Rare2030

Foresight in Rare Disease Policy

A knowledge-base summary:

BASIC, CLINICAL, TRANSLATIONAL AND SOCIAL RESEARCH FOR RARE DISEASES

https://www.rare2030.eu/our-work

1. 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 Orphan Medical Products 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.

There 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:

- 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.
- 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.
- Foster the participation of national researchers in research projects on rare diseases funded at all appropriate levels, including the Community level.

- Include in their plans or strategies provisions aimed at fostering research in the field of rare diseases.
- 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."

2. THE INTERNATIONAL RARE DISEASE RESEARCH CONSORTIUM (IRDIRC)

Established in 2011, and designed to unite researchers with research funders, IRDiRC - https://irdirc.org/ - initially had two major goals: to create 200 new therapies for rare diseases and enable diagnostics for most rare disease, both by 2020. However, given the early success in meeting these goals the consortium revised its objectives 2017 during the 3rd IRDiRC conference which took place in Paris in February 2017.

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 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
- Chrysalis Project
- Clinical Research Networks for Rare Diseases
- Data Mining and Repurposing
- Identification of barriers to patient participation in RD research and recommendations to remove them
- Indigenous Population
- Integrating New Technologies for the Diagnosis of Rare Disease
- International Consortium of Human Phenotype Terminologies
- Matchmaker Exchange

- Model Consent Clauses for Rare Disease Research
- Orphan Drug Development Guidebook
- Patient Centred Outcome Measures
- Privacy-Preserving Record Linkage
- Shared Molecular Etiologies
- Small Population Clinical Trials
- Solving the Unsolved
- RD Treatment Access Working Group

3. EUROPEAN JOINT PROGRAMME FOR RARE DISEASE RESEARCH

The European Rare Disease research field is currently in the first year of a European Joint Programme for Rare Diseases. 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).

35 countries are currently participating in total, from 26 EU Members States, 7 Associated Countries, as well as Canada and the UK.

Part of the EJP RD 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 the last seven years, 56.4 Million Euros were invested to fund 79 research projects involving 347 research teams (NB figures are from May 2019 and will be updated in time)

The main goal of the EJP RD is to build and expand the grounds of the rare disease research ecosystem by:

- Improving 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;

- Implementing and further developing 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 a central coordination, strategic and transversal activities, together with 4 interconnected pillars:

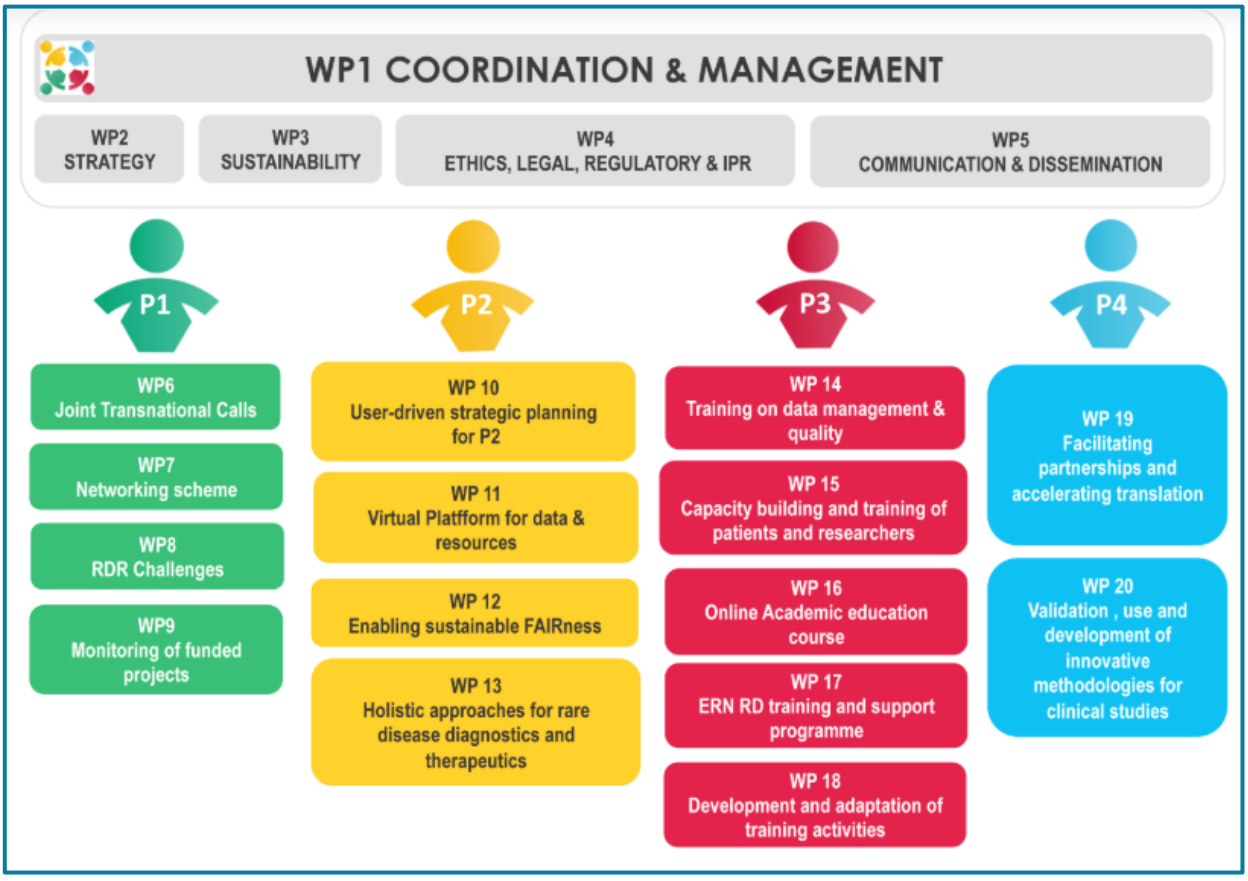


Image from EJP-RD website

4. BUILDING A BETTER DATA ECOSYSTEM FOR RARE DISEASE RESEARCH

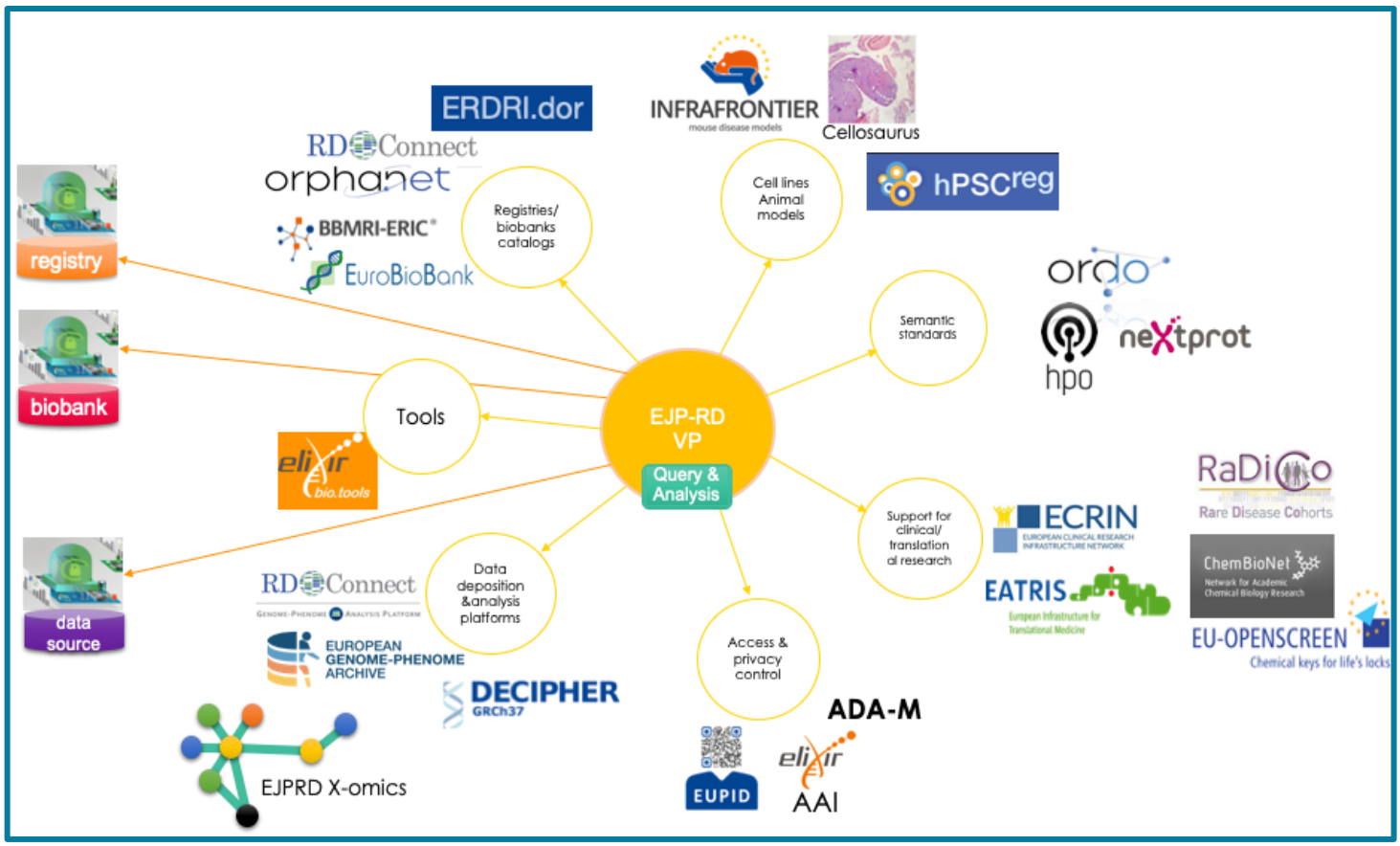
In recent years, rare disease research has increasingly emphasised the importance of linking and somehow sharing or federating precious data relating to rare disease patients, which traditionally is fragmented and siloed. RD-Connect, for instance, initiated several major drives to increase the usability 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 RD 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:



5. 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:

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

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

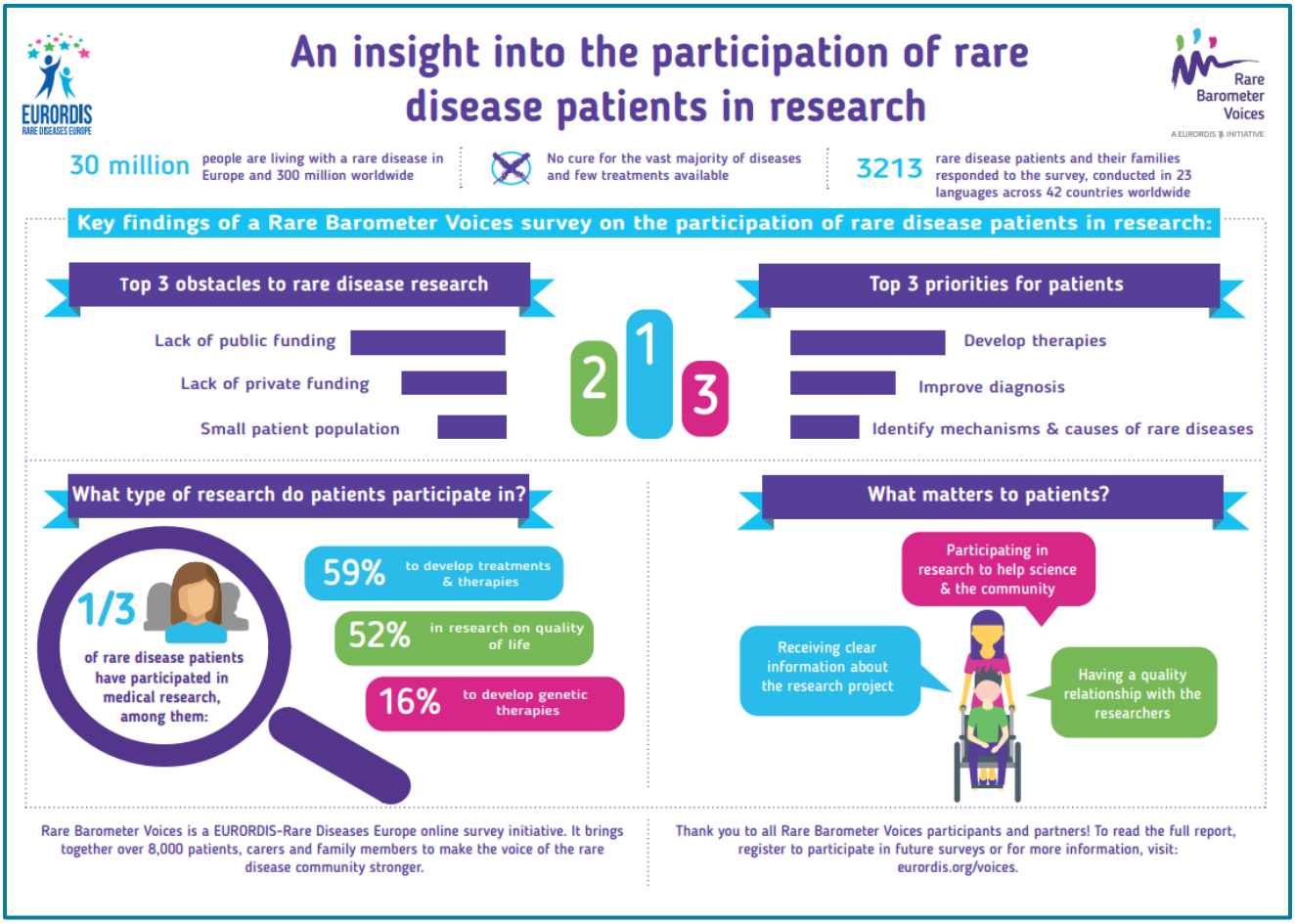
- Patients' representatives involved in EMA scientific committees and working parties
- Protocol assistance
- Scientific Advisory Groups (SAG) at the Committee for Human Medicinal Products
- Other meetings such as discussions on guidelines and risk management programmes

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)

Since the launch of the EJR RD, patients and patient organisations are stipulated as essential partners for joint transnational calls, wherever relevant.

6. 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.

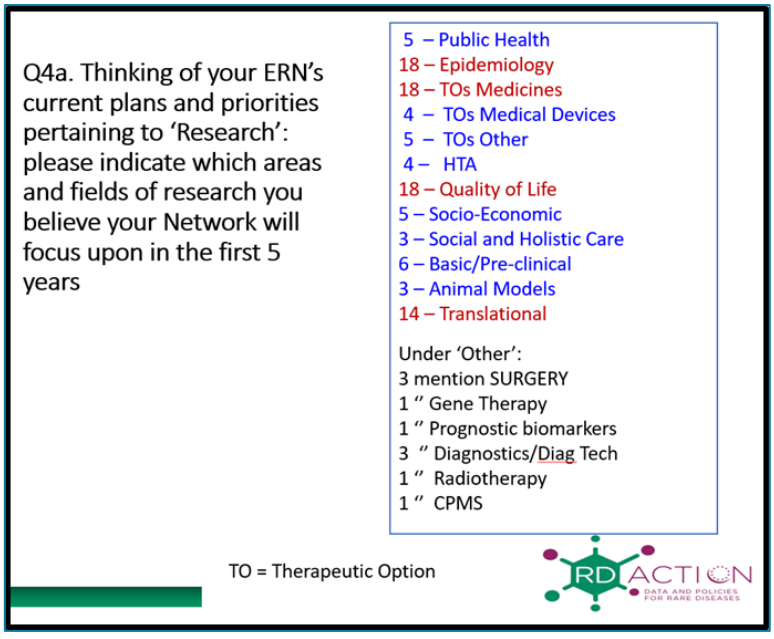
- **Data Generation/Linkage Opportunities:** ERNs provide unprecedented opportunities to collect good quality, relevant, and interoperable data which can be used effectively for a specific purpose at hand (e.g. a clinical consultation through the CPMS, or to elucidate genome-phenome associations through 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.

