes and has launched a momentum of ceaseless transformation. The use of **mobile health or mHealth as well as telemonitoring, has the potential to revolutionise research** as it allows for a constant monitoring of patients and improves their safety as well as, for example, the assessment of the efficacy of compounds (Druegger et al. 2016; Groft and Posada de la Paz 2017; Polich et al. 2012).

Social media is also becoming more central and has a high potential to impact on rare disease research. It is used for recruitment, to solicit patient involvement and input in clinical trials and sometimes collect patient data (The Lancet Oncology 2014; Schumacher et al. 2014)

The collection and sharing of personal data also raises **ethical issues concerning patient privacy and protection**. The organisation of clinical trials is a necessity for the development of new treatments and therapies, hence there is a tendency to search for ways to allow vulnerable research patients to benefit from research results without putting their personal data at risk - cf. EU regulation on clinical trials (Gennet et al. 2015). **Regulations and legislation are often pictured as hurdles to the sharing of data**, imposing restrictions and stringent rules of anonymity and data protection (Djurisic et al. 2017; Mascalzoni et al. 2014). There are calls within the research community for less strict rules and some even suggest to reconsider the concept of privacy, extending this to the right to grant access and not only the right to deny access (Mascalzoni et al. 2014). However, generally members of the rare disease

research community emphasise the importance of guaranteeing data protection and are struggling to f**ind ways in order to safely manipulate the data in free and meaningful ways**. A major concern concerns to the **possibility of unauthorised re-identification** even after a step of de-identification; consequently, researchers are trying to develop new and more suitable methods to encrypt data (Hansson et al. 2016). One new system/technology which currently being developed and may gain importance in the years to come is **blockchain technology**. This can be defined as an ever-growing list of records linked using cryptography and containing information that can be simultaneously used and shared within a large decentralised, publicly accessible network. Indeed, this system c**ould ensure patients' ability to retain ownership of their data**, one of the core elements for the respect of privacy according to some experts (Angeletti et al. 2017; Terry and Terry 2011), and hence provides an **innovative way to improve the intelligence of healthcare systems** while keeping patient data private (Yue 2016).

A **trend towards a process of harmonisation and standardisatio**n can also be noted with European and international efforts to find common clinical trial settings and to develop registries and biobanks (Choquet et al. 2014; Lochmüller et al. 2009) whilst encouraging transnational collaboration in this sector (Djurisic et al. 2017;). Indeed, there is an institutional drive towards more coordination between all stakeholders and the integration of multidisciplinary expertise to boost rare disease research (Dharssi et al. 2017; Julkowska et al. 2017). Some organisations, such as **IRDIRC,** also seek to create an international framework of research standards with the creation of guidelines and quality indicator processes (Lochmüller et al. 2017a; Lochmüller et al. 2017b).

Regarding **funding for research,** one can observe a serious commitment of the European Union but also significant disparities at the international as well as the European level with certain countries having implemented few or no initiatives to promote research (Dharssi et al. 2017; Lynch and Borg 2016). Funding agencies and other stakeholders are encouraged to **coordinate their activities in order to maximise the collective impact of investments in rare disease researc**h (Julkowska et al. 2017). Almost all patient organisations are also engaging in funding activities. However, they lack resources and their proliferation and lack of collaboration prevent them from having a more significant impact (Pinto et al. 2016).

A clear trend, which mirrors a more systemic change in the delivery and functioning of European healthcare, is the **increasing involvement of patients in rare disease research**. They are gradually being considered as equal partners as they engage directly in research design and development. A **process of co-learning** therefore emerges between the patients and the investigators and mutual benefits are generated in terms of research design and participant recruitment and retention (Day et al. 2018; Mavris and Le Cam 2012; Young et al. 2019). Consequently, research in this area is becoming more **patient-centered**, making sure that it addresses clinical issues and patient-centered health outcomes (Forsythe et al. 2014; Groft and Posada de la Paz 2017). Patient reported outcomes are thus increasingly used and recognised as a crucial element and tool for quality of research (Slade et al. 2014).

Furthermore, there is a focus on **translational research and the need to ensure that research will translate into effective safe therapies** (Ragni et al. 2012). This interpenetration of research and clinical applications is particularly observable in the case of next-generation sequencing technology which

integrates a double objective of collective knowledge and individual care (Bertier et al. 2018). As a matter of fact, this type of **research-based care allows for clinical information to be constantly re-evaluated and enriched by evolving research results**.

Finally, one of the most striking hurdles for rare disease research, the small sized populations, is forcing researchers to imagine **alternative design** for clinical trials. New methods are appearing and current frameworks are accordingly questioned and challenged (Day et al. 2017; Djurisic et al. 2017; Shash et al. 2013).

***Possible* trends emerging from the Literature Review:**

- Transnational cooperation, including harmonisation of standards
- Dedicated funding for RD research and transnational coordination of targeted funding
- Research-based care
- Personalised medicine focus
- Innovative trial design
- Patient driven research

***Possible* drivers of change emerging from the Literature Review:**

- Scientific and technological advances
- Advent of 'big data' and 'block chain'
- Ecosystems for accelerating/fostering RD research
- Political engagement

References from the rare disease literature review

Full list of articles/publications found in the literature review:
https://docs.google.com/spreadsheets/d/1SRXASsFiD9sdQz286SVo860XdTpGaOIncyjIhGphULI/edit#gid=364400914

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Knowledge Base Summary

Diagnostics

Contents

Introduction to the Topic

This topic is complex and multifaceted. Diagnosing a rare disease entails a definition of what constitutes 'rare'. The 6-8000 diseases falling under this heading are extremely heterogeneous: the majority are genetic but perhaps ca.15% are acquired. For many reasons, the search for an accurate diagnosis is often a diagnostic 'odyssey'; for instance, the sheer number of conditions under the heading of 'rare diseases'; the scarcity (by definition) of patients with any single condition and the corresponding scarcity of experts *acquainted* with each condition; the tendency for rare diseases to manifest as complex, multisystemic conditions; these are but a few explanations. The lack of a diagnosis (or perhaps an accurate diagnosis) can have far-reaching consequences for patients. Heterogeneity of national capacities regarding genetic testing (and changing technologies for such tests) can impact on access to diagnosis. Newborn screening has the potential to detect diagnoses very early in life, for patients in whom very early interventions are essential; however, again there is significant variety from country to country (and even *within* countries). Primary prevention is an evolving but naturally very sensitive topic, and indeed ethical, legal and social issues are transversal across many of these subjects. This document touches upon (but avoids detailed coverage of) themes further addressed in other Rare2030 Knowledge Base Summaries, especially those on Research and on Data Collection & Utilisation.

Some of these topics were highlighted in the **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]:** After affirming that the EU will maintain the definition of a rare disease espoused in Regulation (EC) 141/2000, the Communication states *"**A more refined definition taking into account both prevalence and incidence will be developed using the Health Programme resources and taking into account the international dimension of the problem**."*

There is a dedicated section (5.8) on Neonatal Screening (see below), and a section on Quality management of diagnostic laboratories (see below). Section 5.10 is dedicated to Primary Prevention (see below). Some of these issues were directed as specific Recommendations to Member States (MS) the following year: the preface to the **Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02** reads as follows:
"It is of utmost importance to ensure an active contribution of the Member States to the elaboration of some of the common instruments foreseen in the Commission communication on rare diseases: Europe's challenges of 11 November 2008, especially on diagnostics and medical care and European guidelines on population screening."

Section II, ADEQUATE DEFINITION, CODIFICATION AND INVENTORYING OF RARE DISEASES recommended that MS "*Use for the purposes of Community-level policy work a common definition of rare disease as a disease affecting no more than 5 per 10 000 persons."*

Section V. GATHERING THE EXPERTISE ON RARE DISEASES AT EUROPEAN LEVEL asked MS to "Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support:
(a) the sharing of best practices on diagnostic tools and medical care as well as education and social care in the field of rare diseases;
(c) the development of medical training in fields relevant to the diagnosis and management of rare diseases, such as genetics, immunology, neurology, oncology or paediatrics;
(d) the development of European guidelines on diagnostic tests or population screening, while respecting national decisions and competences;

Several sets of EU-level policies have a direct bearing on the topic of diagnostics for rare diseases; for example:

- **In June 2013, the EUCERD adopted** *NEW BORN SCREENING IN EUROPE: OPINION OF THE EUCERD ON POTENTIAL AREAS FOR EUROPEAN COLLABORATION*
- **In 2015, the EUCERD adopted *Recommendations on Cross-Border Genetic Testing for Rare Diseases***

Guiding Questions for Panel of Experts Discussion – to support the identification of trends and drivers of change

1. **What barriers exist today to receiving an accurate diagnosis?**
2. **What practical actions could address the European heterogeneity and resulting inequalities around diagnosis? Are there any topics which warrant new or updated warrant EU-level (or other supranational level) guidance, for instance?**
3. **How might we improve diagnostics for rare diseases at the national/regional/local levels, European level, and global level?**

Definition of a Rare Disease

The EU Commission definition of a rare disease was confirmed via Regulation (EC) 141/2000 as a condition affecting no more than 5 in 10,000 people. The vast majority of rare diseases are in fact far rarer still, as illustrated by the Orphanet Report Series 'Prevalence and incidence of rare diseases' (January 2019 edition available here). Although most European countries have adopted the EU definition, a few have not (or else opt to apply that definition in varying ways).

The Diagnostic 'Odyssey'

Reaching an accurate diagnosis for many rare diseases can be very challenging and time-consuming: it is unsurprising that this process is often termed the 'diagnostic odyssey'. In 2009, EURORDIS published 'Voice of 12,000 patients: Experiences and Expectations of Rare Disease Patients on Diagnosis and Care in Europe.' Approximately 12,000 patients with one of eighteen focal conditions (ranging from more common to very rare diseases) responded to two EurordisCare surveys across 17 countries (delivered in 12 languages), to share their experiences of seeking a diagnosis (amongst other topics).

The table below shows the median delays in diagnosis. To illustrate the variety in experiences even between patients with the same conditions, the survey results were presented to illustrate:

a) The median delay considering 50% of the respondents
b) The median delay considering 75% of respondents

For Duchenne Muscular Dystrophy (DMD), for instance, for 50% of the respondents the time from first symptoms to diagnosis averaged 12 months, but when including the 25% of respondents who waited the *longest* time, that median rose to 3 years.

Source of information	Delay in diagnosis for 50% of patients	Delay in diagnosis for 75% of patients
CF	1.5 months	15 months
TS	4 months	3 years
DMD	12 months	3 years
CD	12 months	5.8 years
PWS	18 months	6.1 years
MFS	18 months	11.1 years
FRX	2.8 years	5.3 years
EDS	14 years	28 years

Table 1 Median time elapsed between the first symptoms and a correct diagnosis.

Image is taken from EURORDIS (2009) *Voice of 12,000 Patients*

The survey also illustrated the likelihood of receiving an *incorrect* diagnosis (perhaps several): **41% of respondents reported at least one misdiagnosis before obtaining the correct one.** For conditions with an adult onset, these figures were particularly diverse. E.g. 56% of patients with Ehlers-Danlos Syndrome (EDS) reported at least one misdiagnosis.

The consequences of misdiagnosis were also highlighted: besides inappropriate psychological treatment and counselling, **significant proportions of patients also received inappropriate surgical procedures** (again, this was most likely in diseases manifesting in adulthood as opposed to childhood): 29% of MFS (Marfan Syndrome) respondents; 17% of EDS respondents and 17% of CD respondents,

compared to 10% of DMD respondents, 8% of CF (Cystic Fibrosis) respondents, 7% of PWS (Prader-Willi Syndrome) respondents and 6% of TS (Tuberous Sclerosis) respondents. (See the survey results, especially p44-6)

The 6-8000 rare diseases differ significantly in origin, nature and time of onset, which naturally leads to a variety of routes to diagnosis. Diagnoses may be made entirely based on clinical observations, or may be based on/corroborated by genetic analysis. It is important to note that a significant number of conditions are *not* in fact genetically inherited.
A major contributing factor in the length of a patient's 'diagnostic odyssey' is often the speed and efficiency at which a patient can move from primary healthcare and general practitioners (GPs) into more specialised tertiary care centres: ideally, to a centre of expertise in rare diseases, assessed and designated as such by national or regional authorities, but either way a centre with expertise in recognising the patient's presentation, symptom and family history. The pyramid below illustrates the actors and routes to a diagnosis for rare disease patients.

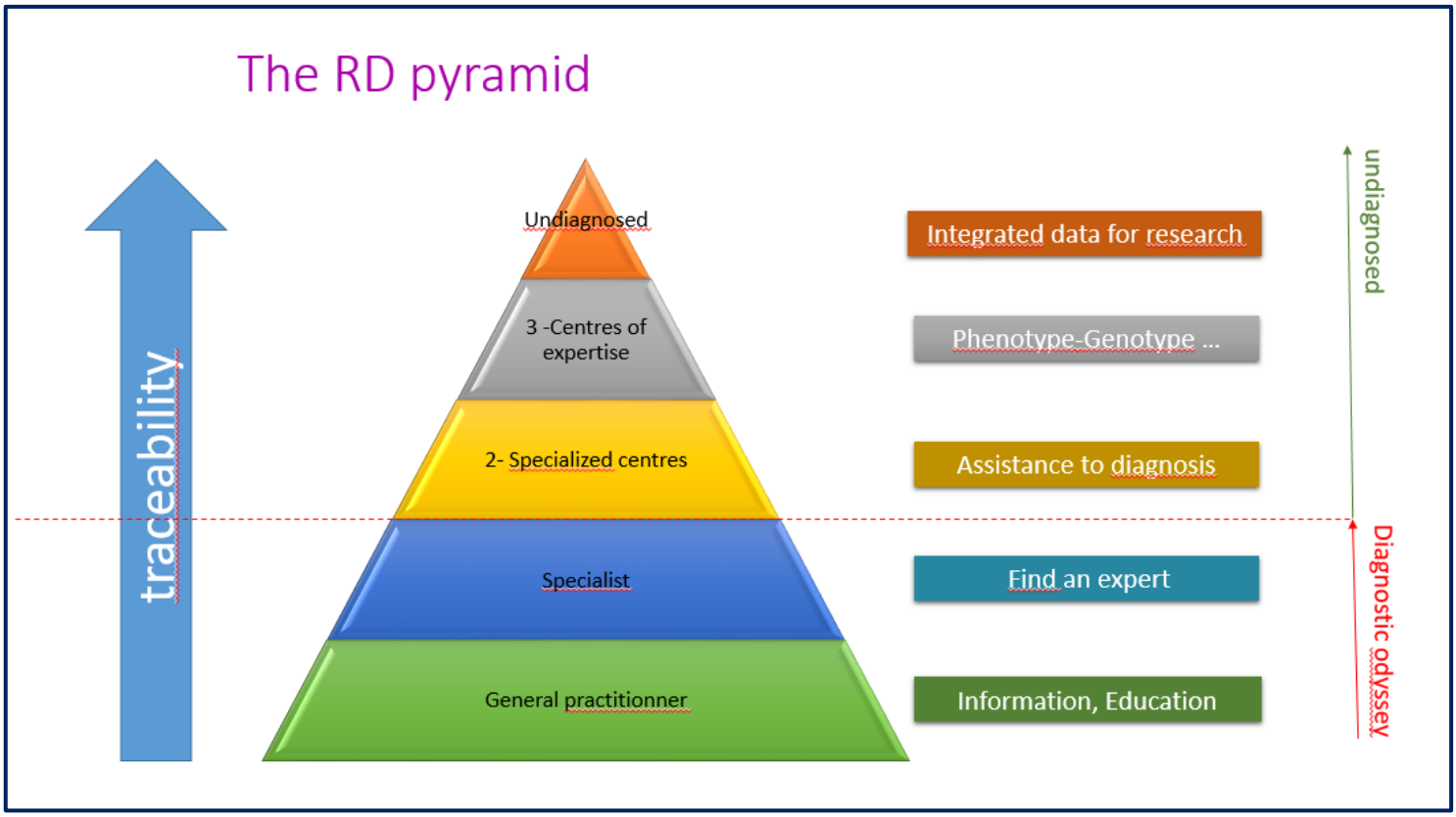

Image courtesy of Orphanet

Advances in Diagnostics through international collaboration

Needless to say, professional guidance on strategies and approaches to utilising techniques such as Next Generation Sequencing have a huge impact on diagnostics for rare diseases: groups such as EuroGentest and European Society of Human Genomics, together with their global counterparts, are really driving forwards the application of NGS knowledge to translate into larger numbers of diagnosed patients (with more specific genetic diagnoses). Increasingly, rare disease diagnoses are enabled by the pooling/querying of data concerning a patient's genotype with 'deep phenotyping' data on the specific clinical presentation and symptoms displayed by that patient. The field of RD diagnostics has

arguably benefited enormously from collaborations internationally, in the broader genomics arena, but also by incorporating the expertise of disciplines such as big-data management and analytics, bioinformatics, ethics, and more.
Numerous global databases now exist, in which genetic variants can be recorded and annotated, to support the identification of additional patients and families (necessary for clinicians/researchers to confirm that a variant found in their patient is pathogenic). Projects specifically dedicated to rare diseases have helped to advance these routes to diagnostics by cementing these sorts of collaborations and enabling the pooling or querying of the necessary data types (an example is the €12 million FP7–funded RD-Connect initiative, summarised in the table of resources below). Increasing emphasis on standardising data through use of agreed and appropriate ontologies (for instance the Orphanet Rare Diseases Ontology and the Human Phenotype Ontology) will continue under, amongst other initiatives, the new European Joint Programme Co-Fund for rare diseases research.

Global goals regarding rare diseases diagnostics

Improved diagnostics for rare diseases (which demands both *better* science and greater *accessibility* of diagnostic solutions to patients who need them) is a key focus of the International Rare Disease Research Consortium, IRDiRC. A new overarching vision was adopted for the period 2017-2027: **'Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention'.**

To make this vision a reality, 3 new goals were agreed:

- **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

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Undiagnosed rare disease patients

A major challenge in the field of rare diseases is **'diagnosing the undiagnosed'**. Some patients are undiagnosed because although the condition they have *is* diagnosable, their clinical team has not yet 'solved' the case and determined the precise diagnosis. For other patients without a diagnosis, however, the field at present *has* no diagnosis to offer (i.e. the origins of the symptoms they are experiencing have not yet been identified or explained.) Dedicated groups and entities exist to attempt to address both types of issues.

Since approximately 2015, Europe has participated to the Undiagnosed Diseases Network International (UDNI). Based upon the United States' Undiagnosed Diseases Network, this is a platform to unite patients, researchers and clinicians. In 2018, a €15 million 4 year H2020 initiative 'Solve-RD: Solving the Unsolved Rare Diseases' commenced operations. These activities are summarised in further detail in the table in Annex I.

Unsurprisingly, enabling a diagnosis for all rare disease patients is a key priority for rare disease advocacy groups world-wide. In 2016, a number of umbrella patient organisations (representing patients in Australia, Europe, Japan and North America) united to issue a set of ***International Joint Recommendations to Address Specific Needs of Undiagnosed Rare Disease Patients***. The 5 high-level recommendations are as follows:

The 5 Recommendations to address specific needs of undiagnosed rare disease patients

1. **Undiagnosed Rare Disease Patients should be recognised as a distinct population** with specific unmet needs by national authorities to enable development of personalised health and social care. Although some undiagnosed diseases are common, the vast majority are rare. Hence, in this paper we refer to undiagnosed patients as "undiagnosed rare disease patients".
2. **National sustainable programmes** dedicated specifically for undiagnosed diseases should be developed and supported by appropriate authorities in each country to enable rapid and equitable access to diagnosis and social support.
3. **Knowledge and Information sharing should be structured and coordinated** at national and international levels to optimise use of existing resources and facilitate access for all undiagnosed rare disease patients.
4. **Patients should be equally involved** with other stakeholders in the governance of undiagnosed diseases programmes and international networks to adequately address the priorities of undiagnosed rare disease patients and contribute to improved healthcare.
5. **Ethical and responsible international data sharing should be promoted** through existing initiatives to support diagnosis, increase clinical collaboration, facilitate research, and accelerate treatment of undiagnosed and rare conditions.

