Rare 2030

D4.2 Report on trends and drivers of change for RD, resulting from stakeholder interviews and workshop

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Report Information	
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Executive summary

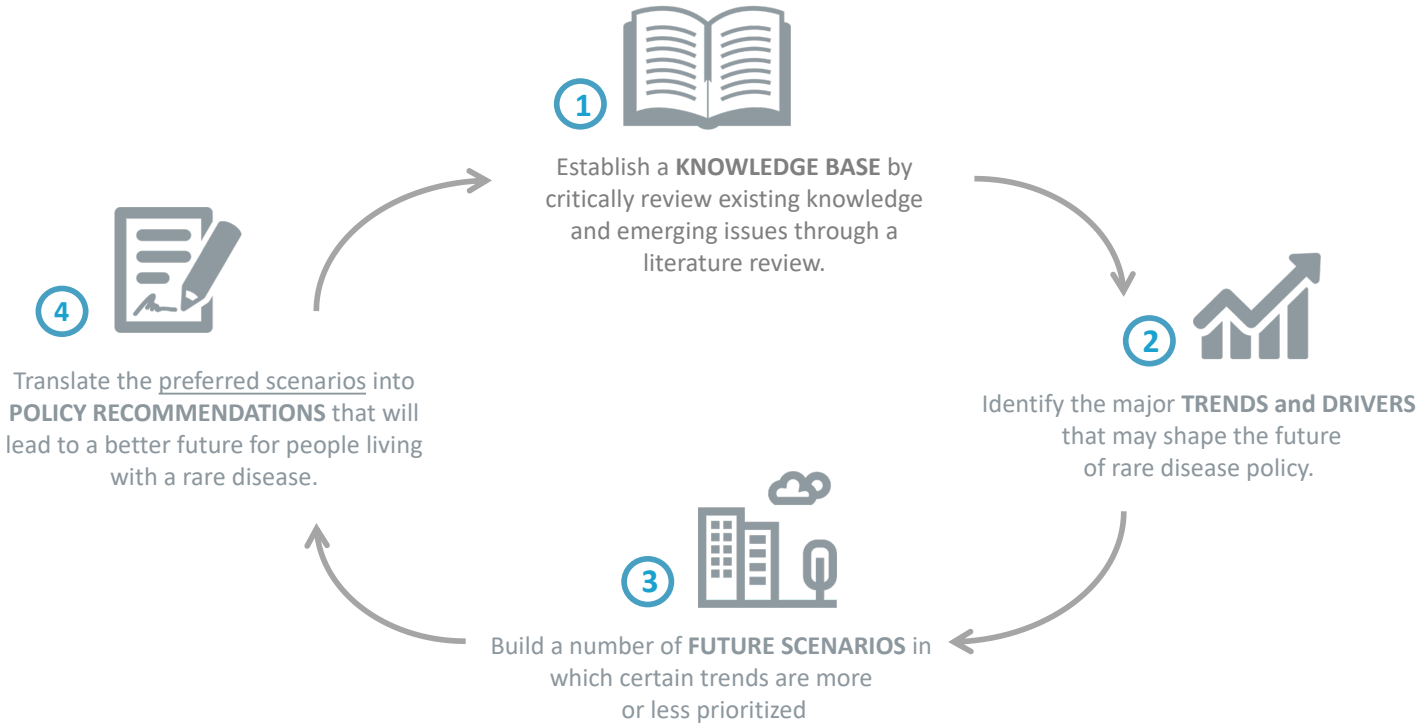
Rare2030 applies foresight methodologies and tools to explore the future policy framework for Rare Diseases (RD). The foresight approach is designed to envisage alternative future scenarios and set out roadmaps for their implementation through changes in policies and strategies, so as to better shape our tomorrow. The scenario building process has the following objectives:

- identify trends and changes that will influence the future EU and national RDs governance, diagnosis, care, treatment and quality of life of people living with a RD (general);
- identify those emerging technologies and social practices that will trigger the need for new regulations, demanding innovative tools and procedures (domain specific);
- inform policies in order to adjust regulations more quickly to social and technological changes;
- set priorities for investments in order to anticipate/adapt regulatory infrastructures and services supply (including human capital) to future needs

The Rare2030 Scenarios are developed according to the 'intuitive logics foresight school'[1], which originated with RAND and is now strongly associated with Shell Oil and the Global Business Network. The overall process is characterized by a highly participatory dimension, involving hundreds of experts and thousands of people living with RDs through surveys, workshops and interviews. While they primarily aim at drawing up policy recommendations at 2030, the Scenarios are developed with a 2040 horizon. This longer-term time frame is essential to envisage paradigmatic changes in terms of policies and behavioural change. The Scenarios are focused on Europe, but local and international trends are considered - particularly to assess how EU level policies can be supportive and integrated into and reflect national legislation and policies.