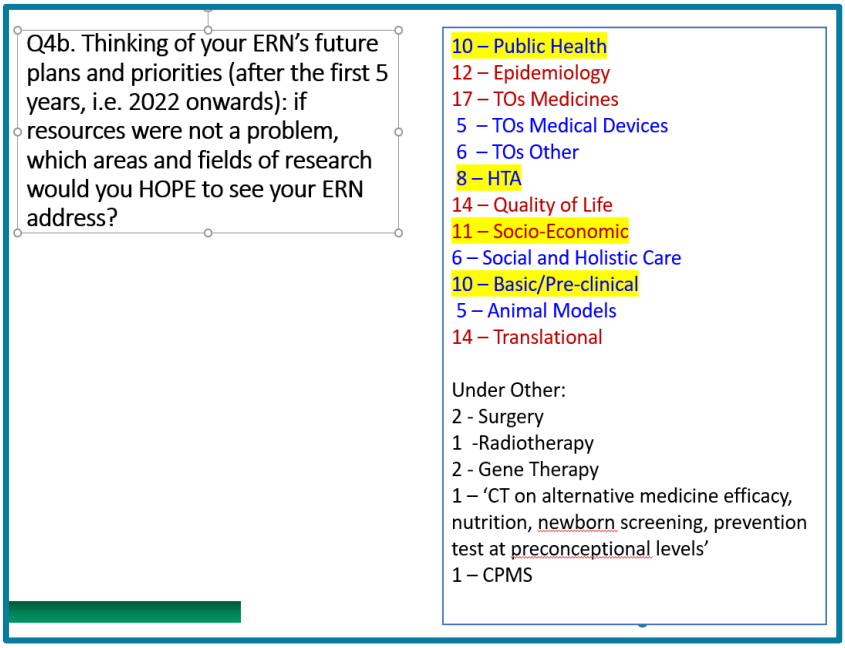
- **Patient Involvement:** Patients sit at the heart of the ERN concept (indeed the concept *emerged* largely from the patient community in Europe). The Addendum to the EUCERD Recommendations stipulated that Patients should have a meaningful role in all levels of ERN activity, governance included. Also, 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).