Translating Next Generation Sequencing (NGS) to the clinic

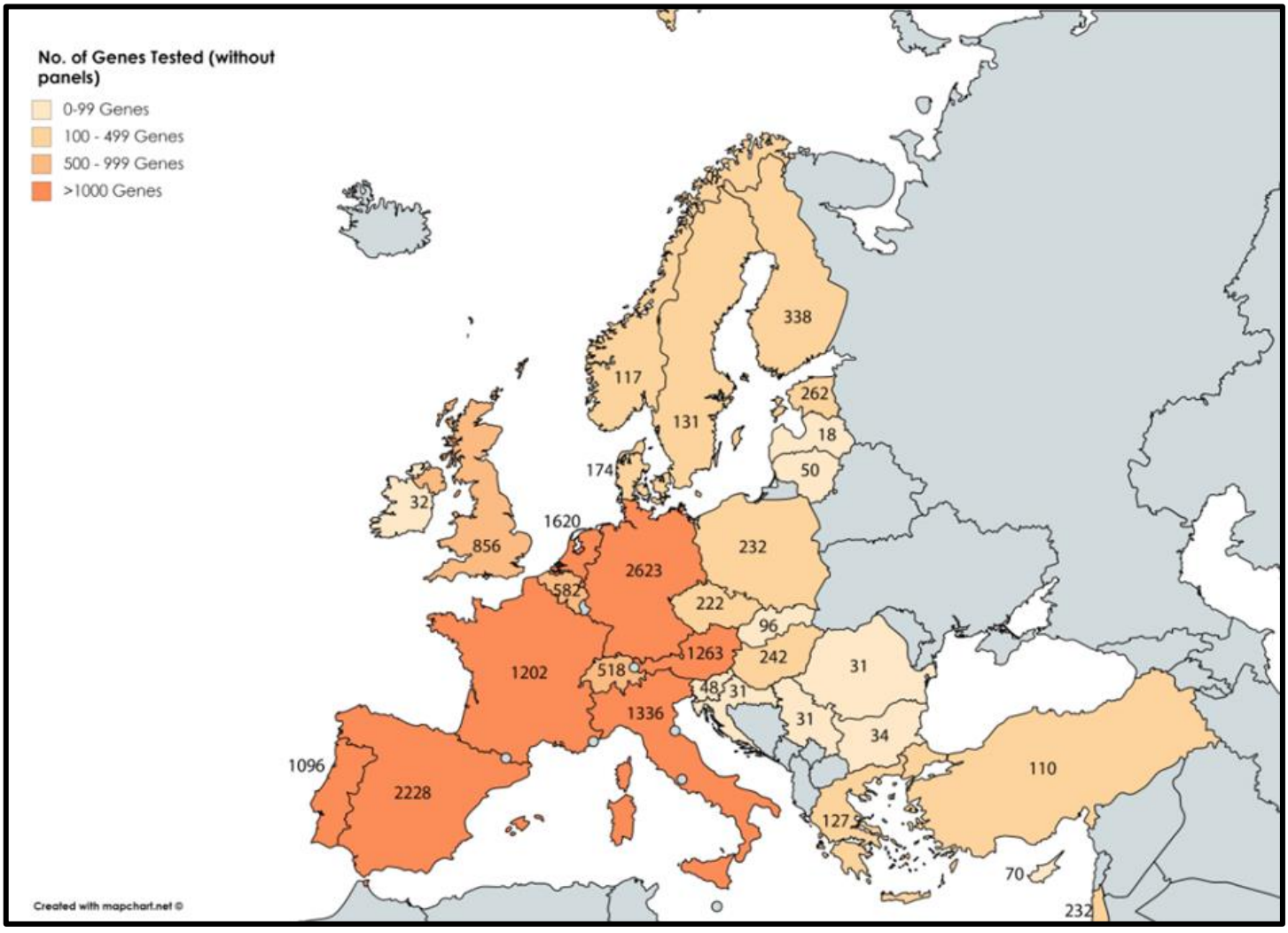
Traditionally, patients entering NGS pipelines have often done so via research-oriented projects/ courtesy of research funding. Confirmation of a diagnosis reached in this way would be followed-up with more traditional confirmation in the clinic, for instance through southern blotting. In recent years, however, initiatives have started to explore how NGS may be used as an increasingly routine part of a patient's diagnostic pathway in national health systems. A (non-RD-specific) example at European level was 3GbTest 'Introducing diagnostic applications of '3Gb-testing' in human genetics'. (See below, Annex I). Early national efforts to incorporate NGS to the clinic include the UK's 100,000 genomes project, which to-date has sequenced 100,000 genomes from around 85,000 people, with the goal of creating a new genomic medicine service for the NHS. The initiative, announced in 2012, sought to bring concrete diagnoses to patients within the NHS with suspected rare diseases, whilst also facilitating new medical research by pooling omics data with medical records.

Genetic Testing Laboratories in Europe - the Status Quo

Expert clinical laboratories and diagnostic tests are an essential part of quality healthcare in the field of rare diseases. Major progress in gene identification has translated into diagnostic tests: these tests are now being offered internationally, through both public and private sector genetic testing services. Orphanet set up a database of medical laboratories in the field of rare diseases in 1997 and over time,

this resource has evolved to include information on quality management. Over time, the number of laboratories registering their activities with Orphanet has increased, to reach **1599 as of April 2019.** The Orphadata extractions enable a comparison of genetic testing capacity over time, both for single gene tests and also for panels (as panel testing becomes more commonplace in clinical settings).

	No. of Laboratories registered in Orphanet	No. of genes these laboratories test for **(excluding panels)**	No of diseases these laboratories test for **(excluding panels)**	No. of genes these laboratories test for (***with*** panels)	No of diseases these laboratories test for (***with*** panels)
June 2011	1049	1764	NA	NA	NA
Jan 2017	1301	2897	3658	4017	4421
Jan 2018	1388	3018	3737	4303	4421
April 2019	1599	3107	4105	5069	4399



Map created using OrphaData from April 2019

As the map illustrates, the variation in genetic testing offer between medium and small sized countries in Europe is substantial, **and now ranges from 18 diseases and 18 genes (Latvia) to 2854 diseases and 2623 genes (Germany) without panels.**

The Orphanet data provides further evidence of the heterogeneity in genetic testing capacity across Europe:

Significant numbers of Genes are only tested in 10 or fewer countries (Excluding Panels):

- 590 genes are tested in just one country;
- 1966 genes are tested only in 5 countries or fewer
- 2813 genes are tested in 10 countries or fewer

Significant numbers of genetic Diseases are only tested in 10 or fewer countries (Excluding Panels):

- 776 diseases are tested for in just one country;
- 2944 diseases are tested for in only in 5 countries or fewer
- 3823 diseases are tested for in 10 countries or fewer

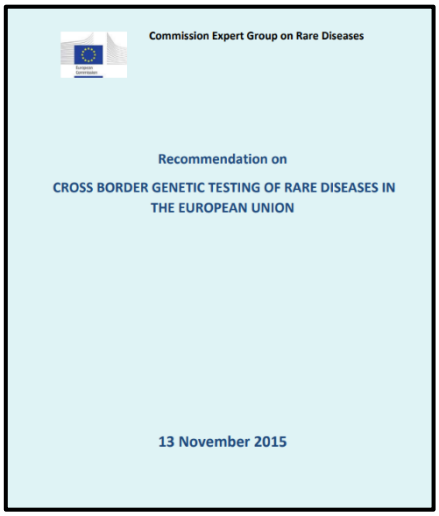
These figures alone demonstrate the need for a substantial cross-border exchange of specimens, as concluded by a 2015 study conducted as part of the EUCERD Joint Action. Quality Management of diagnostic laboratories is also a major factor, especially where countries are sending samples abroad for testing unavailable in-country. The topic was highlighted in the **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]** as follows:

5.9. Quality management of diagnostic laboratories

"Many rare diseases can now be diagnosed using a biological test which is often a genetic test. These tests are major elements of an appropriate patient's management as they allow an early diagnosis, sometimes a familial cascade screening or a prenatal test. Given the large number of tests and the need to design and validate a specific set of diagnostic assays for each, no single country can be self-sufficient in the provision of testing and in an efficient external quality assessment of the provided tests. There is a need to enable and facilitate the exchange of expertise through clearly stated, transparent, EU agreed standards and procedures. This could be achieved through the establishment of European reference networks of expert diagnostic laboratories (e.g. EuroGenTest). These laboratories will be encouraged to participate in proficiency testing with special attention to result in reporting and in the provision of pre- and post-test genetic counselling"

Recommendations on Cross-Border Genetic Testing of Rare Diseases

An appreciation of the status quo, particularly as highlighted via the aforementioned EUCERD Joint Action study, led to the preparation and eventual adoption in 2015 by the Commission Expert Group on Rare Diseases of a set of *Recommendations on Cross-Border Genetic Testing of Rare Diseases*.



RECOMMENDATIONS TO THE EUROPEAN COMMISSION AND MEMBER STATES

1. Obtaining an accurate and timely diagnosis is a priority for all people with a potentially genetic RD; therefore, access to genetic testing -whether provided locally or on a cross-border basis - should be ensured, to facilitate such diagnoses, when there is a clear clinical indication.

1.1 The importance of adequate access to genetic testing for RD - including cross border genetic testing (CBGT) - when there is a clear clinical indication, should be stipulated in future National Plans and Strategies (NP/NS) for RD and should be incorporated when existing NP/NS are evaluated and revised.

1.2 MS should provide openly accessible information on genetic testing availability at the national level.

1.3 MS should have a transparent policy pertaining to CBGT: such policies should seek to streamline the process of CBGT, as far as possible.

1.4 The possibility of developing shared resources to facilitate CBGT of RD should be explored at the EU level.

2. The expert group underlines the importance of assessing genetic testing, on the basis that early diagnosis through clinically-guided genetic testing may avoid the need for further invasive and/or unnecessary exploratory and therapeutic procedures.

2.1 MS should consider, where possible, to share data on the assessment of genetic tests for RD - with full regard of the need to preserve patient anonymity - and further explore whether this exchange could be taken into consideration within the framework of the Joint Action 3 EUnetHTA on this basis.

2.2 Decisions on the purchasing/procurement of CBGT should be made on the same basis as any other medical investigations that are considered clinically indicated.

3. Whether genetic testing is provided on the national/regional level or on a cross-border basis, expertise should be shared at the EU (or global) level.

3.1 MS should promote the use of - and active contribution to - international variant databases when conducting genetic testing for RD, to improve the assessment of the pathogenic potential of genomic variants.

3.2. Cross border collaboration between laboratories, clinical genetics centres, and research initiatives dedicated to RD diagnostics should be supported, as this holds major potential for the RD field.

3.3 The organization of the collaboration between expert laboratories should be set within the context of European Reference Networks (ERNs), as per Directive 2011/24/EU by integrating expert laboratories in the different thematic networks linked to their area of expertise. The potential for ERNs to support the process of CBGT for RD should be explored.

4. Appropriate information on genetic testing laboratories should be made available to facilitate cross-border genetic testing of rare diseases, particularly when pertaining to the quality of laboratories.

4.1 MS should support laboratories within the national territory in contributing - and updating - defined data elements to the Orphanet database (which at present is the main source of information on genetic testing laboratories for the RD field at European level).

4.2 To facilitate informed decision-making when selecting laboratories for CBGT, laboratory testing websites should display as a minimum their accreditation status, scope of the test offered, turn-around-time, and transparent pricing parameters.

4.3 Given the critical importance of quality for genetic testing of RD, MS should promote accreditation and the participation of laboratories in EQA.

Prevention

Prevention is traditionally categorised as primary, secondary or tertiary.

- Primary: aims to prevent the *onset* of the disease. This can range from greater education on medical risks to measures to decrease the risks of developing a disease, both at the personal and the community levels; for instance, preconception carrier screening, prenatal genetic and diagnostic testing, and preimplantation genetic diagnosis could fall under this heading
- Secondary: aims at an early detection of disease and actions taken to halt disease progression. A good example is newborn screening for inborn errors of metabolism (see below) and hearing defects
- Tertiary: activities to minimise further impact of conditions on functioning and disability by focusing on mental, physical, and social rehabilitation

This topic naturally carriers particular ethical sensitivities, particularly *primary* prevention. Patients and families sometimes fear an emphasis on primary prevention will only enhance the isolation which often accompanies life with a rare disease. In the wider fields of genetic testing and prevention, many policies, recommendations and reports exist: for the rare disease field, specifically, the topic was incorporated to the **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]** as follows:

5.10. Primary prevention: *"There are very few rare diseases for which a primary prevention is possible. Still, primary preventive measures for rare diseases will be taken when possible (e.g. prevention of neural tube defects by Folic Acid supplementation). Action in this field should be the topic for a debate at EU level led by the Commission aiming to determine for which rare diseases primary preventive".*

One notable example of subsequent EU-level activity was the **2012 collaboration between EUROPLAN** (European Project for Rare Diseases National Plans Development) **and EUROCAT** (European Surveillance of Congenital Anomalies) to generate guidance on primary prevention.

The final output was entitled ***'Primary Prevention of Congenital Anomalies: Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies of Rare Diseases'***

The recommendations are grouped into several areas, which -it is proposed- could benefit from policy actions to prevent congenital anomalies:

- **In the field of medicinal drugs** (recommendations here range from women taking medications to seek medical advice before trying to conceive, to providing a teratogen information service);
- **In the field of food/nutrition and lifestyle** (recommendations here range from the periconceptional supplementation of folic acid, to the promotion of effective information on diet and nutrition in women of childbearing age);
- **In the field of health services** (recommendations here range from making preconceptional care include genetic testing and counseling for families at risk, to ensuring evidence-based

vaccination policies to protect women against infectious diseases associated with congenital anomalies);

- **In the field of environmental pollution** (recommendations here range from ensuring a sustainable surveillance system where environmental risks can be identified through the integration of congenital anomaly registers and biomonitoring, to minimizing the exposure of pregnant workers to workplace risks (chemical, physical and biological));
- **Types of primary preventive actions and their effectiveness** (recommendations here range from including health education campaigns targeted to potential future parents, to an integrated primary prevention plan involving all relevant health professionals)

Newborn Screening

Newborn screening (NBS) programmes for rare diseases emerged from the recognition that for some inherited diseases, the absence of a quick diagnosis would lead to irreparable damage for infants born with these conditions. Screening is still usually performed based upon a heel-prick blood test. NBS has been heavily influenced by the screening criteria published by Wilson and Jungner in 1968:

The development of enzyme replacement therapies and advanced therapies makes early detection of patients particularly important. The **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]** highlighted the issues as follows:

Section 5.8. *"Screening practices Neonatal screening for Phenylketonuria and congenital hypothyroidism is current practice in Europe and proved highly efficient in preventing disabilities in affected children. As technology evolves, many tests can now be performed, including those by robots, at low cost for a wide range of rare diseases, especially metabolic disorders and genetic conditions in general. It is recommended to encourage cooperation in this area to generate evidence on which decisions should be based at Member States level. An evaluation of current population screening (including neonatal screening) strategies for rare diseases and of potential new ones, will be conducted by the Commission at EU level to provide Member States with the evidence (including ethical aspects) on which to base their political decision. The Commission will consider such support as a priority for action."*

A European Tender was subsequently launched in 2009 ("Evaluation of population newborn screening practices for rare disorders in Member States of the European Union") through the EU Program of Community Action in Public Health. The Tender established a European Union Network of Experts on Newborn Screening (EUNENBS) to support activities and the creation of its outputs. The EUNENBS included experts from national competent institutions of all the EU MS and experts from European professional and scientific organizations involved in neonatal screening.

The main output of this tender was an Expert Opinion, the goals of which were as follows:

- "To provide as far as possible a shared view of the factors that should be considered in the whole process of implementation of a neonatal screening, from the evaluation of its opportunity and definition of its benefit, to its actual implementation and the assessment of its efficacy and quality.

- Moreover, this document identifies the activities for which the mechanisms of Community cooperation can be exploited profitably."

This document included a decision-making matrix, on the development of European policies in the field of NBS for rare diseases. The Tender also produced a report on the status quo in 2011, noting for instance that countries still usually refer to the Wilson & Jungner criteria. The number of diseases screened in EU countries at the time ranged from 2 to 29 and it was noted that number did not correlate to GDP.

Whilst respecting the principles of MS subsidiarity in healthcare, the EU Committee of Experts on Rare Diseases was asked to consider the results of this Tender. **In June 2013, the EUCERD adopted** *NEW BORN SCREENING IN EUROPE: OPINION OF THE EUCERD ON POTENTIAL AREAS FOR EUROPEAN COLLABORATION* **.** This document summarises the main outputs and findings of the Tender and proposed a list of topics for potential European collaboration in this field:

Topics for potential European collaboration

The topics which have been identified as areas for potential European collaboration are the following (in no particular order):

- Production of Standard Operating Procedures for the organisation and management of a Newborn Screening Process;
- Production of good practice guidelines for the management and follow-up of patients, for each screened disease;
- Adoption of Standard Operating Procedures for the communication with parents;
- Production of information material for prospective parents and the public, and for parents whose child was screened positive but whose diagnosis is not yet confirmed;
- Adoption of Standard Operating Procedures for the training of health professionals involved in the screening process;
- Organisation of European training schemes;
- Networking between laboratories to ease collaboration and resource sharing in order to improve the quality and cost-efficiency of national operations;
- Establishment of shared databases between NBS laboratories and centres of expertise in charge of the follow-up of patients to gain better knowledge of the screened diseases and to assess the benefit of the screening strategy;
- Discussion on the Wilson and Jungner criteria and other criteria to be used when considering any expansion of NBS, as views diverge in many countries on this issue;
- Common assessment of new proposals for NBS, between MS wishing to do so, when new technologies allow for such a consideration, via EUnetHTA;
- Establishment of public health key indicators for the continuous evaluation and monitoring of the screening programs.

Status Quo of Newborn Screening across Europe

There is significant heterogeneity between European Member States in terms of NBS programmes. The table and map below show the status quo as of May 2019. The *national* programme for screening ranges from 1-26, with certain regions of Italy offering screening for at least 58 diseases.

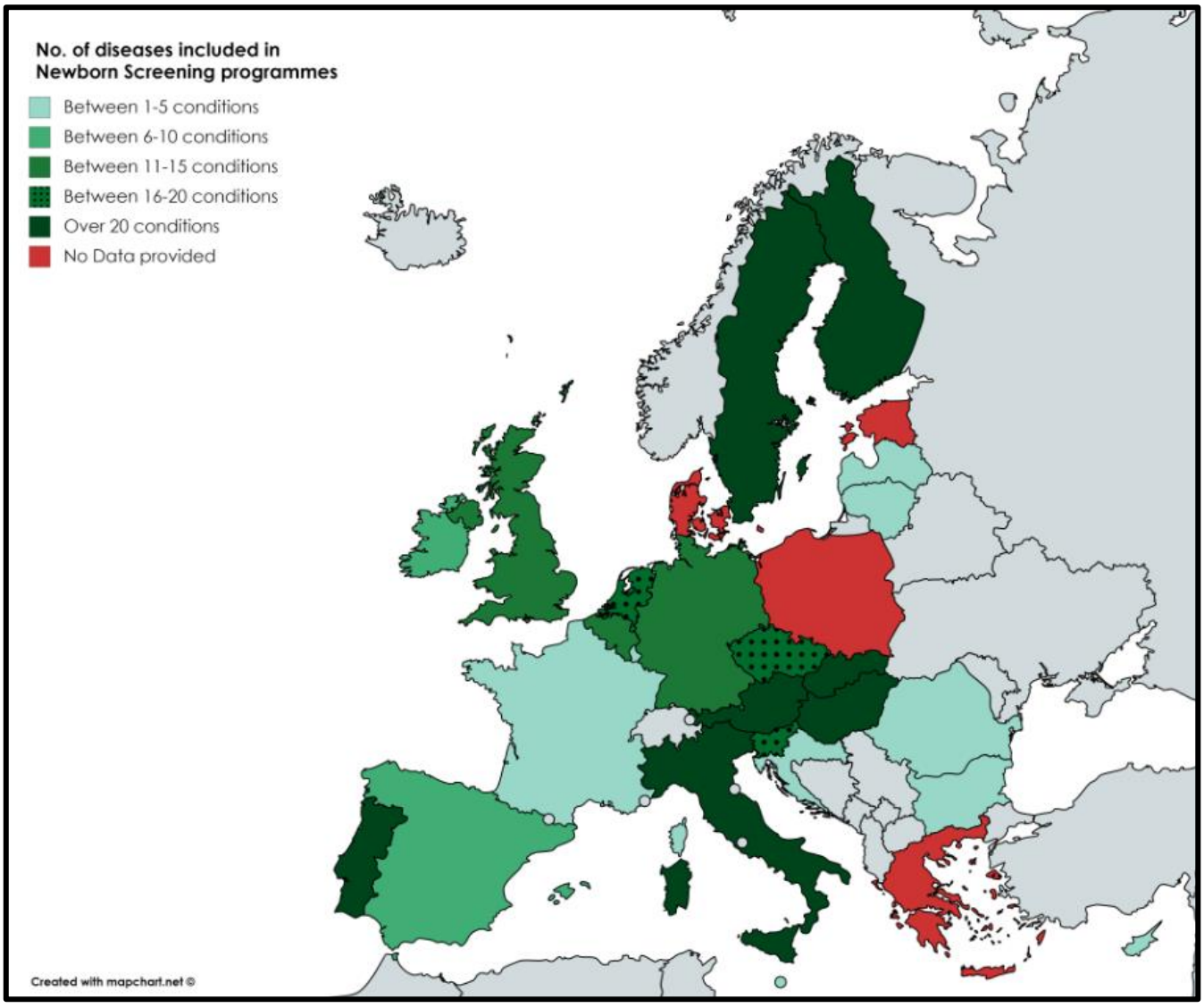
The data comes from the *Resource on the State of the Art of Rare Disease Activities in Europe (SotAR).* Countries are asked to provide information on their national activities pertaining to rare diseases by responding to a structured survey. The questions in this survey are designed to enable countries to provide the data they pledged to submit when adopting the *EUCERD Recommendations on Core Indicators for Rare Disease National Plans and Strategies* in 2013. Here, countries were asked "*How many rare diseases are covered in the neonatal screening programme in your country?*"

NB:

- Please note that data for a number of countries is still awaiting update; **therefore, these figures may change slightly in the coming months**
- Hearing tests and vision tests have *not* been included in the calculations below
- Note that Spain and Italy report significant variety between the national and regional level practices: Italy has been included in the higher category on the map, as specifics were provided

EU MS	No. Of Diseases in NBS Programme	Comments Provided in the SotAR submissions
Austria	25	
Belgium	11-13	11 in Flanders; 13 in French Community
Bulgaria	3	
Croatia	2	Potentially several more metabolic but no details provided
Cyprus	2	Plus congenital hearing defect screening
Czech Republic	19	
Denmark	??	No data provided
Estonia	??	No data provided
Finland	21	
France	4	Also sickle cell anaemia but only for those at particular risk
Germany	15	
Greece	??	No data provided
Hungary	26	
Ireland	8	
Italy	3 - 58	3 diseases in the national programme **14 regions guarantee screening for between 25-58 metabolic diseases** Consensus has been reached between the Ministry of Health and Regions on a technical proposal for a panel of 38 inherited metabolic diseases to be screened (not yet implemented it seems)
Latvia	2	Plus congenital hearing defect screening. The NBS programme is due to expand in July
Lithuania	4	Congenital hearing, vision, and heart defect screening also in place
Luxembourg	5	
Malta	2	Clarification needed
Netherlands	19	
Poland	??	No data provided
Portugal	26	
Romania	2	Plus congenital hearing screening
Slovak Republic	23	

Slovenia	18	
Spain	7	7 diseases in the national programme. Most regions cover more, but no specific figures provided
Sweden	24	
UK	14	



Results of the literature review

Obtaining a diagnosis is a crucial step in the patient's odyssey towards adapted care and treatment. Hence, ensuring that the patient receives a correct and timely diagnosis is of prime importance. The diagnostic process has witnessed many changes in past years, notably linked to technological advancements. They enable more precise, non-invasive tests and limit the uncertainty associated with

the detection of rare diseases. Indeed, one of the most impactful changes is the **possibility to sequence the genome** with next-generation sequencing technologies (Behjati and Tarpey 2013). **Whole-exome sequencing and whole-genome sequencing as well as newborn screening have revolutionised the practice of diagnosis** and one can easily distinguish a tendency to rely more and more on these tools for rare genetic diseases (Boycott 2019; Fernandez-Marmiese et al. 2018; Johnston et al. 2018). The adoption of these new technologies goes hand in hand with the emergence and development o**f precision medicine** focusing on the patient's personal characteristics (Baynam et al. 2016; Gainotti et al. 2018).