The Rare 2030 Foresight study includes 4 major steps:

[1] Bradfield R. et all "The origins and evolution of scenario techniques in long range business planning" Futures 37 (2005) 795–812



This report presents the findings of the second step of this process: the so called "Horizon scanning" phase – which is consequential and builds upon the in-depth analysis of the state of art of RD policies published as Rare2030 Knowledge base (D.4.1).

Scenarios are usually built around trends, changes and phenomena likely to strongly affect the future if they come to pass or reach a critical level, but whose realization or evolution remains uncertain at the present time. In order to identify those more relevant for RD future policies and identify strategic issues that need to be addressed, UNEW has organized 18 interactive calls with a large (ca. 186) Panel of Experts in the Rare Disease field. In addition, the project partners have organized a workshop with patients' representatives and conducted 10 interviews with selected experts in different fields and of varied backgrounds of relevance to health, health-care and RDs Governance. This highly participatory process was complemented by a literature review carried out by ISINNOVA on health and health care foresight and scenarios studies.

Much attention during this explorative phase was dedicated to finding the most appropriate granularity between the rare disease specific trends emerging from the experts' strategic conversations, and macro trends reviewed in the health literature. Two hurdles have been met in this activity. On one hand, there is no previous foresight exercise in the rare disease field, thus, the innovative feature of this study has demanded an evaluation anew of those changes that are considered more meaningful for the RD community. On the other hand, there are few foresight studies on health and healthcare taking a European

perspective and in those that do exist, the main focus is often the rise of Non-Communicable Diseases. As a consequence, the trends analyzed are linked with the risk factors exposure which holds little relevance for RD patients (the large majority of which are genetic and for which exposure factors are do not exist, are unknown or poorly understood).

To overcome these hurdles, the RARE2030 team has decided to give priority to the insights offered by the Panel of Experts whose contributions have been crucial for selecting the 12 trends presented in this report – in the first part of each factsheet. Victoria Hedley, UNEW, and Anna Kole, EURORDIS, have been primarily responsible for ensuring a synthesis able to reflect as much as possible the wide range of the inputs received during the Panel of Experts calls.

In line with this, ISINNOVA has researched and analysed foresight studies relevant for the trends selected, extending the search from healthcare to sectoral foresight studies (e.g Big Data or genomics). The findings – presented in the second part of each factsheet – offer a brief synthesis on the current knowledge found in the literature review in relation to the selected trends.

Before embarking on a journey to explore the future, the first section presents which changes have played a key role in shaping our present. Rare2030 has interviewed experts and patients' representatives on what they considered the major changes in the last three decades and what they think we can learn from this.

Looking back to look forward

"Looking back at the past 30-20 years what do you think has been the most important change in the RD diagnosis, treatment and care?" – this question has been asked to three different groups of stakeholders:

- Patients representatives in a face to face workshop, held in Bucharest on the 17th of May 2019;
- Panel of Experts in 10 teleconferences focused on specific RD topics during June-July 2019
- 8 Members of the Research Advisory Board in semi-structured interviews during July-October 2019

The aim of the question was to gain a better understanding of the dynamics of change internal to the RD community along with a clearer view of the gradual trends, having emerged in the past, which are now in full development and should be taken into account in the horizon scanning phase.

The following changes and trends were recurrently mentioned:

- Increased networking capacity, with stronger advocacy, from patient organizations and stronger collaboration among all RD stakeholders
- Improvement in diagnosis and treatment, development of innovative medicines
- Increased awareness of RD

All participants acknowledged the importance of patient self-help groups and the increased capacity of patients in networking and collaboration which has led to better advocacy and raised awareness. Compared with the past, it is recognised that patients, generally, have now a much stronger voice and more opportunities for action. Internet and social media have been repeatedly mentioned as enablers to "break-down the sense of isolation people feel, empower patients and promote policy and actions". The increased availability of technologies had a number of impacts. On one hand, the key importance of enhanced connectivity for reaching-out to patients with the same diseases and "for patients and physicians/researchers to connect" was recognized. By enabling a greater access to information and the creation of support groups, the internet has allowed patients to become more informed about their diseases and has changed the "patient-doctor" relationship. This has accelerated a cultural shift as "patients moved away from just having things done to them, they became less passive patients". As regards this aspect, RD patients have been pioneers of what is now a broader phenomenon of patient empowerment, which is one of the drivers behind the much-needed transformation toward a patient-centred health-care system. In the last decade, technologies have also been increasingly used to share, collect and compare data – and the need to combine a bottom-up approach with the use of common infrastructures and standards which facilitate the cross-comparison and the use on a larger and trans-national scale is increasingly recognized.

On the other hand, technological advances (internet, social media) have enhanced the capacity of networking, improved cooperation, and multiplied training opportunities, leading to greater awareness and political support at national and EU level as "power is in the number". In this respect, the importance of patients advocates, the awareness raising Rare Disease Day and the fact that "the world become smaller due to better internet and social media" were underlined.

As expected, the time to diagnosis and the development of new therapies and drugs are key changes, but RD treatment is also influenced by the opportunity to participate in therapy development and e-health devices. For improvements in diagnosis and treatment, the drivers more often citied were a greater understanding of the disease-causing pathways and mechanisms, and improved screening technologies.