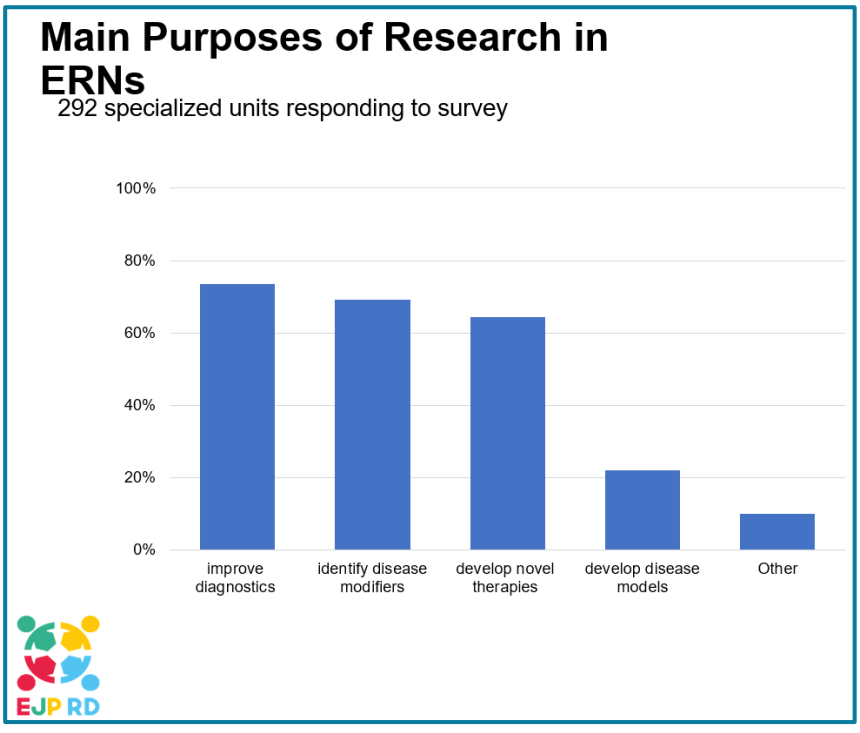


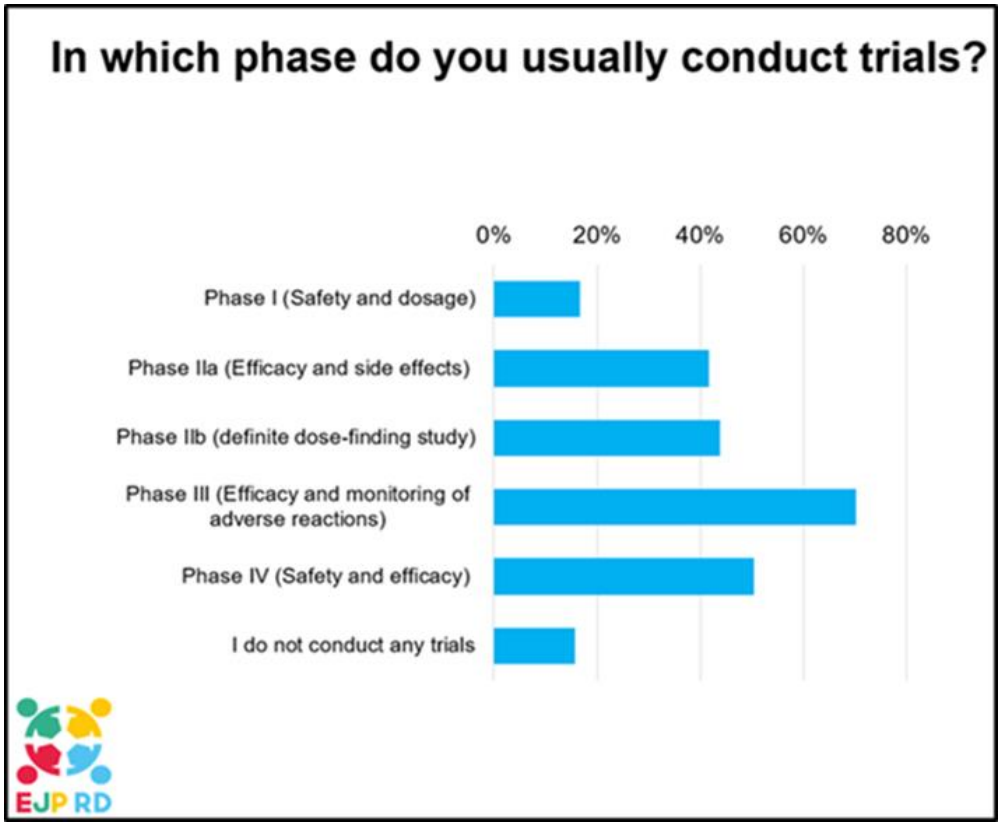
When asked about research priorities beyond 5 years, a number of additional types of research gained popularity (as highlighted in yellow)



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:





7. 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**

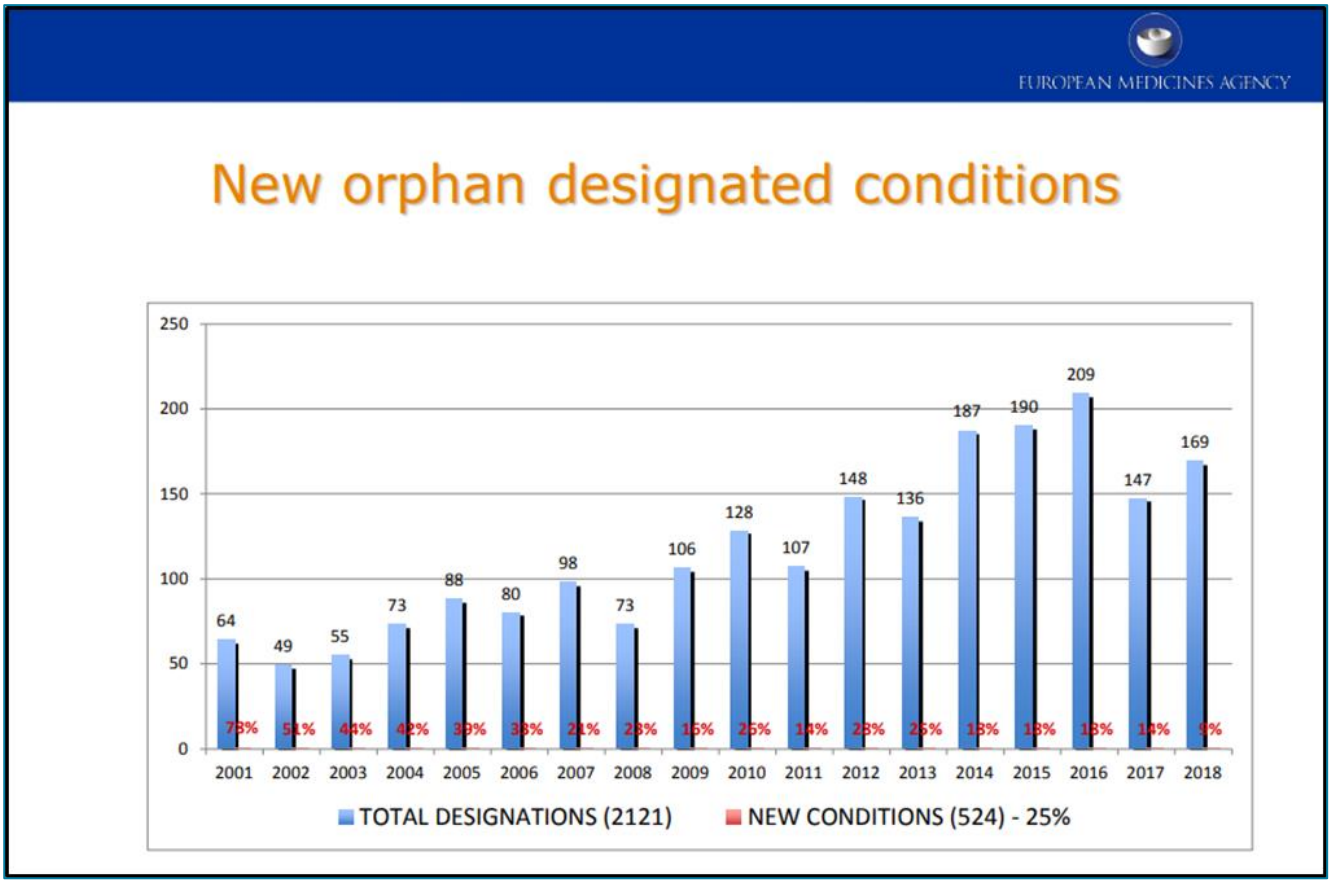
The following table from the EMA (COMP) annual report on OMPs shows the trajectory of orphan designations since 2000:

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

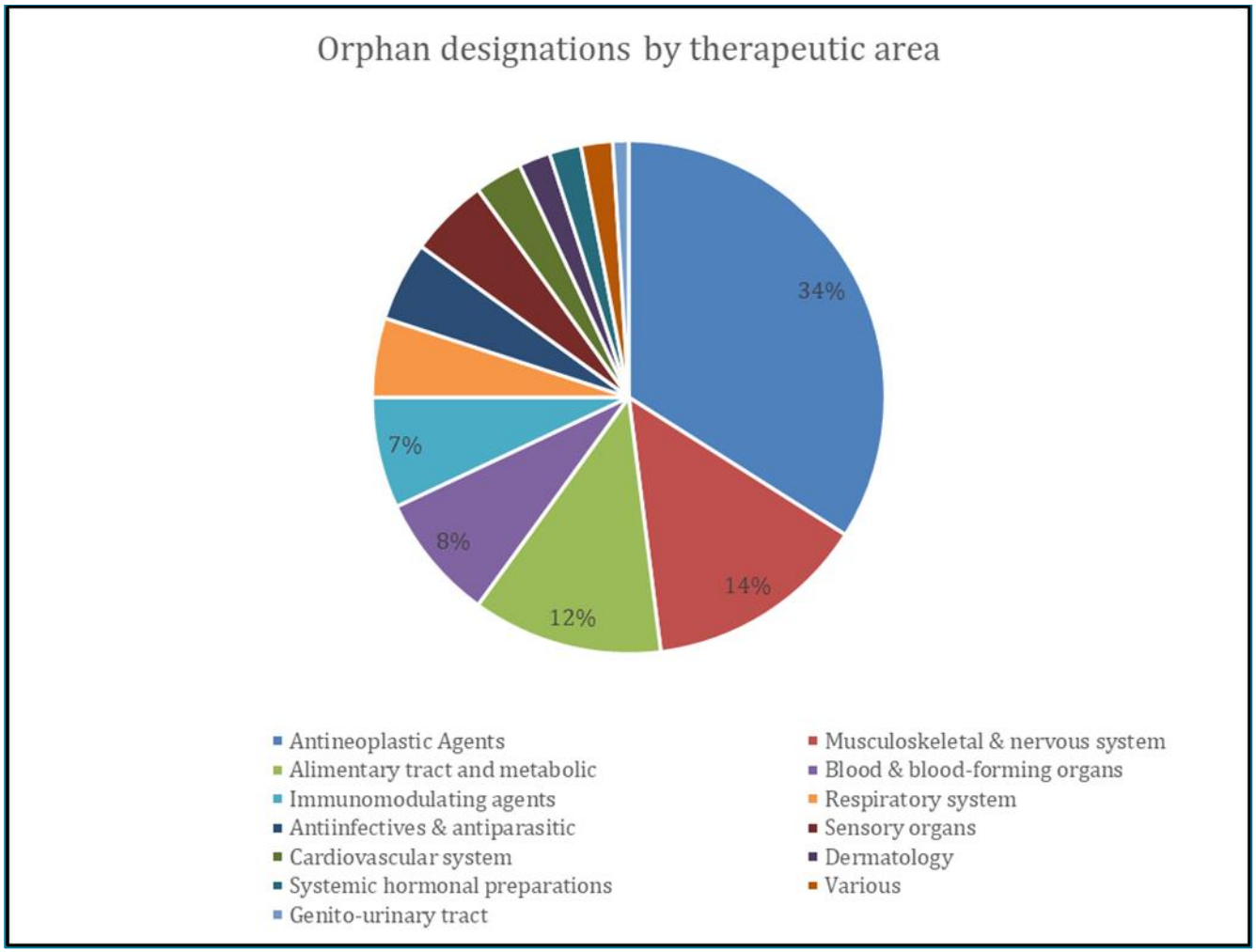
The vast majority of new orphan designations, since 2003, have been for conditions which already have an indication. This table from the EMA (COMP) annual report illustrates the percentages of orphan designations each year awarded to new conditions



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



8. 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.

9. 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.

10. 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".

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.

11. 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. These RIs now participate in the EJR RD and are thus contributing and implementing rare disease specific services as part of the rare disease research ecosystem that the EJP RD is building.

12. RESULTS OF THE LITERATURE REVIEW*

**The earlier sections of this document were elaborated via research, partner expertise, and data stemming from the Resource on the State of the Art of Rare Disease activities in Europe. This final section is a summary of the results of a literature review performed by INSERM Orphanet, and is designed to highlight peer-reviewed publications which may suggest trends in this broad topic.*

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).

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#gid=364400914

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Rare2030

Foresight in Rare Disease Policy

The health of 30 million people living with a rare disease in Europe should not be left to luck or chance. The Rare 2030 foresight study prepares a better future for people living with a rare disease in Europe by gathering the input of a large group of patients, practitioners and key opinion leaders to propose policy recommendations.

Since the adoption of the Council Recommendation on European Action in the field of Rare Diseases in 2009, the European Union has fostered tremendous progress to improve the lives of people living with rare diseases. Rare2030 will guide a reflection on rare disease policy in Europe through the next ten years and beyond.

PARTNERS

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