Our literature review also detected **voices calling for a more cautious use of these techniques** and a need for restraint. For instance, some researchers emphasise the fact that if used indiscriminately, they might have a negative impact, notably leading to the disruption of family dynamics, a waste of medical resources and may affect public trust (Johnston et al. 2018). The review also raised fundamental issues in terms of **ethical considerations** such as the intrusion in the genetic characteristics of an individual, the issue of informed consent, and the possibility of discrimination and stigmatisation. There is a current call for norms and standards regarding the implementation of genetic testing (Dhondt 2010; Johnston et al. 2018; Lohmann and Klein 2014). Furthermore, the **limitations of next-generation sequencing methods** are also pointed out - problems of limited coverage, lack of accuracy, the generation of false positive results - which prompt a current effort to improve precision, adapt and facilitate the interpretation of the results of these diagnostic tools (Lohmann and Klein 2014).

Another trend regarding diagnostic approaches is the **integration and combination of various approaches in order to produce a more detailed and valid diagnosis.** One can observe a tendency to include more **phenotypic analyses** and combine them with genotypic information in order to link all types of data and create a disease-phenotype-genetic association network (Gainotti et al. 2018; Shen et al. 2018). Regarding this use of phenotypic information and of a multidisciplinary approach, some scientists even suggest to include anthropological methods and knowledge in the diagnosis processes most notably to help detect phenotypic variations for diseases with a common cause (Anthropology). The development of **deep-phenotyping methods** are also used for the design of imaging techniques and tools for diagnosis such as facial recognition via an artificial intelligence programme (Baynam et al. 2017, Gainotti et al. 2018).

As regards the trend pushing for the establishment of more precise and stringent rules and standards, it is specifically noticeable in the EU. Indeed, the drive and particular need for **harmonisation** for the advancement of rare diseases research and treatment requires common practices among the Member States. However, this is not currently the case and the variations in reimbursement, authorisation policies and required documentation act as a hurdle for cross-border testing and create an unequal access to genetic testing in the European Union (Pohjola et al. 2016). A distinguishable tendency is the organisation of networks for collaboration on diagnostic research, for instance the Rare and Undiagnosed Network as well as European initiatives within the ERNs or the Solve-RD programme (Baynam 2016, Ren and Wang 2019). Furthermore, some supra networks such as EuroGentest, a network of networks, are established in order to gather all expertise and critics on diagnosis procedures as well as genetic testing and counselling so as to set up standards and improve the overall quality of the services across European borders (Cassiman 2005). There is also a drive towards the

development of inclusive approaches, for example taking into account the specific case of isolated and genetically less referenced populations such as indigenous communities (Baynam et al. 2017).

Another theme derived from our academic scanning is the delicate process of **diagnosis delivery.** More attention is paid to the various negative or positive psychosocial impacts which the announcement of test findings might have on a patient and their surroundings, such as acceptance of the situation, better coping with feelings of guilt, loss of hope, loss of social network of peers, anxiety, creation of tension and conflict in the family (Dhondt 2010; Krabbenborg et al. 2016). Overall, there is a recognition that parents experience ambivalent feelings from the findings, partly due to their high expectations regarding the test, and finally find themselves in a complex context of uncertainty (Chassagne et al. 2019). All of these considerations lead to an appraisal of genetic counselling and to demands for more psychosocial support for the patient, the caregiver and the family (Chassagne et al. 2019; Mendes et al. 2019). It is notable that, in spite of the ability to deliver a genetic diagnosis, a trend has emerged whereby some families and patients choose not to know the results of tests (Mendes et al. 2019).

***Possible* trends emerging from the Literature Review:**

- expansion of testing with increased genome knowledge
- knowing the unknown
- combination of diagnostic approaches - Integrated Genotype and Phenotype Analysis
- inclusive approaches
- attention to delivery of diagnosis
- networking

***Possible* drivers of change emerging from the Literature Review:**

- technology
- commercial offer expanding... push in DTC testing (attractiveness to companies)
- cost-effectiveness?

References from the rare disease literature review

Full list of articles/publications found in the literature review:
https://docs.google.com/spreadsheets/d/1SRXASsFiD9sdQz286SVo860XdTpGaOIncyjIhGphULI/edit#gid=364400914

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Annex I: Table of Relevant Resources, Initiatives and Outputs

Given the various disciplines involved in the broad issue of 'diagnostics', it is unsurprising that many initiatives and resources are focused on enhancing diagnostic capacity and availability for people living with rare diseases. Given the challenges in diagnosing complex rare diseases, it is also unsurprising that several of these initiatives span the healthcare and research domains. The table below seeks to summarise –***far from exhaustively***, particularly with regards to the scientific outputs behind this topic- a number of key initiatives of particular relevance to this topic. Initiatives and outputs more relevant to Newborn Screening and primary Prevention are at present included in the dedicated sections above.

Initiative/ Collaboration/ Resource	What is it?	Why it is relevant to this debate?
Solve-RD: 'Solving the Unsolved rare diseases'	Solve-RD is a ca. €15million project, funded under the H2020 call 'Disease characterisation of rare disease (SC1-PM-03-2017)	The project will run from 2018-2022. Solve-RD contributes towards the IRDiRC goal of delivering diagnostic tests for most rare diseases by 2020. ▪ The partners seek to solve undiagnosed cases with unknown molecular causes, via sophisticated combined 'omics' approaches (incorporating not only genomics but proteomics, cell activity, and more). ▪ The second major goal is to improve diagnostics of RD patients through contribution to, participation in and implementation of a "genetic knowledge web" which is based on shared knowledge about genes, genomic variants and phenotypes Particular emphasis is placed on integrating with European Reference Networks (both in terms of partners ERN-RND; ERN-ITHACA; ERN-EURO-NMD, and ERN GENTURIS plus an additional 6 ERNs.) This reflects the acknowledgment that ERNs will increasingly become hubs for complex, unsolved cases, and hold major potential to capture omics and deep phenotypic data from Europe's RD population. Outputs will be available here:
RD-Connect	RD-Connect was established as an FP7 Initiative 2012-2018, establishing a platform to support RD research by linking data from biobanks, registries, databases and bioinformatics. Funding period expired, but the core output is sustained	The RD-Connect platform consists of three systems: Genome-Phenome Analysis Platform; Registry & Biobank Finder; and Sample Catalogue, which are open to any rare disease. ▪ The Genome-Phenome Analysis Platform (GPAP), which is the main outputs of the funded period, is not only a data repository but also a full-featured genomic analysis interface *with a particular focus on diagnosis and gene discovery*. It enables researchers and clinicians (even without bioinformatics training) to easily identify disease-causing genes and find matching cases across databases.

		▪ RD-Connect also conducted a considerable body of ELSI research on issues related with capturing and ;sharing' data in the RD field, which has some relevance to the question of diagnosis ▪ The GPAP will be further developed under the European Joint Programme Co-Fund for Rare Disease Research (see below)
IRDiRC (the International Rare Disease Research Consortium)	IRDiRC was established in 2011 to unite researchers with research funders, to advance RD research globally. It currently has over 56 member organisations.	A new overarching vision was agreed, for the period 2017-2027: '**Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention'.** To make this vision a reality, 3 new goals were agreed. The first in particular is very relevant to this topic: ▪ 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 IRDiRC operates through three Scientific Committees, one of which is dedicated to Diagnostics. Within each Committee, there are a number of dedicated Task-Forces, uniting experts worldwide. The following are particularly relevant to the topic of Diagnostics (however the boundary between diagnostics and 'research' for RD is often quite indistinct, and the work of other TFs will have a bearing here too): ▪ Indigenous Populations ▪ Solving the Unsolved ▪ Matchmaker Exchange – a joint TaskForce with the Global Alliance 4 Genomics and Health Reports generated by each TF are available here:
EJP for Rare Disease Research	The European Joint Programme Co-Fund (EJP) will run from 2019-2023, funded under H2020 to a maximum EC contribution of €55 million (likely exceeding €110 million in total budget)	The activities of EJP Pillar 2, in particular, should have an impact on diagnostics for rare diseases (Pillar 2 will create a sustainable and interoperable ecosystem of resources -the 'EJP RD virtual platform'- coupled to robust standards, tools and procedures that will infuse 'FAIR' principles into advanced and secure forms of data discovery, linkage and sharing)
Undiagnosed Diseases Network International	UDNI was inspired by the 2013 U.S Network funded under the NIH. https://undiagnosed.hms.harvard.edu/	Undiagnosed Diseases Network International seeks to improve the level of diagnosis and care for patients with undiagnosed diseases through the development of common protocols designed by a large community of investigators. The UDNI operates on a number of set principles, including the following (abbreviated): 1. Patients enrolled in the UDNI should be selected for the unique characteristics of their disorder and for its potential to inform new aspects of cell biology, pathogenetic mechanism(s) and therapy.

		Candidate patients should have been extensively examined already, so that obvious diagnoses have been eliminated. 2. Accepted patients should be thoroughly evaluated by the UDNI, preferably at no cost to the patient. 3. Patients should consent to share their data with other investigators within the group. NGS and other -omics analyses should be performed on enrolled families/patients(trios or quartets when possible), and analysed with some uniformity and according to state-of-the-art protocols. The -omics and phenotypic data should be shared among members of the UDNI. 4. Functional studies should be performed to substantiate causal relationships between a candidate gene and the phenotype and address novel therapies.
SWAN (Syndromes Without A Name) Europe	SWAN UK has been supporting UK patients without a diagnosis since 2011, as part of the UK's Genetic Alliance UK. A European branch was launched in 2017.	SWAN Europe is a coalition of groups, organisations and support networks working with families and/or patients affected by syndromes without a name and/or undiagnosed genetic conditions. The aims of SWAN Europe are as follows (from launch announcement)
Global Commission to end the diagnostic odyssey for children with a rare disease	The Global Commission is a multi-disciplinary enterprise established in 2018, combining knowledge and technological expertise	Established in 2018, the Commission is co-chaired by Takeda, EURORDIS and Microsoft Health Services. In February 2019 it launched a series of actionable recommendations around 3 'tracks': 1. Empowering patients 2. Equipping frontline providers with tools for diagnosis and referral 3. Reimagining the genetic consultation These tracks are accompanies by 3 pilot proof-of-concept projects:Multifactorial machine learning to recognize symptom patterns; Enable Collaboration Tools for "Intelligent Triage" and Clinical Geneticist Virtual Panel Consultation; Explore a Blockchain-based Patient Registry and Rare Disease Passport
International Joint Recommendations To Address Specific Needs Of Undiagnosed Rare Disease Patients	A set of 2016 Recommendations issued by global advocacy groups (on behalf of patients living with undiagnosed and rare diseases across Europe, North America, Australia and Japan).	This resource consists of a series of 5 high level recommendations to address the specific needs of undiagnosed rare disease patients. Each of those 5 recommendations is accompanied by an explanation of the needs and several proposals to improve the situation. The document was co-created by SWAN UK (the support group run by Genetic Alliance UK), the Wilhelm Foundation, EURORDIS, Rare Voices Australia (RVA), the Canadian Organization for Rare Disorders (CORD), the Advocacy Service for Rare and Intractable Diseases' stakeholders in Japan (ASrid) and the National Organization for Rare Disorders (NORD).

Orphanet	The portal for rare diseases and orphan drugs	Orphanet provides information on clinical laboratories and diagnostic tests for rare diseases, searchable geographically or by specificity. Details on Accreditation and EQA (External Quality Assessment) are also provided, where possible.
European Society of Human Genetics	The European Society for Human Genetics (ESHG) was established in 1967 and is a founding member of the International Federation of Human Genetics Societies	A long list of Recommendations and policies relating to diagnostic issues (not specifically for rare diseases) is available here:
EuroGenTest	EuroGentest was funded as a Network of Excellence by the European Commission back in 2005. A joint committee was established with the ESHG, in 2013.	The goal of EuroGentest was to develop tools and guidance to harmonise and improve the quality of genetic services (not purely for rare disease, but with a natural relevance to this community). Amongst the most important outputs of the joint committee were the 2016 EuroGentest and ESHG Guidelines for Diagnostic Next Generation Sequencing Additional activities of EuroGentest include: ▪ Supporting the evolution of Orphanet's directory of genetic testing services (which now includes quality management information). ▪ Creation of clinical utility gene cards (CUGCs) intended for multistakeholder audiences and regarding the clinical utility of genetic testing.
Global Alliance 4 Genomics and Health	GA4GH is a research-oriented, international, non-for-profit initiative uniting over 500 leading healthcare, research, patient advocacy, life science, and information technology organisations.	GA4GH seeks to 'create frameworks and standards to enable the responsible, voluntary, and secure sharing of genomic and health-related data.' Though not directly focused on diagnostics, the activities of GA4GH hold significant potential to advance RD diagnostics. GA4GH supports 'driver projects' to develop and pilot the tools and resources created. They have dedicated workstreams which should advance RD diagnostics, such as those dedicated to Clinical & Phenotypic Data Capture and to Genomics Knowledge. Many of the current driver projects **also** have a relevance to RD diagnostics, and should help guide development efforts and pilot GA4GH tools
3GbTest	FP7-funded project 'Introducing diagnostic applications of '3Gb-testing' in human genetics'	3GbTest was funded under FP7 until 2015. This project sought to increase Europe's level of preparedness for innovations in molecular testing, factoring i the need for quality assessment schemes, HTA support, change management amongst health systems and healthcare professionals). Deliverables of the 3GbTest project are available here

Knowledge Base Summary

Integrated, Social and Holistic Care for People with Rare Diseases

Introduction to the topic

'Holistic care' covers the 360° spectrum of the health, social and everyday needs of people living with a rare disease and their families. Holistic care involves, for example:

- The provision of timely, high-quality, integrated care according to the unmet needs;
- Breaking down barriers in access to care, treatment, education, employment, leisure, psychological support and all aspects of social inclusion;
- Enabling people to fully enjoy their fundamental human rights, on equal footing with other citizens.

This topic is thus very broad: it encompasses everything from ensuring the coordination between health and social care, to paramedical support (such as dietary, psychological support etc.), to the social care sphere (e.g. adapted habitation, respite care, resource centres), to a person's inclusion in broader societal life (e.g. education, employment, relationships, etc.). Please note that 'Integrated Care' as a concept is also further explored in the Knowledge Base Summary for Sub-Group 8, 'Accessing Healthcare' (see below, p 10).

A significant challenge for patients, professionals, and health and social systems in Europe is the absence of streamlined, integrated pathways to allow people living with RD to navigate health and social care systems. This is particularly problematic in view of the **complexity** of many of these 8000 rare conditions, and the **lack of awareness and understanding in all sectors of society regarding the full impact of the conditions** (e.g. how they manifest in patients and the myriad ways in which different aspects of daily life can be adversely affected). Very often there is poor communication and collaboration between even the different 'medical' actors delivering specialised care: the disjoint becomes yet more notable when attempting to integrate paramedical and social care professionals.

The need for a holistic approach to person-centred care is particularly important in the rare disease field, where only ca. 5% of conditions have a dedicated therapy of any kind; in such cases, the integration of paramedical and social disciplines alongside the classical 'medical' approach to treatment and management is hugely valued *and* valuable. Evidence from the first European survey on the everyday impact of rare diseases - 'Juggling care and daily life: The balancing act of the rare disease community'' - confirms that the consequences of living with a rare disease are far-reaching, beyond the health niche. 85% of the respondents declared that the rare disease impacts upon several aspects of their health and everyday life. 7 in 10 people living with a rare disease or caring for an affected relative have to reduce or stop their professional activity and 69% also face an income decrease.

The Policy Perspective

The importance of the subject for rare and specialised conditions has long been acknowledged in European Policy and so-called 'soft law' documents. The Commission Communication of 2008, entitled Rare Diseases: Europe's Challenges dedicates a Section (5.2) to these issues:

"Access to specialised social services Centres of expertise may also have an essential role in developing or facilitating specialised social services which will improve the quality of life of people living with a rare disease. Help Lines, Respite care services and Therapeutic Recreation Programmes, have been supported and need to be sustainable to pursue their goals: awareness-raising, exchange of best practices and standards, pooling resources using Health Programme and the Disability Action Plans."

The **Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02** addresses this topic in several ways (the **emphasis** is our own, added here for clarity):

- Member States (MS) were asked to elaborate and adopt NP/NS to guide and structure "relevant actions in the field of rare diseases within the framework of their **health and social** systems"
- MS were asked to "Identify needs and priorities for basic, clinical, translational **and social research** in the field of rare diseases and modes of fostering them, and promote interdisciplinary cooperative approaches to be complementarily addressed through national and Community programmes
- MS were asked to **gather** national expertise on rare diseases and **support the pooling** of that expertise with European counterparts in order to support [amongst other things] the sharing of best practices on diagnostic tools and medical care **as well as education and social care in the field of rare diseases**

An important policy document, specific to rare diseases, is the set of *Recommendations to support the incorporation of rare diseases to social policies and services* drafted under the rare disease Joint Actions and adopted by the Commission Expert Group on Rare Diseases in 2016 (see below for more details)

Guiding Questions for Panel of Experts Discussion – to support the identification of Trends and Drivers of Change

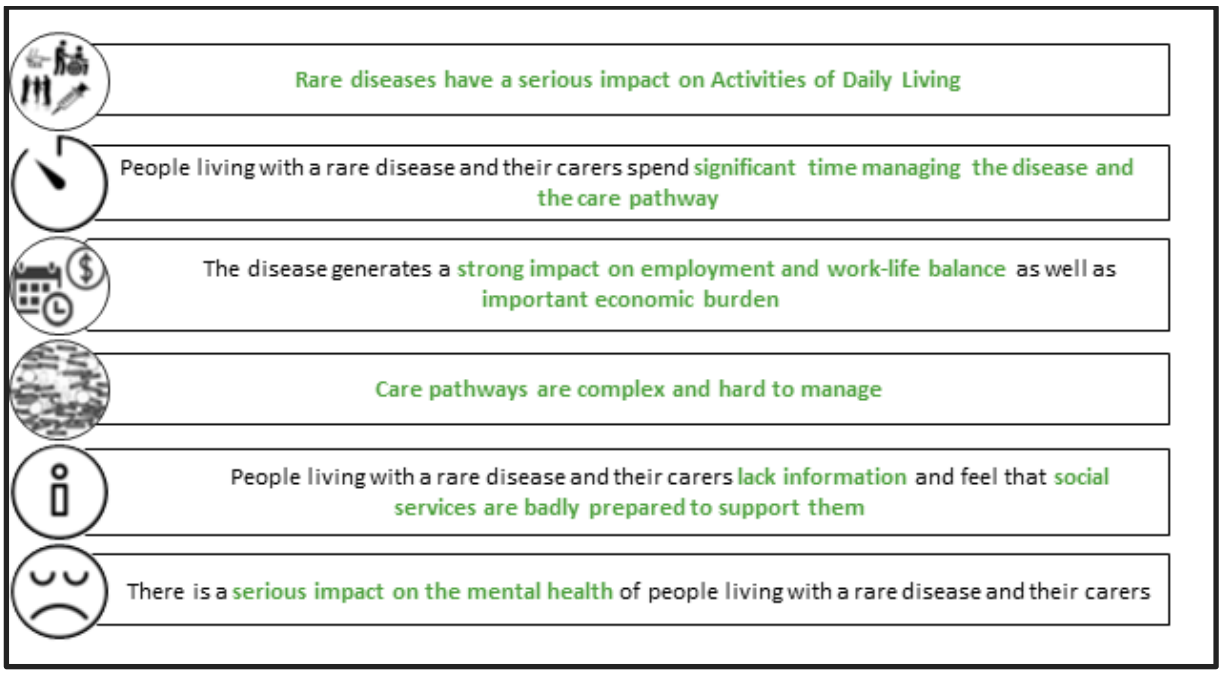
1. **What are the biggest barriers preventing people with rare diseases and their carers from receiving holistic care?**
2. **What concrete good practices promote more integrated, holistic care for people living with rare diseases?**
3. **How do we build momentum in advancing this topic? At national and at European/International level?**

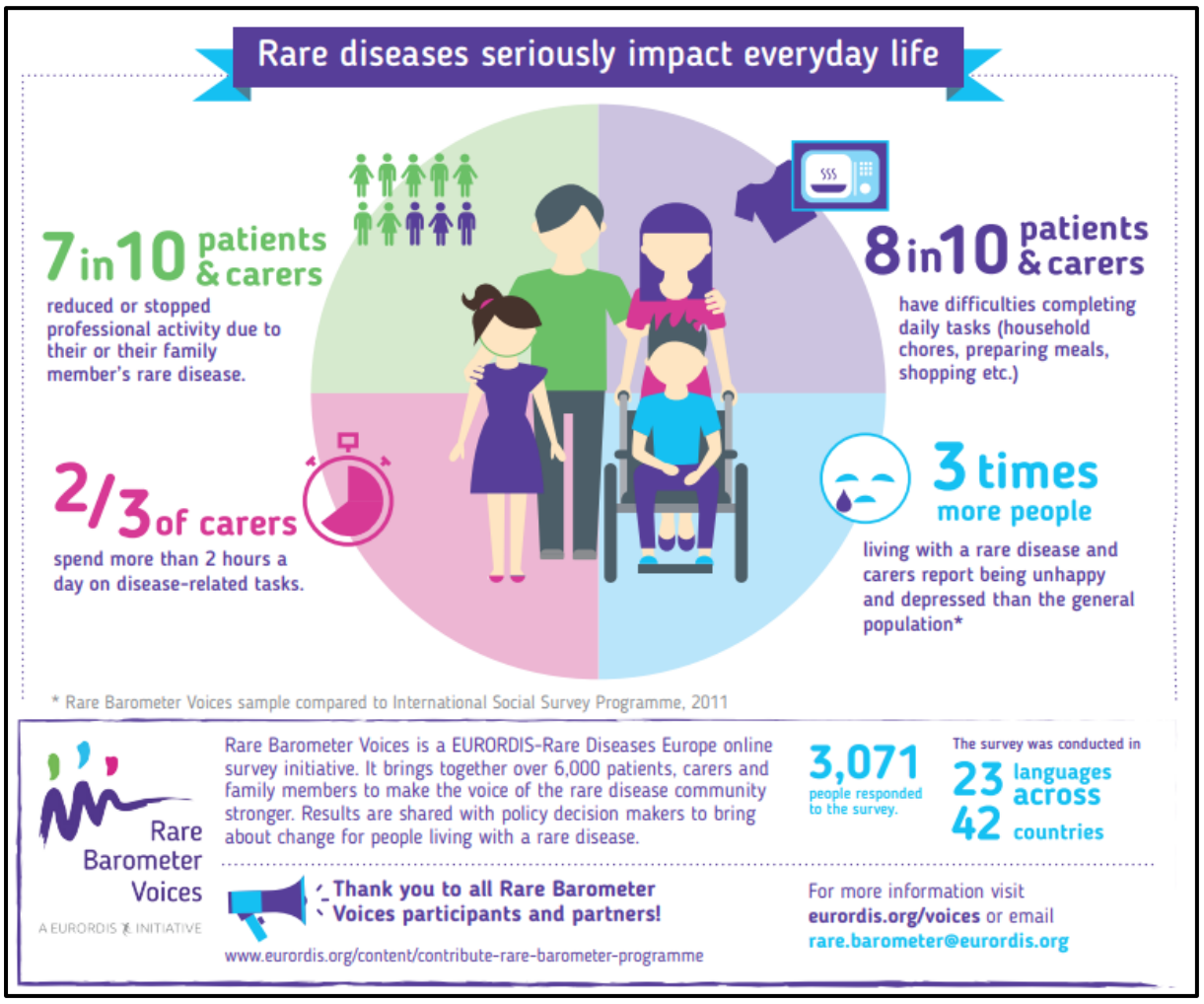
The impact of rare diseases on everyday life: Rare Barometer Voices Survey of 2017

In 2017, a survey entitled 'Juggling care and daily life: The balancing act of the rare disease community' was conducted by EURORDIS-Rare Disease Europe via Rare Barometer Voices, in the scope of the EU-funded project INNOVCare. The purpose of the survey was to assess the impact of rare diseases on oft-overlooked areas of life, including mental, social and physical functions, household budget,

employment and job careers, family life and well-being. 3071 people responded to this survey. The full report can be accessed here .

The main findings included the following:





Initiatives, Projects and Outputs of Direct Relevance to this topic

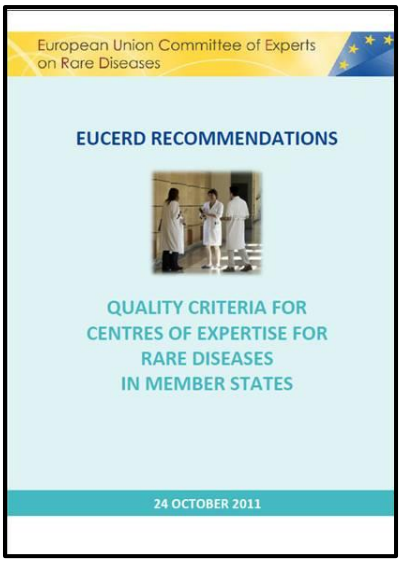
Several initiatives have answered the call of the Commission Communication, the Council Recommendation, and other major policy and legislative documents, and have attempted to better understand the realities and needs of patients and create resources to address these. The following table showcases a number of past and ongoing initiatives and organisations.

Initiative/Body	**Achievement and Outputs to advance this cause**
Commission Expert Group on RD (mandate expired)	2016 Recommendations aimed towards the Member States and the European Commission, focusing on "empowering health services' attempts to facilitate integrated care provision to enable them to play the role they need to play in supporting the incorporation of RD specificities into mainstream social and support services, within a holistic and person-centred approach and a human rights perspective." ▪ **Recommendations to support the incorporation of rare diseases to social policies and services**
INNOVCare project (no longer funded)	✓ *INNOVCare* published a set of Recommendations in 2018 to support the implementation of integrated care and integrated service delivery, coordinated between health, social and community services. ✓ A pilot of case management for RD was implemented and evaluated within INNOVCare, with various positive outcomes for people living with a RD: increase in the level of information about their disease, their rights and available services as well as in their capacity to manage their own care; reduction in burden faced by caregivers; improvement in coordination between care providers. ✓ The project also produced sample training curricula for case managers for RD. ▪ **INNOVCare Recommendations** ▪ **Results of INNOVCare, including outcomes of pilot on case management for RD** ▪ **Training Curricula for Case Managers for RD** ▪ **Full list of resources can be found here: https://innovcare.eu/resources/**
EURORDIS	EURORDIS-Rare Diseases Europe and its over 800 member organisations launched a position paper calling for the provision of holistic care for the 30 million Europeans living with a rare disease and their families, by 2030.

	EURORDIS proposed strategy to achieve holistic care by 2030 is based on 3 pillars: ✓ Pillar 1: Quality and adequate social services and policies; ✓ Pillar 2: Integrated care: bridging health and social care; ✓ Pillar 3: Equity of rights and opportunities. EURORDIS and its members call upon the EU, all European countries and all stakeholders within the health and social sector, to take action based on its ten recommendations (listed on page 9). ▪ **Position Paper 'Achieving holistic, person-centred care to leave no-one behind' (2019)**
RD-ACTION (no longer funded)	▪ **Breakout session summary on Creating a Sustainable Environment for Holistic & Innovative Care for RD & Complex Conditions** (including specific opportunities for ERNs and their constituent HCPs to add value in this topic. This was the result of a joint workshop organised by RD-ACTION and INNOVCare in April 2018) ▪ **RD-ACTION Policy Brief 'Integrated Care'** ▪ **Forthcoming concept paper: *The role of ERNs in the provision of integrated, holistic care for rare diseases***
RareResourceNet	RareResourceNet – the European Network of Resource Centres for Rare Diseases – aims to accelerate the development and the implementation of holistic high quality care pathways for people living with a rare disease across Europe, to contribute to raise standards of care and support.
EUCERD Joint Action	**Papers and factsheets on the types and functioning of specialised social services for rare diseases:** ▪ **Guiding Principles for Specialised Social Services** ▪ **guiding Principles on Training for Social Services Providers**

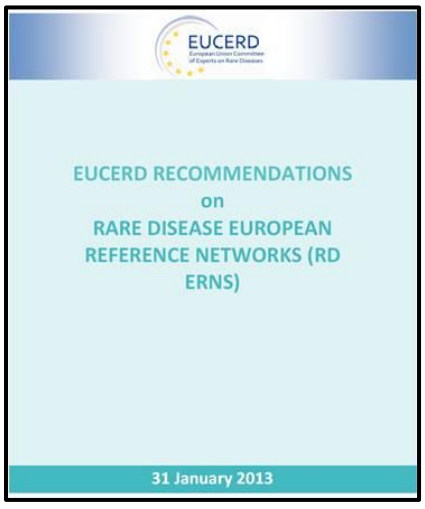
At EU level, several sets of the Recommendations adopted by the EUCERD (European Union Committee of Experts on Rare Diseases) and the Commission Expert Group on Rare Diseases (CEGRD have a bearing on this topic:

Firstly, the ***EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases***. Adopted in 2011, this document includes consensual criteria for designating Centres of Expertise (CEs) in European countries (some baseline parity in terms of national perceptions of a CE was essential, particularly as CEs were envisaged to form the 'core' of -then future- ERNs, although ultimately the term HCP (Health Care Provider) was used in the ERN-related legislation.) The most pertinent criteria for *this* topic are as follows:



- ✓ (4) CEs bring together, or coordinate, within the specialised healthcare sector multidisciplinary competences/skills, including paramedical skills and social services, in order to serve the specific medical, rehabilitation and palliative needs of rare diseases patients.
- ✓ (9) CEs provide education and training to healthcare professionals from all disciplines, including paramedical specialists and non-healthcare professionals (such as school teachers, personal/homecare facilitators) whenever possible.
- ✓ (10) CEs contribute to and provide accessible information adapted to the specific needs of patients and their families, of health and social professionals, in collaboration with patient organisations and with Orphanet.
- ✓ (25) Demonstration of a multi-disciplinary approach, when appropriate, integrating medical, paramedical, psychological and social needs (e.g. RD board).
- ✓ (26) Organisation of collaborations to assure the continuity of care between childhood, adolescence and adulthood, if relevant.
- ✓ (27) Organisation of collaborations to assure the continuity of care between all stages of the disease.

There is no official data to illustrate how many CEs -or indeed ERN HCPs- in fact comply with the criteria above, and thus with the European vision of a *true* centre of expertise for rare diseases.



Secondly, the ***EUCERD Recommendations on Rare Disease ERNs*** reinforce the importance of CEs for rare diseases -and by extension, ERN HCPs- functioning in a truly multidisciplinary manner, complying with the aforementioned 2011 Recommendations.

Thirdly, of course, the policy resource most explicitly and powerfully linked to rare diseases is the set of ***Recommendations to support the incorporation of rare diseases to social policies and services*** adopted unanimously by the Commission Expert Group on Rare Diseases in 2016. These **ten recommendations** mainly focus on empowering health services' attempts to facilitate integrated care provision, to enable them to play the role they need to play in supporting the incorporation of Rare Diseases specificities into mainstream social and support services, within a holistic and person-centred approach and a human rights perspective:

RECOMMENDATIONS TO THE EUROPEAN COMMISSION AND MEMBER STATES

1. **The incorporation of RD specificities into mainstream social services and policies is a necessary element to be considered in future National Plans and Strategies (NP/NS) for RD and should be incorporated when existing NP/NS are evaluated and revised. In particular:**
    - Training of professionals should be promoted;
    - High quality information should be made available.

2. **Centres of Expertise have a key role in facilitating integrated care provision in line with the EUCERD recommendations on Quality Criteria for Centres of Expertise on Rare Diseases22 (4, 9, 10):**
    - Centres of Expertise (CEs) bring together, or coordinate, within the specialised healthcare sector multidisciplinary competences/skills, including paramedical skills and social services;
    - CEs provide education and training to (…) non-healthcare professionals (such as school teachers, personal/homecare facilitators);
    - CEs contribute to and provide accessible information adapted to the specific needs of patients and their families, of health and social professionals.

3. **European Reference Networks for RD have a key role in facilitating integrated care provision in line with the EUCERD recommendations on European Reference Networks for Rare Diseases (10)**23 **and the Directive on patients' rights in cross-border healthcare (Article 12, 4-ii)**24**:**
    - Rare Disease European Reference Networks (RD ERNs) need to collaborate with each other, as well as with patient groups, health and social care providers;
    - RD ERNs follow a multi-disciplinary approach;
    - RD ERNs could function as a platform to share experiences and promote cooperation between MS, to develop precise descriptions of the services required and elaborate common guidelines.

4. MS should promote measures that facilitate multidisciplinary, holistic, continuous, person-centred and participative care provision to people living with rare diseases, supporting them in the full realisation of their fundamental human rights. In particular:
    - MS should ensure that people living with a RD are afforded the same standards of care and support as the ones available to other citizens with similar requirements;
    - MS should recognise the particular challenges posed by rare and complex conditions.

5. MS should promote measures that support patients/families affected by RD to participate in decisions regarding their care plan and their life project:
    - MS should develop information and training tools for patients and families affected by a RD which empower them and increase their capacity to undertake a participative role in care provision;
    - Care providers should be prepared to give non-directive assistance and support patients and families to express their wishes, set priorities, take decisions and direct their own services if they wish to do so.

6. Transfer of information between care providers, within the limits of data protection legal frameworks, should be promoted to support holistic care provision.

7. MS should promote coordination and networking between all parties involved in the care provision of persons affected by RD, including public, private and civil society organisations as well as between providers and patient/disability organisations.

8. RD specificities should be integrated into national systems assessing a person's level of functioning, in line with the United Nations Convention on the Rights of Persons with Disabilities.

9. The elaboration and dissemination of good practices for social care in RD should be encouraged.

10. Socio-economic research in the field of RD care provision/organisation should be supported both at MS level and at European Union level. Support should be provided for research on the following topics:

- Socio-economic burden of RD;
- Accessibility and appropriateness of healthcare services, including social services, for people living with a RD and their families;
- Effectiveness and cost-effectiveness of social services and support, as well as rehabilitation and assistive technologies for people with a RD;
- Innovative care practices in health and social services and their impact on the quality of life of people living with RD.

New High-Level Recommendations from EURORDIS Position Paper of 2019 In May of 2019, EURORDIS issued a Position Paper to raise awareness of the needs of people living with a rare disease and their families in this broad area. The document highlights complementary policy-based approaches to this topic, incorporating the **UN Convention on the Rights of Persons with Disabilities** and the **UN Sustainable Development Goals** relating to health, non-discrimination, and inclusivity.

(Image from https://sustainabledevelopment.un.org/sdgs)

10 high-level Recommendations were agreed in the EURORDIS position paper, each accompanied by more specific points and advocacy approaches.

1. **Making full use of EU instruments and European networks to implement holistic care for rare diseases**
2. **Creating a supportive political environment at national level for holistic care for rare diseases**
3. **Gathering and disseminating knowledge and good practices, to ensure that the needs of people living with a rare disease and their carers are adequately addressed by specialised and mainstream services**
4. **Implementing specific mechanisms that ensure integrated care provision to rare diseases**
5. **Guaranteeing meaningful engagement of organisations and representatives of people living with a rare disease in the design and implementation of policies and services**
6. **Implementing specific measures that ensure access of people living with a rare disease and their carers to adequate social services and social protection**
7. **Ensuring the recognition and adequate compensation of the disabilities experienced by people living with a rare disease**
8. **Creating the conditions for people living with a rare disease and their carers to access adapted and sustainable employment**
9. **Implementing specific mechanisms that empower people living with a rare disease and their carers, in co-creation and co-delivery with organisations representing people living with a rare disease**
10. **Eliminating all types of discrimination, ensuring that people living with a rare disease have access to social, labour, educational, leisure inclusion on equal footing with other citizens**

How might ERNs support the provision of more integrated and holistic care for people with rare diseases?

ERNs, at first glance, have a less clear responsibility to act in the integrated & holistic care sphere (compared to, for instance, the duty to support cross-border virtual consultations for complex cases) – at least when 'integrated' is defined as connecting medical, paramedical and social actors. Nonetheless, the ***EUCERD Recommendations on Rare Disease European Reference Networks*** defined several responsibilities in this area, which were reinforced in the ***Recommendations to support the incorporation of rare diseases to social policies and services***, as can be seen above, page 7

The first large-scale workshop on this topic, organised by RD-ACTION and INNOVCare initiatives in 2018, demonstrated that there are in fact several areas in which ERNs -or at least, the HCPs of which they are composed- can make a significant difference to patients living with a rare disease (see further the forthcoming concept paper on this topic):

- ✓ Spread understanding of the benefits of joined-up, holistic care pathways for patients (encompassing less strictly medical professionals, such as physiotherapists, psychological therapists, and social support appropriate to the specific needs of people with rare diseases and their families)
- ✓ Support and propel the drive to identify how best to provide care for patients with rare and complex conditions and define patient pathways (e.g. ERNs may help to define best practices and support their inclusion to comprehensive clinical practice guidelines or care guidelines)
- ✓ Create personalised health and social care plans for people with rare diseases, possibly both those receiving virtual referrals and the patients visiting constituent HCPs
- ✓ Engage in tertiary prevention activities, including the creation of dedicated guidance from the ERN for patients and families and for local health and social actors (some activities may of course sit more logically with the actual Centres of Expertise i.e. the HCPs here)
- ✓ Embed good practices to support integrated care for patients in their constituent HCPs (and eventually 'affiliated' partners), and in time help to diffuse good practices to broader heath systems
- ✓ Contribute to the collection and integration of data, to improve knowledge and understanding of rare diseases and the impact of patients and wider society

NB: the role of ERNs in supporting the delivery of integrated care at a national level will be addressed in the Knowledge Base Summary for the topic 'Accessing Healthcare'. In June 2019, the ERN Board of Member States adopted a statement on ***Integration of the ERNs to the healthcare systems of Member States***. This important document provides guidance around 5 topics: national rare disease plans/strategies and legal framework for ERN integration; patient care pathways; referral systems to the ERNs; support by Member States to ERN Coordinators, full members and affiliated partners; and information on ERNs provided at Member States level. Although several of these titles have a definite relevance for '*holistic* care', and for the issues explored in this Summary document, the focus of the BoMS Statement is primarily on the healthcare domain.

Research on the socio-economic burden posed by rare diseases

Few projects to-date have sought to estimate the full socio-economic burden of rare diseases. Individual disease communities may have conducted research in this area: some seeking to demonstrate the benefits of truly multidisciplinary care approaches, as delivered by genuine expert centres able to unite all necessary specialists across not only medical but also psychological, social,

and educational actors. However, research on the full impact of rare diseases to society at large seems scarce and fragmented: the field is missing broad studies assessing, for instance, the costs of disjointed medical and social care for patients and health systems, and the economic impact (to patients and families and to society at large) of patients/family members being forced to abandon or reduce employment due to affliction with the disease or the need to act as -potentially unpaid- carers.
A 2010-2013 project, BURQOL-RD, was funded by the 2nd Public Health Programme. The project set out to conduct the first comprehensive analysis on this scale in the rare disease field, by employing a single methodology to assess both direct costs and indirect costs of rare diseases across numerous health systems. The team assessed the socio-economic burden for 10 different rare diseases, using what they termed the *BURQOL-Metre*, and also proposed a methodological framework to measure the health-related quality of life (HRQOL) of patients and their caregivers (see http://burqol-rd.eu/pag/publications.html for publications).

However, there has been limited activity in this sphere since the end of this project, despite the fact that the CEGRD Recommendations explicitly call for a renewed focus:

"Recommendation 10. Socio-economic research in the field of RD care provision/organisation should be supported both at MS level and at European Union level. Support should be provided for research on the following topics:

- Socio-economic burden of RD;
- Accessibility and appropriateness of healthcare services, including social services, for people living with a RD and their families;
- Effectiveness and cost-effectiveness of social services and support, as well as rehabilitation and assistive technologies for people with a RD;
- Innovative care practices in health and social services and their impact on the quality of life of people living with RD".

Quality of Life Data

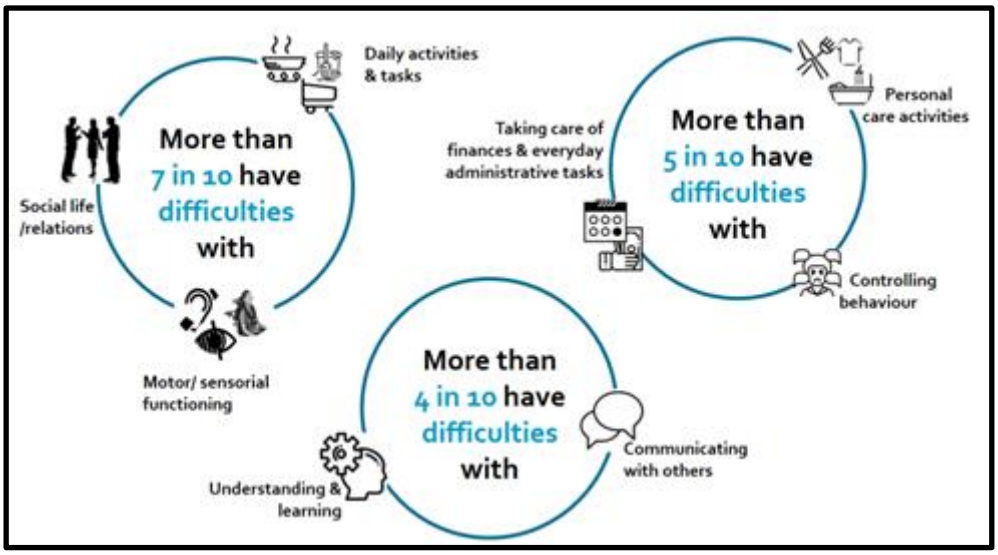
One solution to better understand how complex and often multisystemic conditions (whether rare diseases or otherwise) affect patients is to explore quality of life using approved tools and scales. The issue of how best to capture Health related quality of life (HRQoL) for those living with a rare disease or requiring highly specialised procedures and interventions, is challenging. On the one hand, particularly when assessing health technology (for instance via clinical trials), decision-makers seek comparable data to determine the relative effectiveness of medicinal products/aids/devices etc. At the same time, however, generic HRQoL measures such as EQ-5D often omit the sorts of specificities and dimensions which really matter to patients. More appropriate, relevant, and *standardised* QoL measures would provide a broader base for the selection and measurement of Patient-Centred Outcomes.

Measuring the functionality of people living with rare diseases

A high percentage of people with a rare disease are affected by motor, sensorineural or intellectual impairments, which can occur simultaneously. 72% of people living with a rare disease involved in

EURORDIS' recent European survey on the impact of rare diseases on daily life, reported having difficulties with motor or sensorial functioning.

According to the same survey, people living with a rare disease face serious limitations in their Activities of Daily Living (ADLs):



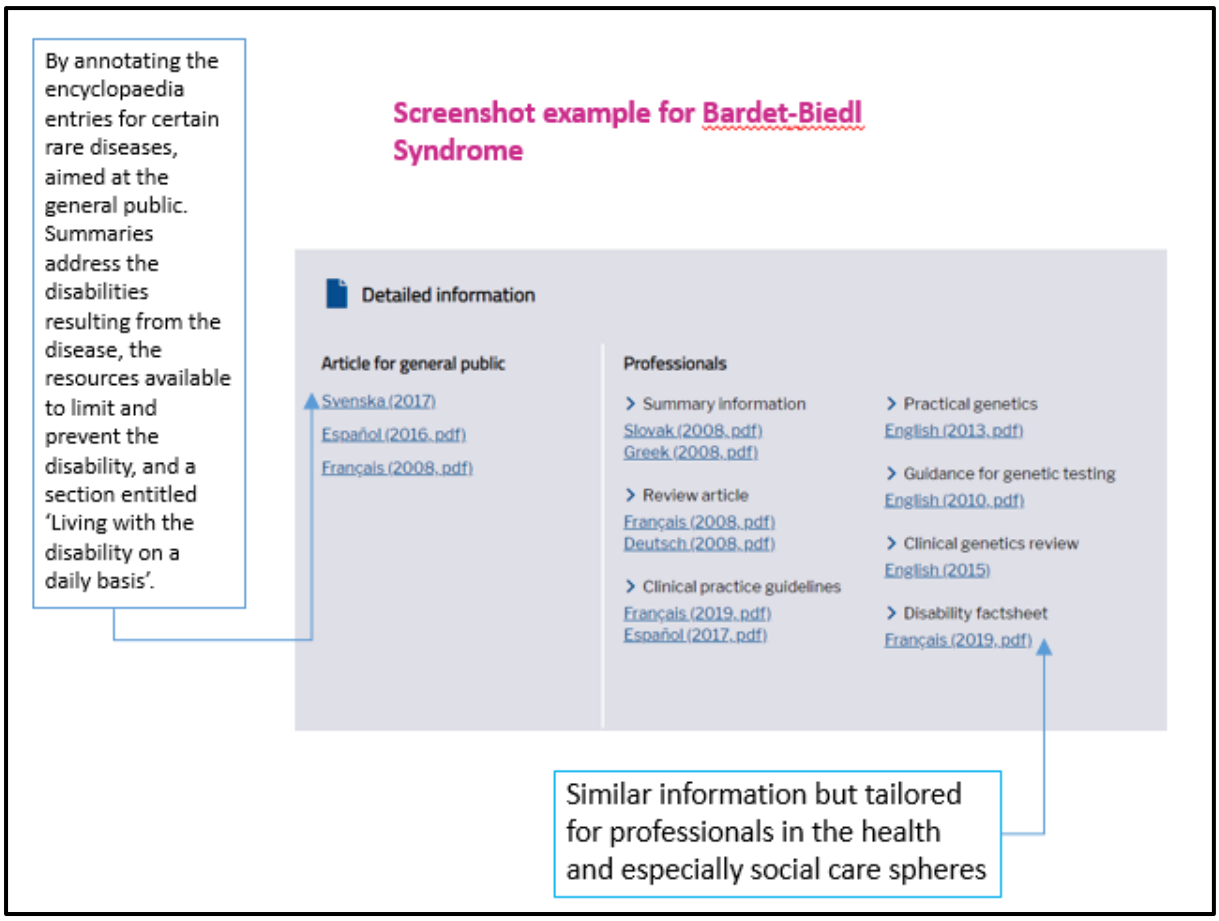
A major challenge for many rare conditions is the complexity of the phenotype and the lack of awareness by social (and often more generalist medical) professionals of the diverse and often hidden ways in which a condition can impact on a patient's life. Disabilities due to rare diseases are typically poorly understood by all but the most specialised professionals, which makes it difficult to find up-to-date reliable information on the manifestation of a disease, not purely in terms of *medical* problems but also considering how the condition could affect eating, sleeping, working, studying, behaviour, etc.

Indeed, the recognition of their disability is the main challenge for people living with a rare disease:

- 34% of the EURORDIS survey respondents who had undergone a disability assessment felt that the percentage of disability assigned to them was too low;
- 19% of the survey respondents had not been enrolled to any sort of disability assessment, despite feeling this would be warranted.

The Commission Expert Group on Rare Diseases recommends to Member States that rare diseases specificities should be integrated into national systems when assessing a person's level of functioning, in line with the United Nations Convention on the Rights of Persons with Disabilities.

An important avenue to address some of these issues is the creation of robust and RD-sensitive systems to categorise disability (and also ability, respecting what patients are able to do and the areas in which they can engage in ordinary societal activities, perhaps with a little additional support). The ICF is a good baseline in the sense it is an international framework that allows for exchange between MS but also between different actors such doctors, social workers etc. in a single country. AS it stands, however, ICF is often inadequate for rare diseases and requires adaptations. **Orphanet** is attempting to address this situation, in several ways, through the information resources available when searching for given conditions in the encyclopaedia (see image below)



The **Orphanet Disability Project** , involving experts and patients from 43 countries, is developing RD disability core sets **derived from and compatible with** the ICF-CY (the International Classification of Functioning, Disability and Health-Children & Youth version). The goal is to map activity limitation/restrictions by disease, using the Orphanet Functioning Thesaurus. The information is gathered via a questionnaire sent to medical experts, disability specialists and patient organisations. Users can find information relating to activity limitations and participation restrictions; frequency in the patient population (i.e. what proportion of the patient community will be affected by each of these limitations or restrictions – are they common to all patients or only a small subset?); whether the disabilities permanent or transient; the severity of the limitations and restrictions; whether they relate to delay in the development of abilities or to *loss* of abilities, etc. The data is analysed and standardised to constitute the Orphanet Functioning Database. Over 857 RDs have been mapped so far, with the support of the French *Caisse Nationale de Solidarité pour l'Autonomie.* However, there are many thousands of rare diseases, and often the resources generated are only available in certain languages.

Results of the literature review:

Rare diseases are often incapacitating and life-limiting diseases which have a tremendous impact on the patient's life, as well as the lives of caregivers and families. Whilst traditional healthcare concentrates efforts in treating the disease *per se*, patients often require supplementary support in order to improve their life experience and face the many obstacles to be surmounted in relation to their disease. Nonetheless, often this **aid and support is not provided by the healthcare system or else is not accessible** (8; 9; 12). Hence, a whole range of unmet needs are waiting to be filled in order to alleviate the difficulties and suffering faced by patients. By extension, **caregivers and families of patients also see their life very deeply affected by the condition** and express as well a need for support which is rarely filled (8; 9; 12; 13).

Consequently, the trends show that **patients and caregivers tend to feel the socioeconomic burden of the disease very heavily**. Most patients need assistance in many areas of their life such as domestic life, transport/mobility, personal mobility/posture, leisure activities, educational or professional activities and self-care (10). A majority of patients are **barred from employment prospects and many caregivers or family members are obliged to either reduce their working hours or cease their activity altogether.** This results in patients living well beneath the poverty line, with them and their caregivers having to grapple with economic difficulties (9). Indeed, many are forced to incur substantial out-of-pocket costs, which greatly affects their lifestyle.

Caregivers, patients and families also suffer from **psychosocial effects**. In addition to the psychosocial effects and mental health issues arising from the patient's condition, individuals report **exclusion, discrimination and moral suffering** (1; 6). Parents for instance report feeling **socially isolated and desperately lonely**. They often express emotions of anxiety, fear, anger, frustration and uncertainty and **share common unmet needs regardless of what disease their child has** (13). Moreover, **very little social and economic support is offered for caregivers** who are most of the time not even recognised as such (12; 14).

Furthermore, the **difficulty in accessing care and the labyrinthine structure of the healthcare system complicates the tasks of caregivers who are forced to put much of their energy into accessing the right service and care available**. The **lack of information** from which patients and caregivers alike suffer leads them to **adopt multiple roles** placing them in complex and highly demanding situations (1; 2).

Nevertheless, in spite of these trends which seem to indicate that there is still much to be done in order to offer holistic care integrating all aspects of the condition, some efforts and changes can be distinguished in the support services developed and in the healthcare frameworks. **Social inclusion, psychological and educational considerations are gradually being integrated in national health programmes and frameworks** (6) and more specialised and support services are available (8). Services thought to greatly benefit rare disease patients and their surroundings include the following: therapeutic recreation programmes (8); one-stop-shop services such as resource centres offering family programmes; respite care; summer camps; familial support (6; 8); and the intervention of case managers who ensure the coordination between team members and the user, fill information gaps, and provide expertise in navigating the healthcare system (6; 10). The **use of internet support groups**

has also been evaluated as helpful for emotional support, finding medical information and psychological support (5).

The Commission Expert Group on Rare Diseases **Recommendations to Support the Incorporation of Rare Diseases into Social Policies and Services** also points towards the right direction, recommending that Member States should ensure that people living with a rare disease are afforded the same standards of care and support as anyone else, and that the specific challenges posed by rare and complex conditions need to be recognised (6; 7). This document also **promotes the development of holistic and integrated care pathways for rare diseases** and requests Member States to include special measures in their national plans and strategies.

Finally, the time-limiting nature of many rare diseases makes **palliative care** a central component of the care management of patients: emphasis is placed on the need to focus on ways to improve this critical discipline. Such attention is key for **the establishment of a complete holistic healthcare system as regards to rare diseases**. Therefore, some researchers emphasise some elements which are crucial in order to fully accompany and ease the suffering of the patients, their family and their caregivers on this challenging path. Examples of such efforts for holistic end-of-life experiences include (1): improving **education on palliative care** approaches; identifying and responding to the **unmet needs of caregivers and families** who are affected by the evolution of the disease, including lack of information, emotional distress, feelings of uncertainty; attention on **ways of communicating, and facilitating decision-making**; consideration of **ethnic and cultural differences** (4); and **integration of the transitions experienced by the patients** during the last stages of the evolution of their disease.

***Possible* trends emerging from the Literature Review:**

- Recognition and efforts to address needs/ challenges for patients in the following areas:
  - employment
  - acceptation in society
  - support services
  - out-of-pocket costs
  - holistic care
- Recognition and efforts to address needs/challenges for caregivers and families
  - out-of-pocket costs
  - psychosocial support
  - caregiver status recognition and financial assistance
  - palliative care science
  - spectrum of palliative care
  - expert caregiver

***Possible* drivers emerging from the Literature Review:**

- Societal views/value system supporting a move to a more inclusive model
- eHealth and related technologies
- Economic landscape

References from the rare disease literature review

Full list of articles/publications found in the literature review:
https://docs.google.com/spreadsheets/d/1SRXASsFiD9sdQz286SVo860XdTpGaOIncyjIhGphULI/edit#gid=364400914

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Rare2030
Foresight in Rare Disease Policy

Knowledge Base Factsheet

Rare Disease Patient Partnerships

Introduction to the topic

It is now well-recognised that people living with rare diseases (RD) and their families are experts on the diseases that affect them and have a valuable contribution to make to shaping meaningful RD research, policies and services. 'Patient partnership' can be defined as a mutual relationship between researchers, policy makers and health and social care providers (on the one hand) and people and families affected by rare diseases, which improves the quality of service and benefits both sets of stakeholders. It implies a relationship of trust and the active engagement of people or family members living with the disease in shaping decisions at the direct care, organizational and system level. Patient partnership implies patients as equal partners and encompasses patient empowerment and engagement. Patient engagement is "a process through which individuals and communities are able to express their needs, present their concerns, devise strategies for involvement in decision-making, and take political, social, and cultural action to meet those needs" (EPF 2015)

The term patient empowerment is often used interchangeably with others such as patient involvement and patient-centred care. The same 2015 EPF position paper uses the following definition of patient empowerment:

> Empowerment is "a multidimensional process that helps people gain control over their own lives and increases their capacity to act on issues that they themselves define as important." Collective empowerment is "a process through which individuals and communities are able to express their needs, present their concerns, devise strategies for involvement in decision-making, and take political, social, and cultural action to meet those needs."

Advocacy by patient organisations is recognised as an important element in defining policies on rare diseases. The need to fully engage and empower patients in all issues relating to rare diseases is emphasized in the 2009 **Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02**. Paragraph (20) states that "*The WHO defined empowerment of patients as a 'prerequisite for health' and encouraged a 'proactive partnership and patient self-care strategy to improve health outcomes and quality of life among the chronically ill'. In this sense, the role of independent patient groups is crucial both in terms of direct support to individuals living with the disease and in terms of the collective work they carry out to improve conditions for the community of rare disease patients as a whole and for the next generations.*" It proceeded to recommend (paragraph

21) that "*Member States should aim to involve patients and patients' representatives in the policy process and seek to promote the activities of patient groups*".

Section VI of the document is entitled EMPOWERMENT OF PATIENT ORGANISATIONS, and Member States are explicitly asked to

- Consult patients and patients' representatives on the policies in the field of rare diseases and facilitate patient access to updated information on rare diseases.
- Promote the activities performed by patient organisations, such as awareness-raising, capacity-building and training, exchange of information and best practices, networking and outreach to very isolated patients.

At the EU level, a remarkable example of the adoption of the latter principle is the 2015 ***Addendum to EUCERD Recommendations on European Reference Networks (ERNs) for Rare Diseases*** (31 January 2013) whereby "Patients and patient representatives should play an integral role in the decision and opinion making process in RD ERNs and be involved in structural and clinical network activities. It is recommended that RD ERNs demonstrate meaningful patient involvement, patient-centredness and empowerment through recognition of the role of patients, as experts by experience and co-producers of knowledge, in RD ERN structural and clinical activities and therefore demonstrate meeting the legal requirements in the Delegated Acts".

Guiding Questions for Panel of Expert Discussion –
to support the identification of determinants of health & wellbeing and drivers of change

1. **What does true 'patient partnership' mean? How best can patients be engaged and empowered to address rare disease issues?**
2. **Are current efforts to encourage partnerships with rare disease patients sufficient? What are the bottlenecks? How can they be overcome?**

Patient advocacy, organisations and support groups

Rare disease patient organisations and support groups initially emerged in the United States in the 1980s, to support patients and their families. Since these beginnings, disease-specific patient support groups have multiplied, as have umbrella organisations for rare diseases in a number of countries across the world and international umbrella organisations linking them all together.

With this increased number of patient advocates and their matured organisation in the form of support groups, their role as advocates has also expanded to include active roles in research, research planning and development of new therapies.

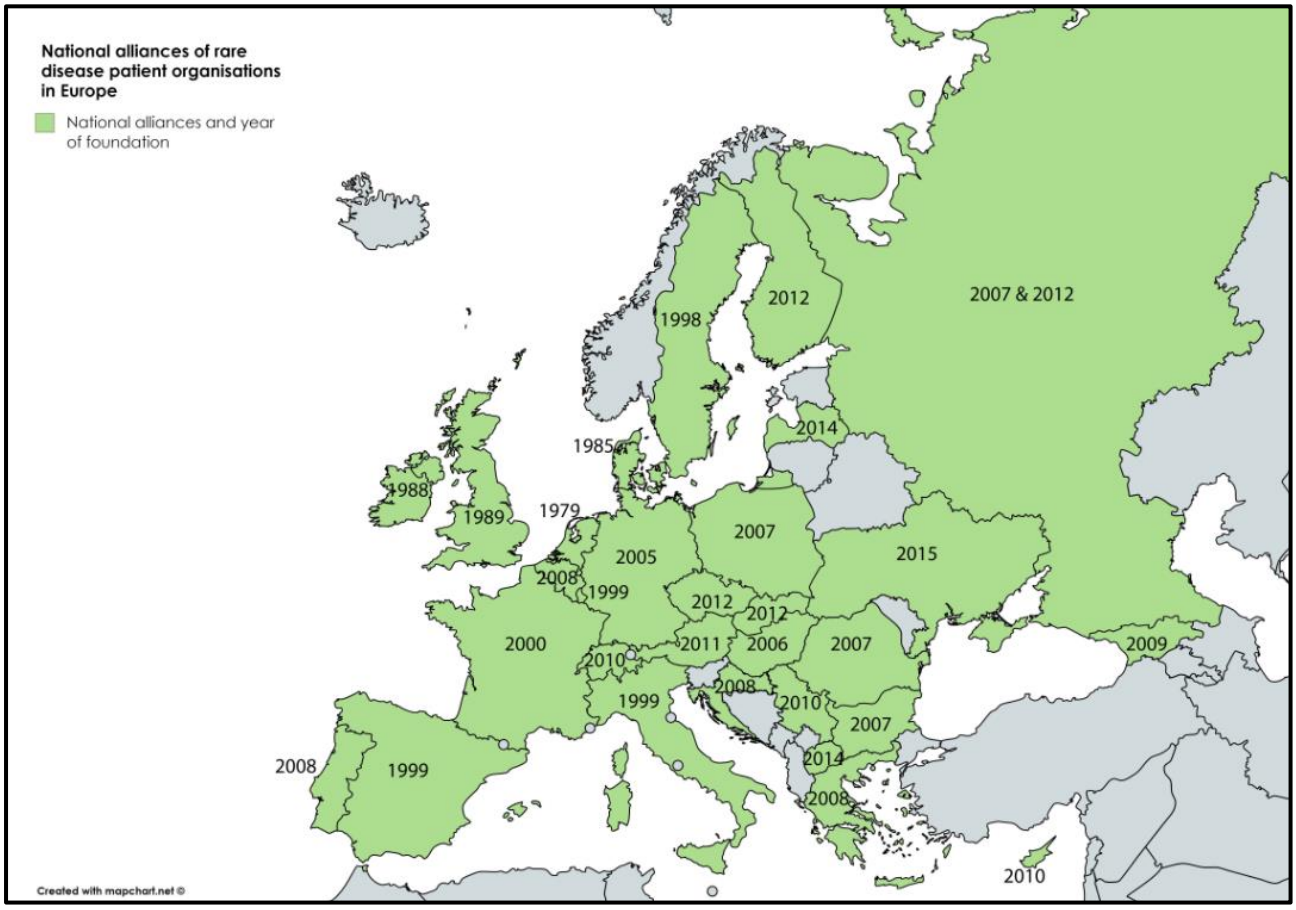
Patient participation or engagement is increasingly viewed as an innovative and viable approach to ensuring appropriate care in the current environment constrained by limited resources. Shared decision-making is the process by which a clinician and a patient jointly make a health decision after

discussing options, potential benefits and harms, and considering the patient's values and preferences. The key is the recognition that in every medical or health decision, there are at least two sources of expertise: the clinician has had lengthy and extensive medical training; but only the patient knows his/her attitude to risk, how the illness is experienced in his/her particular social circumstances, and his/her values and preferences.

National Alliances of patient organisations

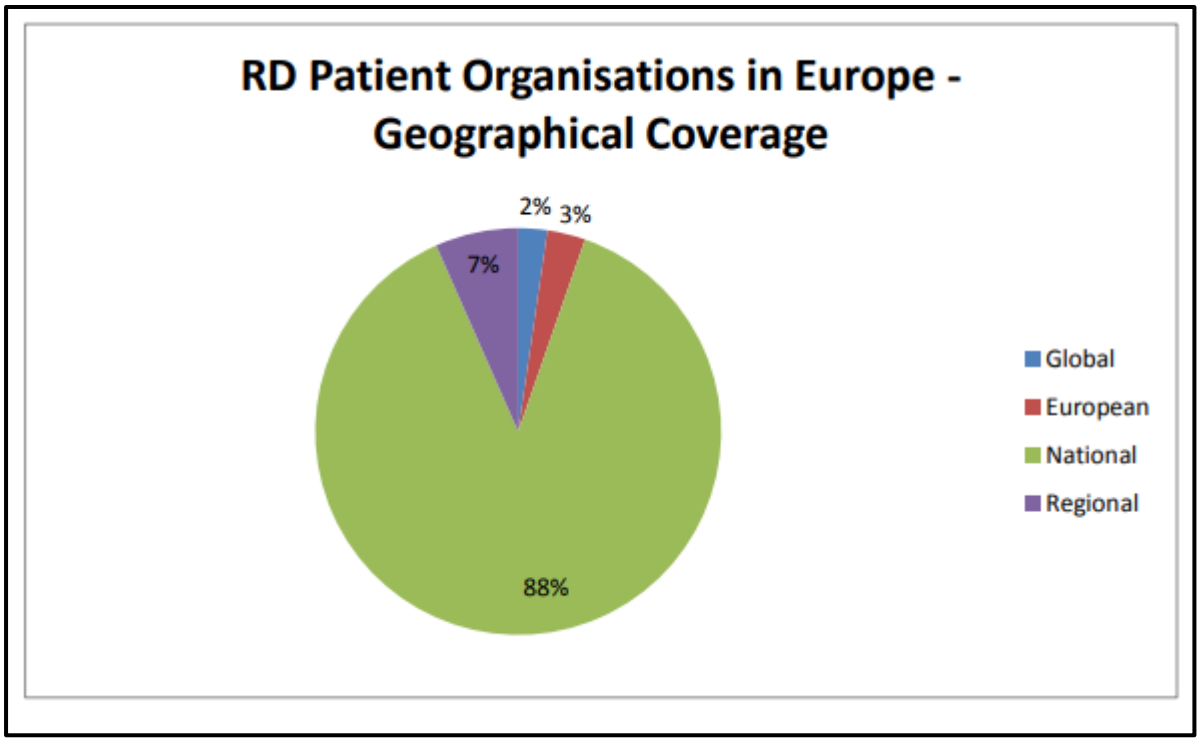
National alliances of rare diseases patient organisations play a key role in advocacy and governance: they provide patients with a common 'home' (essential for very rare conditions, which may not otherwise be able to set-up dedicated patient organisations) and enable stakeholders to impact national policies by speaking with a single cohesive 'voice'. Many national alliances have played (or are playing) key roles in elaborating the national plans or strategies for rare diseases under development or already in place. **Europe has many national alliances for rare diseases: 29 of these are members of the European Network of National Alliances for Rare Diseases**. This network is governed by a EURORDIS-established Council of National Alliances for rare disease patient organisations, which unites the majority of Alliances in Europe with Alliances in the USA and Canada. The Council allows national representatives of rare diseases to work together on common European and international actions, for instance Rare Disease Day.

The map below shows the founding dates of individual National Alliances in Europe:



The table below shows patterns in terms of number of disease-specific patient organisations (POs) registered in the Orphanet database between 2011 and the present day (POs were able to select more than one option)

	No. of disease-specific POs registered in Orphanet in 2011	No. of disease-specific POs registered in Orphanet in 2018	No, of disease-specific POs registered in Orphanet in 2019
National level	1885	2078	2078
Regional level	122	181	181
European level	70	83	83
Global level	45	63	63
Total No. of distinct POs registered	2376	2405	2405



Patient Advocates Supporting Rare Diseases as a Global Health Priority

Following the success of rare disease patient movements in the United States, Europe, Japan, Canada and Australia, EURORDIS initiated **Rare Diseases International**, which today stands along as the global alliance of people living with a rare disease of all nationalities across all rare diseases.

RDI's mission is to be a strong common voice on behalf of rare disease patients around the world, to advocate for rare diseases as an international public health priority and to represent its members and enhance their capacities. RDI brings together national and regional rare disease patient alliances from around the world as well as international rare disease-specific federations to create the global alliance of rare disease patients and families.

RDI has more than 50 member organisations from over 30 countries, which in turn represent rare disease patient groups in more than 100 countries worldwide.

Following this international expansion, **the NGO Committee for Rare Diseases** was initiated by the Ågrenska Foundation and EURORDIS, with a view to bringing greater political recognition of the challenges of rare diseases at the global level. Its formation was approved by a vote of 27 CoNGO (Conference of NGOs in Consultative Relationship with the United Nations) member organisations in April 2014, and its inception meeting as a Substantive Committee within CoNGO took place in October 2015 in New York.

The NGO Committee for Rare Diseases aims to promote multi-stakeholder collaboration and actions for rare diseases within the United Nations system. It is established under the umbrella of the CoNGO and acts as a forum of interested parties such as NGOs from the field of rare diseases and beyond; United Nations bodies and agencies; as well as individual experts. The NGO Committee for Rare Diseases is a multi-stakeholder, inclusive, global ecosystem focused on rare diseases, which aims:

- To increase visibility of rare diseases at the global level
- To extend and share knowledge about rare diseases and their unmet needs
- To connect NGOs interested in rare diseases and their partners within a global platform
- To promote international, multi-stakeholder collaboration and actions for rare diseases
- To align rare diseases as a global priority in public health, research and medical and social care policies

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Building capacity for patient engagement - training and development initiatives

Improving health literacy and education not only empowers patients but also contributes to the sustainability of healthcare systems. Health literacy is a dynamic, interactive process that encompasses capacity-building and aims to influence individual lifestyle decisions, but also raises awareness of the determinants of health, and encourages actions which may lead to a modification of these determinants. Education and training can be for all stakeholders: patients, health professionals and institutions. It allows to promote innovative and high-quality, truly patient-centred, sustainable health systems of the future. Patient organisations often fulfil the task of ensuring education for patients and healthcare professionals through helplines, information and ad hoc trainings. Due to the lack of knowledge about most rare diseases, patients are often experts on

their diseases and have a valuable contribution in shaping meaningful rare disease research, policies and services.

By providing training, patient advocacy groups empower patients and ensure they have the confidence and knowledge needed to bring their expertise to discussions on **leadership, digital health, health care, research and medicines development** with policy makers, industry and scientists.

Examples of such trainings at the European and International level include:

1. EURORDIS - Rare Diseases Europe Open Academy
2. European Patients Academy (EUPATI)
3. Patient Centred Outcomes Research Institute (PCORI) Training for Rare Disease Patient Advocates
4. Numerous patient trainings by national or disease-specific patient organisations

EURORDIS identifies and supports rare disease patient representatives for participation in:

- Patients' representatives involved in EMA scientific committees and working parties
- Protocol assistance
- Scientific Advisory Groups (SAG) at the Committee for Human Medicinal Products
- Other meetings such as discussions on guidelines and risk management programmes

EURORDIS also provides the link between its trained alumni and research, regulatory and healthcare provision by:

- nominating patient representatives to the European Medicines Agency (EMA), where trained patients actively engage in scientific committees and working parties, protocol assistance, Scientific Advisory Groups (SAG) at the Committee for Human Medicinal Products, other meetings such as discussions on guidelines and risk management programmes
- creating the European Patient Advocacy Groups (ePAGs) in every European Reference Network to promote a patient-centric approach in both delivery of clinical care, service improvement and strategic development and decision-making
- representing patient needs alongside 13 international organisations on the International Rare Disease Research Consortium (IRDiRC) Patient Advocates Constituent Committee (PACC)

With the growing recognition that patients can and should be more involved in the medicines development process, a multistakeholder effort to develop a framework for structured, effective, meaningful and ethical patient engagement supporting the integration of patient perspectives into drug development is underway via the landmark PARADIGM IMI project.

Role of rare disease patients in data collection

Historically, the involvement of patients in public health research consisted solely of subject-based participation. By encouraging patient input in the development, design and distribution of the surveys and treating them as *de facto* experts on their respective diseases and actors of their research, patient advocacy organisations like EURORDIS have successfully achieved a paradigm shift in the role of patients in the generation of quantitative data on their own health, as well as on the provision of healthcare services through programs and activities such as:

- Eurobarometer
- Rare Barometer Voices
- Patient-led/initiated registries
- The inclusion of Patient Centred Outcome Measures in data collection initiatives

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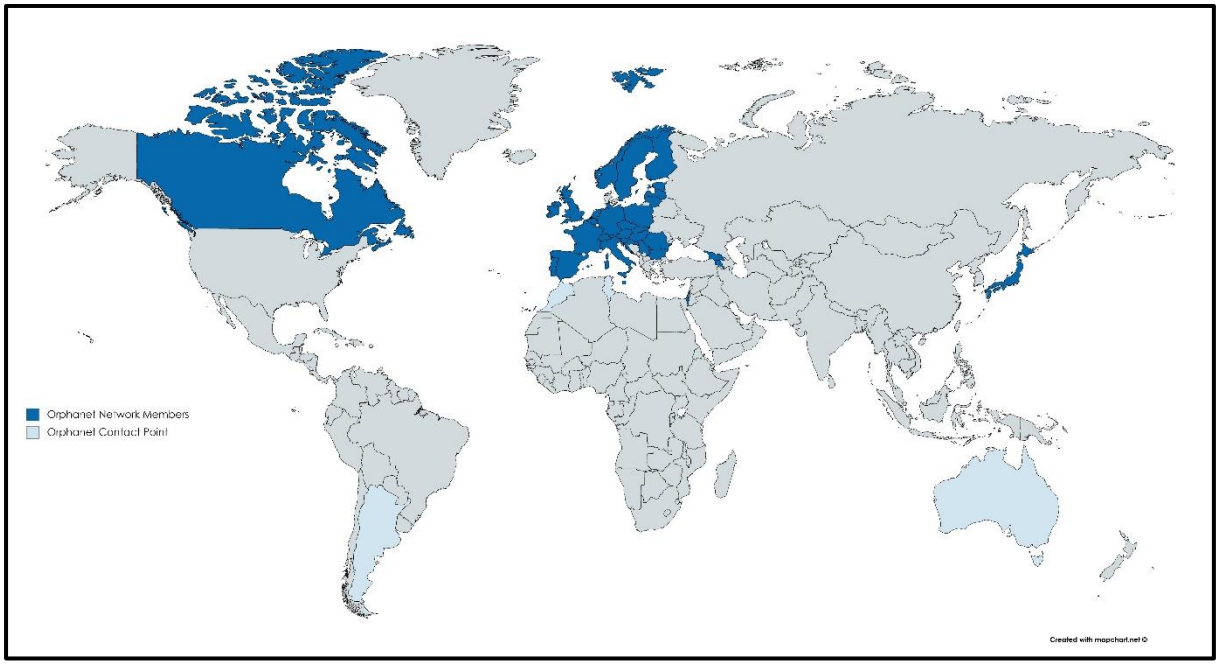
Information services and resources on rare diseases

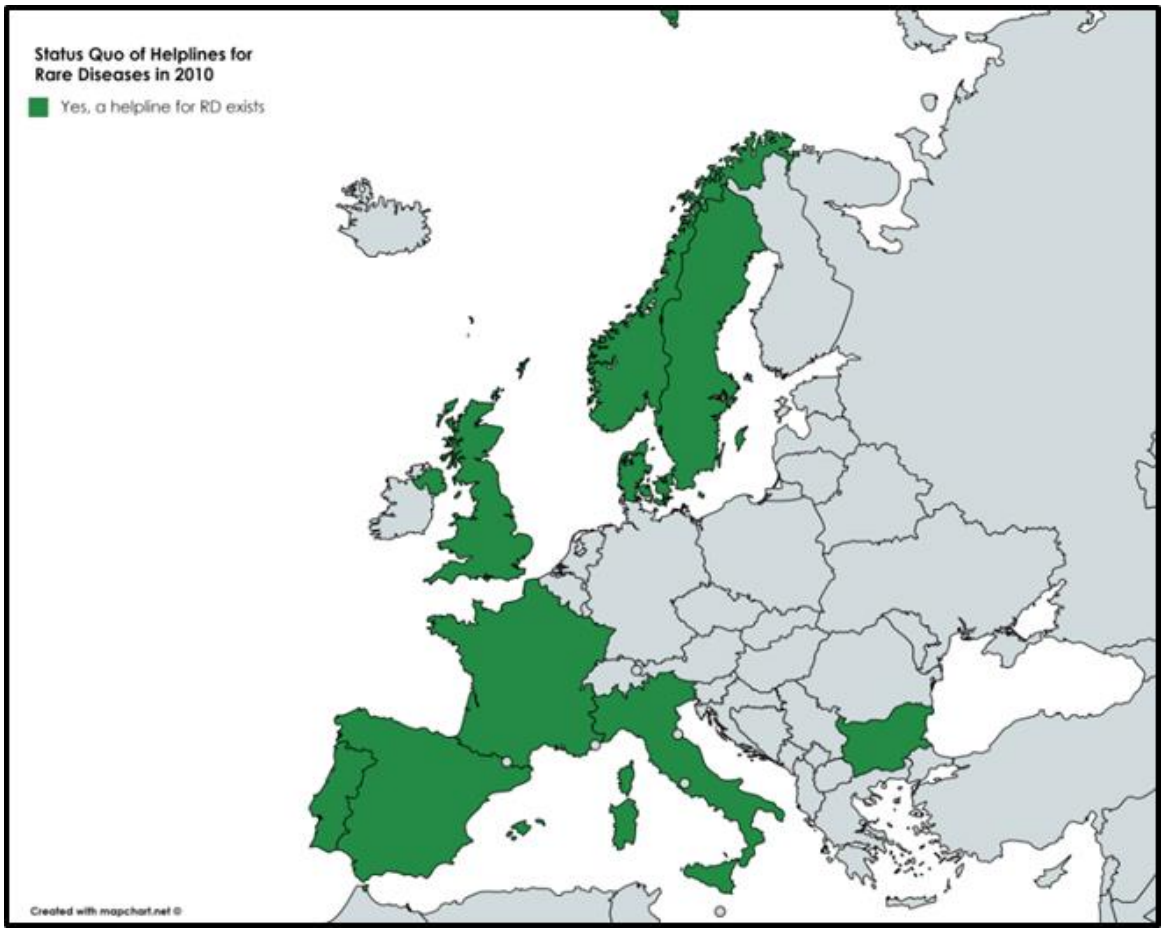
Orphanet (www.orpha.net), the rare disease and orphan drug database, has been delivering information to, and for, patients since 1997. Orphanet aims provide expert-reviewed and accessible free information on rare diseases to all audiences, including patients. Indeed, around a quarter of Orphanet's users are patients and their families. The multilingual approach of Orphanet means that information is available now in 8 languages; information is only accessible to patients when it is in their national language, so efforts are being made when the budget exists to include more languages. Orphanet produces the Orphanet nomenclature of rare diseases, an essential resource to improve the visibility of rare disease patients in health information systems.



Map courtesy of Orphanet

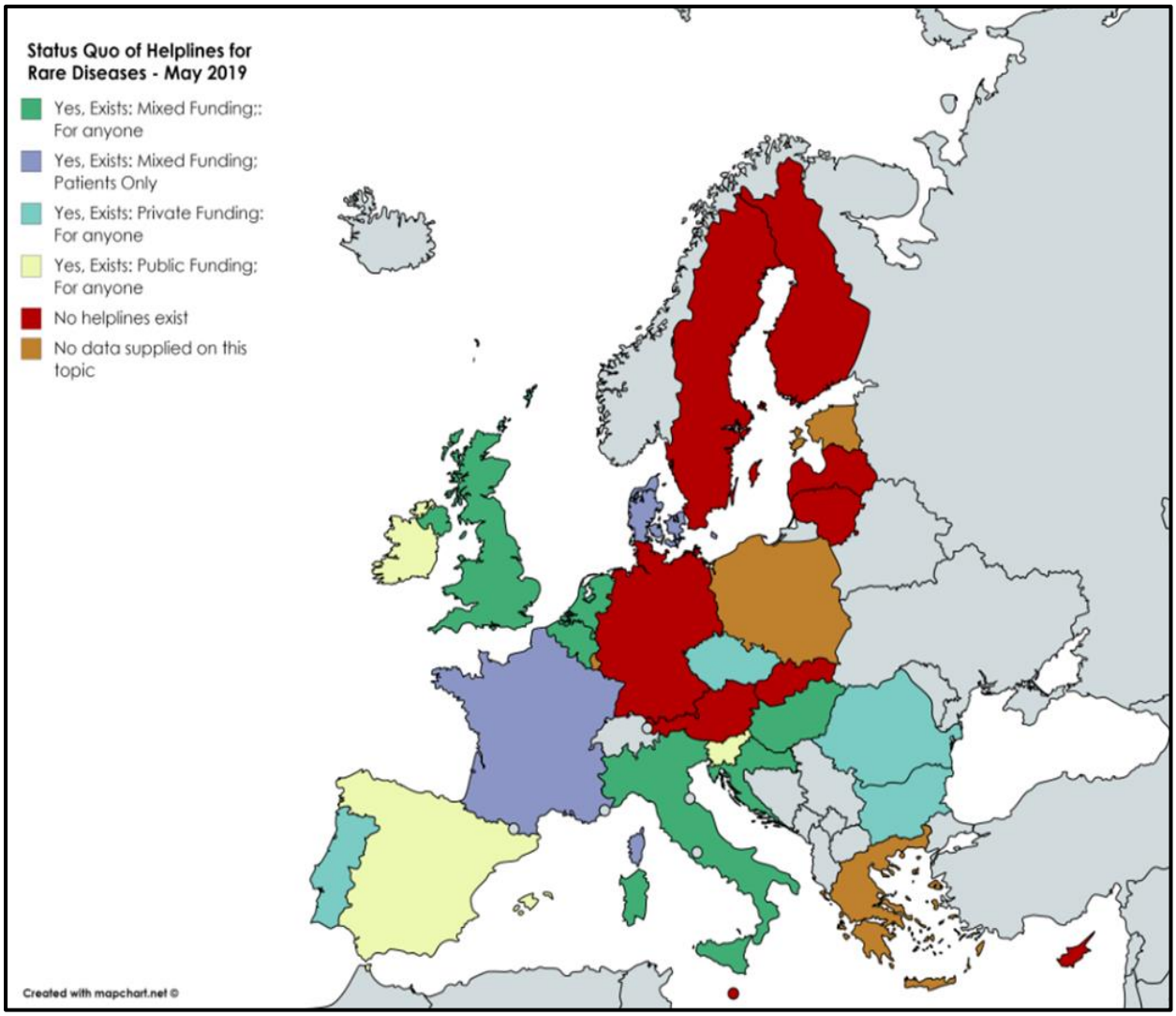
The wide range of information available via the Orphanet website can help empower patients, in many ways. They are able to learn more about a disease through the quality texts on their disease (including texts geared to patients, and emergency/clinical practice guidelines and handicap factsheets). They can find expert resources (centres of expertise and European Reference Networks, for example) in their country to orientate them, and they can find support through the directory of patient organisations for specific rare diseases in 35 countries across the world, as well as alliances and federations of patient organisations and helplines in each country. Orphanet thus also provides increased visibility to patient organisations. Orphanet also provides cross-linking to the Genetic and Rare Disease Information Center (USA's NIH) website, which provides information dedicated to patients, so as to provide additional resources. In order to incorporate the patient perspective in the determination of Orphanet's strategy, a patient representative is part of Orphanet's International Advisory Board.

An important information resource, in many countries, are **helplines dedicated to rare diseases**. The *Resource on the State of the Art of Rare Disease Activities in Europe* (SotAR) collects data from all EU Member States (MS), through Data Contributing Committees composed of representatives of the following: National Competent Authority; Orphanet national team; national alliance of RD patient organisations. The Committees provide data in response to strategic questions designed to allow MS to share information on their national activities in accordance with the EUCERD *Recommendations on Core Indicators for Rare Disease National Plans and Strategies*.



The map above records the status quo back in 2010, when only 8 MS (plus Norway) reported the existence of national helplines (however, these were identified as *official* helplines)

From 2015 onwards, countries were asked more specific questions on their helplines, in accordance with the EUCED Recommendations on Core Indicators… Where helplines exist, the Recommendations asked countries to specify the audience of these helplines (just patients, just professionals, or anyone?) and the means of support (private funding, public funding, or a mixed model?). The map below is based upon data received through the SotAR as of May 2019(please not that this data may change slightly later this year, as countries clarify their responses)



In 2019, as per the map avove, 15 EU MS reported the existence of helplines for RD (note however the greater number of options in terms of reporting *types* of helpline – it is likely that patient organisation-run helplines existed in 2010 but were not counted as official by the CNA representative providing the information)

Results of the rare disease literature review

Recently, **a paradigm shift may be observed when considering the place, role and attention directed towards the patient**. Indeed, it seems as if an underlying change in patient management and public health structures is emerging in certain parts of the world. The patient is no longer attributed a *de facto* passive role but becomes **an actor in the health system realm**. The model also tends to **place the patient, as an individual with specificities, and personal experience, at the centre of the model** (23). This results in the design of increasingly **personalised healthcare pathways** (7; 29) which implies that healthcare systems take more responsibility for patient management and necessitates optimised **information provision for patients to be able to make informed choices** (21). Care is becoming less focused on the disease and the treatment but rather **takes into account the patient's experience and perspective for modelling a system** (4). Hence, a distinctive trend is the **change in the relationship between the patient and the healthcare professional towards a more collaborative relationship** (21). Improved communication is one of the key attributes of this system model which requires **constant and free flow of information between all participants** including patients, caregivers and parents of the patient in the case of paediatric care.

With the accumulation of knowledge, thanks in part to the ease with which knowledge is disseminated and the hurdles faced by rare diseases patients in navigating the healthcare system, **patients and caregivers tend to become experts in their diseases** (14; 28). Consequently, this **empowers them to organise, become agents of their own treatment odyssey and shape their own clinical pathway**, although this is often due to the absence of other available options. As such, a number of patient organisations have arisen from personal initiatives. These mobilisation efforts have produced significant results in building **tightly-knit and active communities driving policy**, helping to **break the isolation** of the patients and producing and providing valuable information (2; 8; 9; 16; 30). Over time, **these organisations have gained a strong position and voice in the rare disease community** and now act as representatives for patients on a global scale: EURORDIS at the European level, for instance, and Rare Disease International at the international level (8; 16).

Part of the patient empowerment process is built on the **provision of information to patients,** who are also in demand of such knowledge, as well as capacity building measures. In particular, social networks, such as PatientsLikeMe or RareConnect, specific to rare diseases, have taken up the challenge to respond to the growing request for knowledge provision and sharing, with the support evolution of digital technologies that allow sharing and co-creation of knowledge. Patients are **solicited in their role as experts of their disease to provide data, evaluation and feedback on their experience**. It prompts the emergence of **two-sided informational pathways,** where both patient or experiential knowledge and scientific or medical information are equally valued (29).

In this schema, patients become also **generators of knowledge and data,** informing research, clinical care and treatment. A direct manifestation of this trend is the development of **patient reported outcomes measures** which are valuable reports directly obtained from the patient about their health status or treatment without being interpreted by an intermediary. These instruments make the **patients' voices central to clinical decision-making** (24). This is also the case for research in which **patients' capacity to provide data, and their experiences and views, are increasingly taken into account** as a way to determine research design, to foster patient recruitment, adaptation of patient

intervention, dissemination and vulgarisation of research results. **Patients then reach a status of co-researchers** with the establishment of a bi-directional engagement and a productive and mutually beneficial working relationship (10; 11; 21; 22; 31; 32). For instance, patients and patient organisations are increasingly consulted for biobanking or the setting-up of registries (3).

As a result, it is becoming more **common for multidisciplinary groups of stakeholders to collaborate in order to either formulate new policies, conduct research or improve treatment options and healthcare systems** (1; 32). An area in which patient public and private collaboration is documented to be particularly beneficial is orphan drug development (18; 19; 33; 34), as patient involvement is claimed to be fundamental for improving the likeliness of a drug to complete the orphan drug lifecycle. As a matter of fact, guidelines informed by both patient and pharmaceutical representatives for best practices in terms of patient and industry interactions are also reported (25). Moreover, **patients are increasingly included in strategic, multi-stakeholder committees, expert groups, boards of various organisations** such as the RDTF, EUCERD, the Commission Expert Group on RD, ERNs, IRDiRC and research consortia (12; 17; 20; 32).

The patient empowerment process also occurs thanks to the information dissemination generated by a diversity of sources and means. Over the years, in addition to the development of **Orphanet** resources**,** a number of **helplines for patients to obtain up-to-date quality information have been established (see above):** these lines are able to respond to enquiries on anything related to their condition or status (15). Use of web searches and online tools is also steadily increasing – improvements have been noted, in terms of ability to allow patients to establish their own diagnosis with relatively good results (27), thus completing their expertise.

Another development which forcefully places the patients at the centre of the arena is the range of possibilities afforded by **the use of social media**; not only can social media be used for information and advocacy purposes with undeniable success (29), but it is also a **core resource for seeking, producing, mining and sharing health data** (6; 26).

An additional observed trend concerns **patients' capacity to travel** and choose the location of their treatment centre. On the virtual side, the development of **ePrescription** possibilities and the current efforts to standardise **cross-border patient summary services** allows for the travel of patient *data*, facilitating the solicitation of extraterritorial healthcare services (cf. CEN and HL7 Patient Summary Standards - ehealth standards).

Possible trends around this topic – for discussion

- Move to patient centred care
- Patient as actor/expert of their disease
- Two-sided informational pathways between patient and healthcare professionals
    - Patient as generator of information/data/knowledge
    - Enhanced patient information provision and communication

- Multistakeholder approaches with patient inclusion in governance and decision-making settings of relevance for patients' health and social care
- Patient empowerment
    - Information dissemination
    - Use of social media
    - Choice in treatment centre/possibility to travel (eHealth portability of personal data/ ePrescription)

…

Possible drivers of change for this topic – for discussion

- Patient advocacy - actor from civil society in the political sphere
- Scientific advances as regards personalised medicine
- Rise of access to information
- Social media and the possibility for networking it offers
- Development of an informational and cultural context which facilitates patients' political action
- Patient-centered care and approaches

- ……

References from the rare disease literature review

Full list of articles/publications found in the literature review:

- https://docs.google.com/spreadsheets/d/1SRXASsFiD9sdQz286SVo860XdTpGaOIncyjIhGphULI/edit?usp=sharing

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Knowledge Base Summary

Access to Healthcare

Introduction to the Topic

This document will highlight a number of issues with a broad relevance to accessing healthcare for rare diseases, most notably: the creation and functioning of **Centres of Expertise** for rare diseases; the emergence and evolution of **European Reference Networks** (ERNs); the development and use of **clinical practice guidelines/clinical decision support tools** to reduce inequalities in care; and **eHealth**. The lack of patients living with any single rare disease has traditionally been accompanied by a corresponding lack of experts able to properly diagnose, treat, and care for them. This inevitably created a 'geographical lottery', in which patients 'fortunate' enough to live reasonably close to true experts in their conditions might hope to benefit from the fruits of their knowledge and experience (accrued through a concentration of patient cases across the years). However, the majority of patients would be limited to the best their local hospital or tertiary care centre could offer, even though the expertise in their particular condition may be minimal. Numerous approaches and tools have been identified at European level, to try to eradicate such inequalities (which can often exist *within* countries, as well as between countries).

At the heart of a European system of rare disease healthcare is the concept of a Centre of Expertise. Indeed, in its simplest form perhaps, the vision of an ERN was to connect nationally-embedded centres of expertise for rare diseases and specialised healthcare, via virtual, transnational networks. Unsurprisingly, these concepts occupy an important position in the foundational policy documents which have driven so much of European rare disease activity in the past decade:

The Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final] highlighted the need for "**Improving universal access to high-quality healthcare for rare diseases, in particular through development of national/regional centres of expertise and establishing EU reference networks**" (5.1)

The two topics were grouped together in SECTION 4 of the Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02: specifically, Member States were asked to

- "Identify appropriate centres of expertise (CEs) throughout their national territory by the end of 2013, and consider supporting their creation.
- Foster the participation of CEs in ERNs respecting the national competences and rules with regard to their authorisation or recognition.

- Organise healthcare pathways for patients suffering from rare diseases through the establishment of cooperation with relevant experts and exchange of professionals and expertise within the country or from abroad when necessary.
- Support the use of information and communication technologies such as telemedicine where it is necessary to ensure distant access to the specific healthcare needed.
- Include, in their plans or strategies, the necessary conditions for the diffusion and mobility of expertise and knowledge in order to facilitate the treatment of patients in their proximity.
- Encourage CEs to be based on a multidisciplinary approach to care when addressing rare diseases**"**

Guiding Questions for Panel of Experts Discussion – to support the identification of trends and drivers of change

1. **What are our most powerful 'tools' or 'assets' to improve access to high quality healthcare for every person afflicted with a rare disease in Europe?**

2. **What do you feel are the main achievements of European Reference Networks to-date, in terms of increasing access to high quality healthcare? What 'next steps' would yield the greatest progress?**

3. **What practical actions –at any level: local, regional, national, European and/or global) would yield the most meaningful results across this topic as a whole? Who should do what, and how?**

Centres of Expertise for Rare Diseases

The concept of 'Centres of Expertise' is of major relevance to the rare disease field, as it encompasses a goal of mapping and understanding the existing rare disease expertise available in countries, but also exacts particular standards and quality criteria necessary in highly specialised care. Based upon the work of groups including the High Level Group on Health Services and Medical Care and the EC Rare Disease TaskForce, the EUCERD (EU Committee of Experts on Rare Diseases) elaborated a set of recommendations which were adopted on 24 October 2011: the ***EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States***.

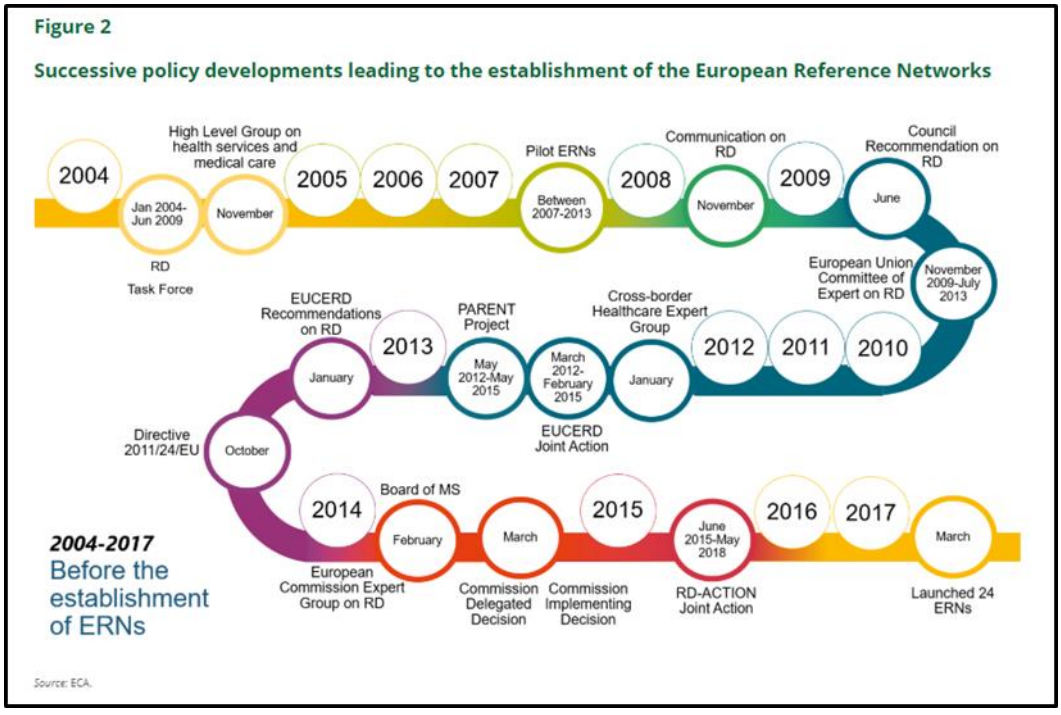
This consensus-building on what constituted a Centre of Expertise (CE) was deemed especially important in the lead-up to the creation of ERNs: the selection and endorsement of national centres to participate in ERNs would presumably be facilitated for countries which had agreed formal processes for designating expertise in rare diseases. The drive for countries to endorse centres to formally join ERNs has, in some ways, reignited the topic of Centre of Expertise designation. Each country was responsible for defining its own procedure by which to endorse a Centre (HCP in the ERN vernacular) to participate, and naturally these criteria varied. For some countries, the logical approach – given the particular relevance of ERNs to rare disease– was to only endorse national centres which had formally been designated as a centre of expertise (or similar) for rare diseases. Other countries, including those which did not have a formal process in place for designating CEs for rare diseases, chose other ways to endorse centres to apply for ERN membership.

The result is a patchwork of over 900 HCPs (some hospital trusts, some individual centres, some specialised units within a wider hospital) organised into 24 ERNs: all should have been designated and evaluated at national level to comply with the core criteria for ERN HCPs as per the Delegated and Implementing Acts. But in some cases, these centres will have gone through detailed national designated processes *predating* the HCP designation in 2016.

The era of ERNs: Policy and legislative origins

- In 2011, the concept of an ERN formed the focus of Article 12 of the Directive on the Application of Patients' Rights in Cross-Border Healthcare (often termed the 'Cross-Border Healthcare Directive')
- The EUCERD adopted ***Recommendations on Rare Disease European Reference Networks*** on 31st January 2013
- These Recommendations were supplemented with an ***Addendum*** in 2015 (proposing a model to thematically group RD into a manageable number of networks, and outlining what meaningful patient involvement in ERNs might look like)
- The European Commission published the Delegated Decision (2014/287/EU) and Implementing Decision (2014/286/EU) on 10th March 2014. The Delegated and Implementing Decisions stipulated transversal criteria for networks to fulfil in order to qualify as ERNs and for healthcare providers wishing to join an ERN

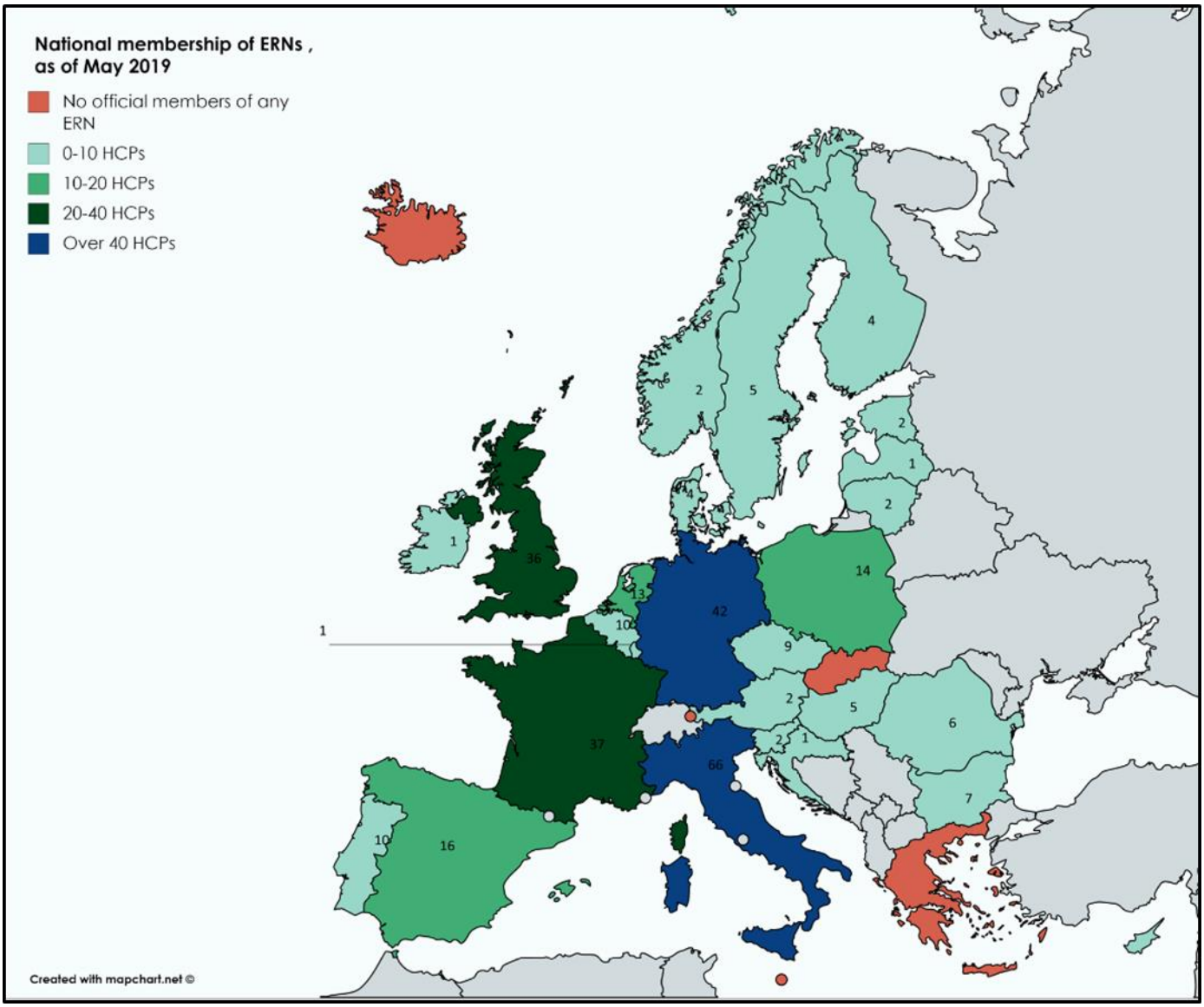
24 ERNs were officially approved as of January 2017, the result of over a decade of advocacy and planning at European and national levels. The road to ERNs is explained in more detail, here (pages 48 onwards).



(Image from the European Court of Auditors Report on the Implementation of Directive 2011/24/EU - http://publications.europa.eu/webpub/eca/special-reports/cross-border-health-care-7-2019/en/)

Support for the conceptualisation and implementation of ERNs was a cornerstone of two European Joint Actions for Rare Diseases – in RD-ACTION particularly, emphasis was placed on enabling the Networks to come together and address challenges around their common responsibilities, by sharing good practices and avoiding the reinvention of wheels.

ERNs offer many advantages, in terms of bridging the care and research divide, which will -it is hoped- help to erode the inequalities observed to-date. A summary of each ERN is available here: https://ec.europa.eu/health/ern/networks_en. Together, the 24 ERNs unite over 900 specialist units in over 300 hospitals across 26 countries (25 EU MS –all except Greece, Malta, and the Slovak Republic- plus Norway, as an EEA nation). This map illustrates the current membership, based upon the official figures appearing on the European Commission websites, here.

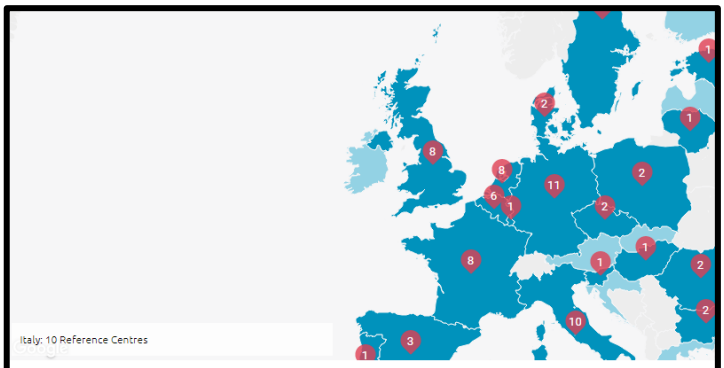


How ERNs are elucidating the status quo for rare diseases and highlighting specialised care in Europe

The disease-coverage of ERNs is expected to increase via a step-wise approach, to ultimately offer the best possible advice and expertise on *all* conditions under each broad thematic umbrella heading (e.g. rare heart disease). Certain conditions could justifiably fall under the 'Grouping' of more than one ERN, thus a comprehensive mapping of which Network is focusing on which conditions is important.

It is important to emphasise that ERNs do not exist solely for rare diseases. They also unite providers of highly specialised healthcare including centres providing specialised procedures and surgeries which, whilst not necessarily associated with a single pathology, require a concentration of expertise and patients and will never be suitable for routine deployment in a large number of centres. Examples include specialised urogenital surgery (as advanced in the eUROGEN Network, for instance; paediatric transplantation (as is the focus of the EuroTransplantChild Network); and techniques such as proton beam therapy.

Many ERNs have carefully mapped the specific expertise of HCPs within their networks, making such information publically available via their own websites (see right, an example from the ENDO-ERN website, illustrating the sub-domains of 'rare endocrine diseases' in which each member centre (here labelled as RC, Reference Centres) possesses the requisite expertise (https://endo-ern.eu/about/reference-centres/)



Distribution of Reference Centres by country

Participating Reference Centres (RCs)

Showing 71 RCs

RC Name	Country	City	Member of MTGs
Cliniques universitaires de Bruxelles – Hôpital Erasme	Belgium	Brussel	1 2 5 6 7 8
Cliniques universitaires Saint-Luc	Belgium	Brussel	1 3 4 5 6 7 8
UZ Brussels	Belgium	Brussel	6 7
Ghent University Hospital	Belgium	Ghent	7
UZ Leuven	Belgium	Leuven	3
Centre Hospitalier Universitaire de Liège	Belgium	Liege	4 6
USHATE "ACAD IVAN Penchev"	Bulgaria	Sofia	4 6
MHAT "Sveta Marina"	Bulgaria	Varna	3 7

A related -and also very powerful- activity is the development of consensus **disease or disease-area specific criteria** for the conditions under the heading of each ERN. Such 'vertical' criteria in fact constitute a robust pan-European attempt to define what truly constitutes expertise in, for instance, inherited metabolic diseases or rare eye disease etc. These criteria specify patient numbers, necessary equipment/procedural skills, and the medical, multidisciplinary and paramedical expertise that should somehow be accessible by any HCP claiming expertise in each domain. As such, they hold major potential for countries perhaps seeking to determine disease-related criteria to supplement the cross-cutting EUCERD criteria of 2011 on Centres of Expertise for RD. These 'ERN network specific criteria' are available to download here.

ERN Operations in 2019

ERNs are now functioning individually, most notably perhaps in building up their numbers of cross-border referrals (see below). However, they are also initiating inter-ERN activity (around registration of patients, for instance) and indeed are cooperating at a strategic level via Working Groups overseen by the ERN Coordinators' Group.

'Data travelling, rather than patients'

A key pillar upon which the ERN concept is based is the mantra that wherever possible, *data* should travel, rather than patients themselves. In reality, this meant the creation of a robust, secure platform to exchange data between HCPs based in different EU MS/EEA countries. The European Commission supported the provision of a suitable platform, which is today known as the CPMS (Clinical Patient Management System). **The CPMS itself offers significant potential to reduce inequalities in accessing healthcare, in terms of, for instance:**

- opening up access to expert second opinions
- seeking guidance on the best route to diagnosis
- advice on suitability of patients for specialised treatments including cutting-edge procedures and specialised surgery
- once panels are closed, if patients provided consent, their details can be retained in the CPMS (in a pseudonymised form) and the cases become searchable, for instance for educational purposes. Medical researchers can request access to data for research purposes

The route by which patient cases enter the CPMS seems somewhat varied. Clinicians from centres which are *not* members of the ERNs can be granted 'guest status' to give temporary access to the System to refer complex cases. The pathways for this seem to lack some clarity (e.g. it is not clear whether such patients must first be referred to an HCP in the same country, before calling upon the expertise of the ERN). Each ERN has experts granted particular types of user profiles, who perform a triage of sorts, in order to filter out cases which can be addressed without the need of a multi-expert and perhaps multidisciplinary panel. These experts then set-up panels and contact panellists for the cases which will go forwards (this person may be the coordinator or a dispatcher). Once the panel has been concluded, the patient will receive findings, recommendations and a treatment plan.

CPMS in numbers:

- **As of May 2019, 1268 active users are registered in the CPMS** (an 'active user' is an individual who has logged in at least once);
- **623 panels have been opened at some stage**
- **245 panels have been closed and archived.**

Ultimately, of course, any recommendation by an ERN expert panel that a patient should receive a particular treatment/procedure/medicinal product which is not usually available in their own country **does not automatically incur preferential consideration** for that patient to actually *access* said treatment/procedure/medicinal product: access remains subject to Regulation (EC) No 883/2004 on the coordination of national social security systems and to the Cross-Border Healthcare Directive 2011/24/EU.

Expansion of the ERNs and Integration into Health Systems

An important topic of direct relevance to the success of the ERNs is how best to integrate ERNs to national health systems. A key assumption of the ERN concept was that not every centre with expertise in a rare disease or a highly specialised procedure should be enrolled as a full member in an ERN; instead, the vision was to embrace a 'hub and spoke' model in which, perhaps, out of a dozen centres in any given country with expertise in a broad group of conditions, only one or two would actually become full members of that Network. Those centres would act as the national 'entry' points to each ERN, allowing a two-way exchange of knowledge, expertise, and -where necessary- patient cases.

Some countries found it challenging to choose such centres from amongst a relatively large pool. Other countries faced the opposite challenge: it was always acknowledged that smaller countries would struggle to find standalone centres of expertise able to meet the expert criteria necessary to join each of the 24 ERNs. In some cases, it would be possible to *build* capacity to allow centres to reach that requisite level of expertise, over time. For others, however, the size of the country alone would preclude this. Nonetheless, for ERNs to realise their potential, it is essential for all European MS/EEA countries to be connected to the Networks in some meaningful way. For this reason, the concept of 'affiliated' partners was born. There are three such categories, defined in the Legal Acts:

- Associated National Centres
- Coordination Hubs
- Collaborative National Centres

In 2019, MS indicated the number of 'affiliated' partners they wish to join the ERNs.

A second call for full member HCPs is anticipated in 2019. **Thus the current picture, in terms of membership and 'affiliation' to ERNs, is set to change rather dramatically.**

Nonetheless, increasing the **number** of member HCPs and implementing the system of 'affiliated' centres will not automatically equal full integration to the national systems. **It is crucial to determine how ERNs intersect with -and indeed optimise- existing national pathways for patients with a rare condition/patients requiring highly specialised expertise**; for instance, how do patients with complex cases requiring a CPMS review actually obtain this service? To which centres in the national territory should they first be referred? How do less specialised doctors/professionals/citizens know what types of rare disease expertise exist in-country and where this expertise can be found (and once this awareness exists, how can more direct pathways be created to guide patient 'journeys' from primary or secondary care?)

In recent months, various groups of stakeholders have sought to address this fundamental challenge.

- The BoMS of ERNs has a Working Group on this subject, which recently produced a '**Statement on the Integration of the European Reference Networks to the healthcare systems of Member States.'** This document was adopted by the full Board in its June 2019 meeting. It provides guidance around 5 topics: national rare disease plans/strategies and legal framework for ERN integration; patient care pathways; referral systems to the ERNs; support by Member States to ERN Coordinators, full members and affiliated partners; and information on ERNs provided at Member States level. It is accompanied by an Annex which proposes practical steps to drive forward improvements in each of those 5 areas; for instance, excellent proposals appear under the first area of national plans/strategies for RD, such as:

- ‘Include ERN Coordinators and/or ERN Members/ Affiliated Partners into policy-making bodies or realise another way to involve their expertise into policy-making’; and
- [create] ‘Clear and if necessary legally defined procedures for the identification and designation of national Centers of Expertise’.

- In November 2018, EURORDIS (Rare Diseases Europe) issued a set of ***Recommendations on the Integration of ERNs into National Health Systems*** https://www.eurordis.org/publication/eurordis-recommendations-integration-european-reference-networks-national-health-systems-0

An essential group of actors in the ‘Integration’ debate are the managers of the hundreds of hospital units and centres of expertise currently directly involved in the ERNs. As Andrzej Rys recently explained “Hospital managers are a cornerstone of the whole ERN system. Only through their active support, particularly in terms of human resource management, will the specialists be able to dedicate part of their working time to the ERNs, either as a coordinator or as a member.”

Given the specificities of rare diseases and the challenges acknowledged at European level, it is perhaps important to think of several forms of ‘integration’:

- Integrating ERNs to the National Health systems, as above;
- Promoting the provision of **Integrated**, multidisciplinary care via the HCPs (CEs) and ‘affiliated’ centres of which ERNs are composed. Integrated care is first and foremost concerned with reducing fragmentation in care and creating more seamless patient journeys, coordinating care with all necessary medical specialists, with the patient at the centre.
- For rare diseases, however, it has been acknowledged that ‘multidisciplinary’ care often needs to involve actors from disciplines *outside* of the traditional medical sphere: the consensus EUCERD recommendations on what comnstitues a Centre of Expertise for rare diseases emphasize the need to also **coordinate** care with **paramedical and social actors**, for instance (see further the Rare2030 Knowledge Base Summary ’Integrated, social, and holistic care for rare diseases’).

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eHealth

The topic of **eHealth** was incorporated to the 2008 **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]** in some detail, as follows:

“eHealth can contribute in a number of different ways to this area [i.e. rare diseases], in particular through:

- Electronic online-services developed by Orphanet and by other EU funded projects, are a clear demonstration of how Information and Communication Technology (ICT) can contribute to putting patients in contact with other patients and developing patient communities, to sharing databases between research groups, to collecting data for clinical research, to

registering patients willing to participate in clinical research, and to submitting cases to experts which improve the quality of diagnoses and treatment;

- Telemedicine, the provision of healthcare services at a distance through ICT, is another useful tool. It can, for instance, enable to bring highly specialised expertise on rare diseases to ordinary clinics and practices, such as a second opinion from a centre of excellence
- Research funded under FP7 in the area of computer assisted modelling of physiological and pathological processes is a promising approach to help understanding better the underlying factors of rare diseases, predicting outcomes and possibly finding new treatment solutions."

In the decade since the adoption of the Commission Communication and Council Recommendation, ICT solutions have impacted significantly on the rare diseases field, most prominently perhaps through the aforementioned Clinical Patient Management System or CPMS. Countries continue to move to eHealth solutions, in favour of paper-based systems. Telemedicine tools to enable virtual consultations at a distance hold major potential, particularly for countries where patient populations are scattered and people live very far away from an appropriate centre of expertise.

An important body in the history of eHealth in Europe was the eHealth Network (eHN), established via Article 14 of the Cross-Border Healthcare Directive. The eHN oversaw the creation and evolution of a number of eHealth Digital Service Infrastructures or eHealth DSIs. This work has been funded within the framework of the Digital Europe Programme and can, in some sense, be considered to stem from (or at least was largely driven by) the epSOS initiative. Ending in 2014, epSOS ("Smart Open Services for European Patients") was a European large-scale pilot testing the cross-border sharing of

a) a patient's most important health data summary, intended for use in an unplanned (e.g. emergency) care situation when travelling or working abroad; and
b) b) an electronic prescription (ePrescription).

In the years since the epSOS project ended, multiple initiatives have sought to move forwards with the maturation and deployment of these two eHealth 'tools'. Whereas the ERNs are primarily concerned with ***planned*** cross-border care, the ePatient Summary and the ePrescription tool are designed for use in ***emergency*** care settings. A small TaskForce initiated under the EU Joint Actions for Rare Diseases has undertaken initial work with eHealth initiatives to highlight the need to consider rare disease patient needs in these two Digital Service Infrastructures.

In 2018 the *Commission Communication on enabling the digital transformation of health and care in the Digital Single Market; empowering citizens and building a healthier society* set out the Commission strategy to transform healthcare under the Digital Single Market. Specific proposals were geared around 3 areas, which may also be relevant to the issue of accessing healthcare :

1. **Citizens' secure access to their health data, also across borders**- enabling citizens to access their health data across the EU;
2. **Personalised medicine through shared European data infrastructure** - allowing researchers and other professionals to pool resources (data, expertise, computing processing and storage capacities) across the EU;

3. **Citizen empowerment with digital tools for user feedback and person-centred care** - using digital tools to empower people to look after their health, stimulate prevention and enable feedback and interaction between users and healthcare providers.

2019 Report on the Cross-Border Healthcare Directive

Directive 2011/24/EU, the oft-named Cross-Border Healthcare Directive, has initiated numerous activities across Europe of relevance to rare diseases and specialised healthcare. However, a recent report from the European Court of Auditors concluded that there is significant scope for improvement: "EU citizens still don't benefit enough from the ambitious actions set out in the Cross-Border Healthcare Directive. EU action includes the right to cross-border treatment, facilitating the exchange of patients' health data across borders, and initiatives for rare diseases; but better management is needed to deliver on these ambitions". Amongst the specific recommendations raised are the following (cited here as they are of particular relevance for this topic):

VI. The Commission has overseen the implementation of the Cross-border Healthcare Directive well. It has guided the National Contact Points towards providing better information on cross-border healthcare, but there remains some scope for improvement.

VII. At the time of our audit, no exchanges of patients' data between Member States had taken place and no benefits to cross-border patients from these exchanges could be demonstrated. The Commission did not establish an implementation plan with timelines for its new eHealth strategy and did not estimate the volumes of potential users before deploying the cross-border health data exchanges.

VIII. The concept of European Reference Networks for rare disease is widely supported by EU stakeholders (patients' organisations, doctors and healthcare providers). However, the Commission has not provided a clear vision for their future financing and how to develop and integrate them into national healthcare systems.

IX. Based on our conclusions, we make recommendations focusing on the Commission's support for National Contact Points, the deployment of cross border exchanges of health data, and EU's action in the field of rare diseases."

Clinical Practice Guidelines and Clinical Decision Support Tools

Amongst the most powerful tools to generate and disseminate knowledge in the clinical and research settings are up-to-date clinical practice guidelines or clinical decision support tools (CDSTs, a broad term encompassing many types of guidance), which may be generated for a range of purposes, such as clinical diagnosis, management and treatment. High quality treatment pathways and clinical guidelines, as well as the presence of a core multidisciplinary team, are important prerequisites for improved clinical outcomes and ultimately survival and improved quality of life of patients living with a rare disease or rare cancer. Often a large number of clinical guidelines exist, but the implementation of and adherence to these evidence-based clinical guidelines is limited (in some cases, less than 40% of patient care is provided according to existing evidenced-based guidelines).

Clinical practice guidelines/CDSTs serve as a great equaliser in the RD field: they can mean the difference between no care/substandard care and patients living longer, healthier lives with fewer complications. Guidelines, whether designed to support diagnosis or care, can serve as a blueprint of

excellence, to advise doctors closer to the patients on how to treat them in a way that reflects the best possible knowledge and will generate the best possible outcomes.

There is no specific section in the **Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02** dedicated to CPGs/CDSTs; however, SECTION VI. 'GATHERING THE EXPERTISE ON RARE DISEASES AT EUROPEAN LEVEL' asked Member States to:

"**Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support: (a) the sharing of best practices on diagnostic tools and medical care** as well as education and social care in the field of rare diseases; … (d) the development of European **guidelines** on diagnostic tests or population screening, while respecting national decisions and competences"

Why do guidelines for rare diseases and highly specialised procedures require a particular approach?

CPGs are traditionally generated in accordance with robust methodological approaches and are based upon a rich body of evidence (the pinnacle of which is usually assumed to be randomised controlled trials). Methodological approaches such as GRADE work well when there is strong data and evidence; however, such instruments typically require substantial adaptation for the rare disease field, where the published evidence is limited (generally speaking, the lower the prevalence of a rare disease, the lower the volume of published evidence). In such cases, alternative methodologies become very important and help to provide assurance for the development of Clinical Decision Support Tools, such as expert opinions and consensus statements.

The European Commission has invested in the topic of CPGs for rare diseases in a variety of ways:

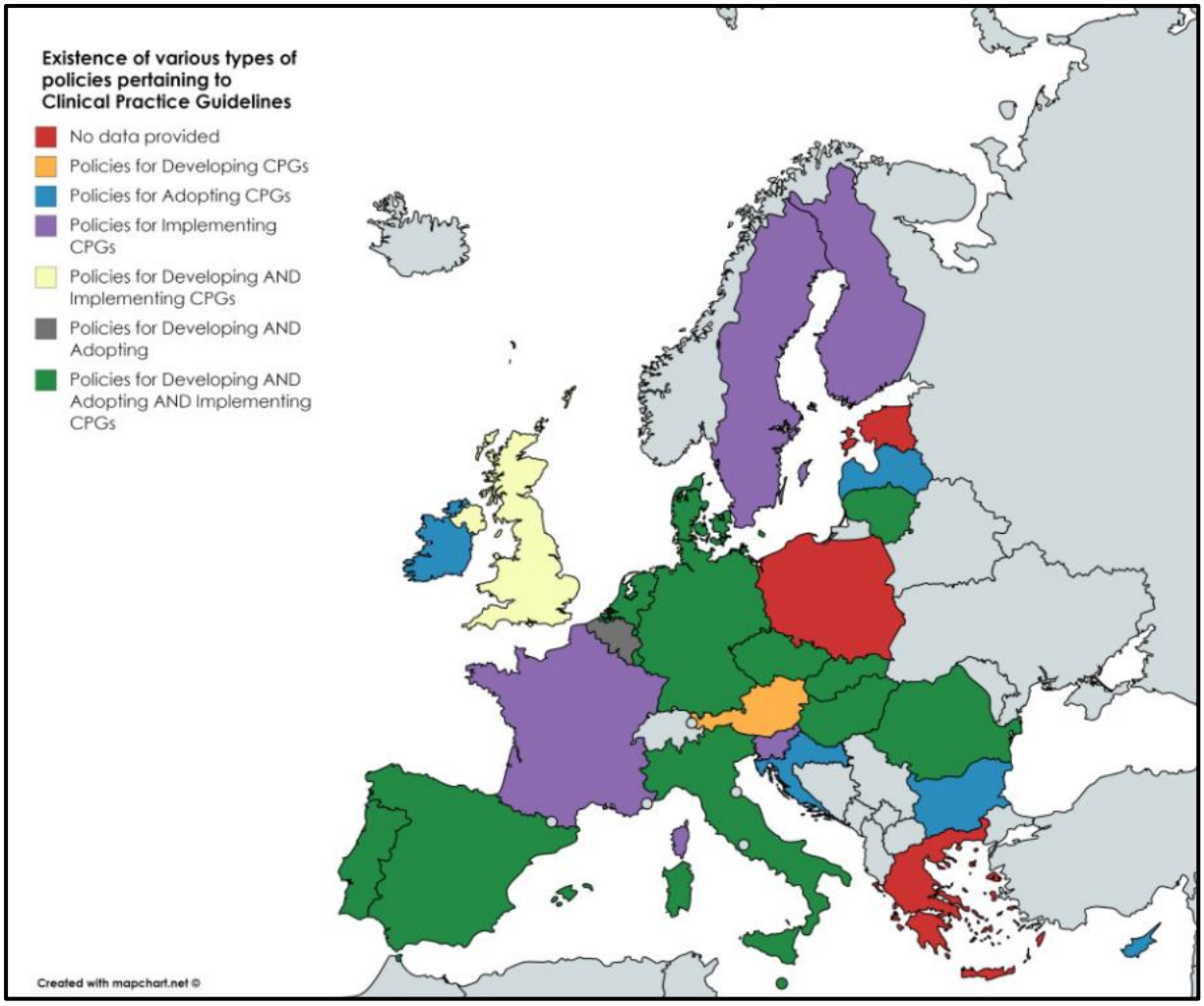
1. The **RareBestPractices project**: this was an FP7 initiative, which developed a platform to collect and exchange information on best practices for the management of rare diseases. Major outputs included the RareGUIDELINE and RareGAP databases
2. **Orphanet** established a procedure for the selection, quality evaluation and dissemination of CPGs, with the aim of providing easy access to relevant, accurate and specific recommendations for the management of RD. Orphanet also produces and disseminates Emergency Guidelines
3. Numerous disease-specific or disease-oriented projects and 'pilot' Networks were funded by DG SANTE in the 2nd and 3rd public health programmes with a focus on developing new CPGs/CDSTs (see for instance the summaries in ***Rare Diseases 2008-2016: EU funded actions paving the way to the European Reference Networks***)

Historically, even where guidance *has* been generated for particular rare diseases/highly specialised procedures, countries have opted to implement this differently across Europe (indeed even within single countries). It has long been recognised that it would be useful to have a better understanding of national policies (where existing) for generating and ***using*** CPGs for rare diseases. To this end, the Data Contributing Committees providing information at the national level for the resource on the State of the Art of RD Activities in Europe, are asked to provide some data on this subject: countries are asked the following question: Has your country produced any CPGs for rare diseases at the national level?
Of 24 MS which responded, 18 stated that they have (although it is likely that this question requires more concrete definitions).

In accordance with the wording of the *EUCERD Recommendations on Core Indicators for Rare Disease National Plans /Strategies*, countries are also asked if they a national policy in place for…

- Developing;
- Adapting;
- Implementing;…

... Clinical Practice Guidelines. The status quo as of May 2019 appears quite heterogeneous, as shown below (please note that a few countries have yet to update their data)



The EC ERN Delegated Decision, Annex 1, point 4(c) states that Networks "shall (…) develop and implement clinical guidelines and cross-border patient pathways" while Annex II, point 1(e)(iv) states that the healthcare providers applying to become members of the Networks "must (…) develop and use clinical guidelines and pathways in their area of expertise". **ERNs are well-placed to add value to the status quo** around generating, appraising, disseminating and -hopefully- using CPGs. If this potential is to be realised, countries will need assurance that guidelines emerging from the ERNs are of sufficient quality and methodological rigour for implementation at national level.

A Tender will be awarded in 2019, to support all 24 ERNs in generating and appraising CPGs/CDSTs, using common methodological procedures as far as possible.

Results of the literature review

The development of services and care dedicated to the treatment and acknowledgement of rare diseases within healthcare systems is not the only hurdle which needs to be overcome to adequately address the challenges that represent rare diseases in this field. Indeed, besides the common d**evelopment of research, clinical and care innovations**, it is necessary to assess and ensure the **accessibility and equity of these services**.
Unfortunately, the literature shows that patients and their caregivers face **many difficulties navigating healthcare pathways**. Many patients have to **wait for long periods of time before being provided specialised care suited to their condition** and are sent from one service to the other, what has been coined a **"diagnostic quest"** (Castro et al. 2017, Merker et al. 2018). They experience a fragmented infrastructure with very little guidance and suffer from the l**ack of communication and coordination between health, social and local services** (Castro et al. 2017). A **geographical barrier** is also often mentioned with the obligation for patients to travel long distances which might incur **significant costs** and act as a practical brake on the provision of specialised care (Fayet et al. 2018, Merker et al. 2018).

However, some trends offering solutions to these issues are currently observable. First, various types of **networking structures**, in Europe and elsewhere, are being designed and implemented in order to better **orient patients and improve the accessibility of existing services** (Castro et al. 2017; Fayet et al. 2018). For instance, in China, attention is paid to the development of a network of hospitals linking local, regional and national services and hospitals and fostering collaboration (Ren and Wang 2019; Soon et al. 2014); networking is also used as a means to improve access to rare cancer care (Frezza et al. 2019); some researchers positively assess the existence of non-profit foundation-sponsored clinic networks contributing to the deployment of specialised care (Merker et al. 2018); and in **Europe, the European Reference Networks have recently been set up.** These networks have been created to specifically resolve access inequalities (Wijnen et al. 2017) and **aim to implement a multidisciplinary approach** as a way to provide the most complete and holistic care possible. One trend observed with the establishment of this framework is therefore a move to establish a **European status for patients and hence a fundamental change in the vision and provision of healthcare services at the European level** (Ferrelli et al. 2017).

Another way to respond to the specific needs of the rare disease community is the implementation of **means to disseminate expertise and knowledge across long distance**s. As such, European Reference Networks are creating a '**levelling-up' phenomenon of expertise with health professionals benefiting from the experience of their European colleagues**. Technological tools enabling remote care, such as telemedicine solutions, are also used (Merker et al. 2018). Many papers also emphasise the importance of **guidelines as a means to disseminate knowledge and consequently improve the accessibility of expert care and treatment** (Pai et al. 2019; Pavan et al. 2017; Fayet et al. 2018; Wijnen et al. 2017), as well as the need to consolidate health professionals' education on rare diseases (Fayet et al. 2018; Ramalle-Gomara et al. 2014).

Another aspect of the '**inequality in access'** debate **concerns the case of members of ethnically diverse communities who are not referenced within genomic and phenotypic databases, such as certain indigenous peoples** (Baynam 2017).

The **global effort towards universal health coverage is also very influential**. The emphasis on equity, quality, responsiveness, efficiency, and resilience should very likely contribute to a better inclusion of

rare diseases in national health policy planning at the global level and hence improve accessibility levels (cf. UHC2030).
Finally, an additional trend is linked to the **economic environment and reduced health expenditure** which might very likely impact negatively on the rare disease field and on accessibility prospects for patients (Ferrelli et al. 2017). Hence, the literature review reveals the **need to re-evaluate the concept of fairness underlining the sharing of the health budget.** Rather than assessing budget allocation decisions according to purely economic considerations (most notably cost-effectiveness, priority to the worst-off and financial risk protection), one could pay more attention to **population social values and assess decisions via a citizen's perspective** (Richardson and Chandler 2019; Norheim 2016).

***Possible* trends emerging from the Literature Review:**

- Revisiting concept of fairness
- Universal Health Coverage
    - Equality of access to health
        - Genetic approach vs phenotypic approach
- Challenges and solutions for healthcare pathways
- Networking capacity building
- Information and knowledge generation (informing best practices and care organisation)
    - Guidelines
    - Orphanet
    - Remote care
    - Sharing of European expertise
- Transferring European approach to other world regions
- Multi-stakeholder governance

***Possible* drivers of change emerging from the Literature Review:**

- ICT innovations
- European funding of health networks
- European policy in cross-border care / European Union
- Patient advocacy
- Social values

References from the rare disease literature review

Full list of articles/publications found in the literature review:
https://docs.google.com/spreadsheets/d/1SRXASsFiD9sdQz286SVo860XdTpGaOIncyjIhGphULI/edit#gid=364400914

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