The main actors who triggered these changes were identified as: European Patient Advocacy Groups, European Reference Networks, EURORDIS, European Commission, European Medicines Agency, EUPATI.

European changes were compared with national changes in order to gain a better view of the differences and similarities among countries. Generally, the emergence of patient organisations and alliances (IT, NL, LT, RO) was considered one of the major changes together with the approval of National Plans (FR, IT, LT) and registries for rare diseases (NL, IT) and the recent diffusion of participatory policy making. In the Netherlands, since 2012, patient organizations have been involved in the accreditation of centres of expertise for rare diseases which could be one of the future developments at EU level. Other relevant trends mentioned at national level were:

- National change – 20 years ago Scotland gained more autonomy and greater control over the healthcare budget. This led also to a greater focus for creating specialist pathways for rare disease treatments in HTA
- Use of off-label medicines (Cyprus)
- Start of European treatment Protocols for RD (example from Spain)
- Development of more opportunities to access education and work (examples from Denmark, Greece)
- Development of faster diagnoses for the "new" patients: it formerly would take up to 5 years to achieve diagnosis, while this process has now become much faster (example for Williams Syndrome, Denmark).
- Creation of discussion on holistic care from the different groups of stakeholders
- Systematic availability of good expertise for each RD (example from France)
- Setting personal budgets for care (Examples from Denmark, Netherlands)
- Improvement for Duchenne Muscular Dystrophy (example from SW Sweden)
- Making medical products available e.g. Spinraza 2018
- Improving drugs' availability and assessment: Netherlands has started a funding for rational pharmacotherapy to stimulate more effective, efficient and safer use of existing medicines in day-to-day health care (since 2012) and since 2019 a project for managing patient registries for expensive drugs (2019) in order to better measure the outcomes of treatment with new drugs in practice.

The tables below summarises the changes mentioned by RARE2030 stakeholders – organised in a chronological order and by the Political, Economic, Social and Technological changes

Political	• Patient involvement – there were no patient organisations for our diseases in past days • Increased awareness and recognition of Rare diseases as a concept and public priority • Collaboration at EU level to improve the not-always effective coordination at national level. • Development of National action plans, National strategies on RD (starting with France, 25 EU MS had adopted a plan or strategy by mid 2019) • Adoption of the regulation on Orphan Medicinal Products (Regulation (EC) No 141/2000), which led to more medicines for RD being launched in EU • Human rights agenda, especially the Disability and Equalities Act of 2010 • Foundation of The Global Alliance for Genomics and Health (GA4GH) in 2013 • Reinforcement of Network Governance in EU policy-making • Increased tendency for more general professionals to act as case coordinators in RD • European Reference Networks have formed, pushing further the levels of awareness of RD, solidarity around it, and building stronger advocacy for RD. • Stronger Patient Advocacy: Creation of European Patient Advocacy Groups (ePAGs) in every European Reference Network (ERN) • Increased interaction with European Medicines Agency (EMA), from a research perspective • Anti-EU sentiments "blowback among member states against real or perceived EC overreach" • Increased cross-sectional research, including The European Strategy Forum on Research Infrastructures (ESFRI)	Economic	• Increased economic attractiveness of orphan drugs, due to incentives • More efficient national policies for reimbursement of expenses • Stronger advocacy for affordable medicine • Emergence of Value Based Care and outcome-based healthcare • Patients are becoming innovators (patients are experts in their condition and are inventing things to address specific unmet needs) • A large number of drugs falling under EMA Orphan Medical Product classification which has led to an increase in drug specific registries in rare disease area (last 10 years) • Increased investment in RD research and research infrastructure

Socio-cultura	• Greater awareness of RD, on the part of patients, doctors, policy-makers etc. thanks also to media, and support groups and increased acceptance in society • Mainstream use of the internet and then later the emerging popularity of social media has made it possible to i)to break-down the sense of isolation people feel and) Connect and empower patients and support group ii)Build their capacity and help them develop a new needed skills • Rise of discussion about integrated care and greater societal understanding of the concept of integrated care • Patient empowerment: greater awareness led to more empowerment of patients. In many cases, patients develop an in-depth knowledge on their RD • Tendency to use virtual communication more often by patient organisations to mobilize support, advocacy and awareness (Facebook, Twitter etc.) • Growing importance of civil society – people understand their rights better than ever before • The value of patient-generated data becoming clearer, i.e. Patient Health Data – tendency for patients to develop their own registries, where no suitable alternatives exist • Move toward self-diagnosis of patients • Scientific organisations are becoming more interested to patient involvement and are forming partnerships with them • Greater emphasis on surveys to understand needs and realities for RD patients to drive research • Greater recognition of undiagnosed patients • More young researchers changing their career paths due to perceived challenges and lack of opportunities in RD research field • Rise of discussion about integrated care and greater societal understanding of the concept of integrated care	Technological	• Development of treatment possibilities for RD – without treatments, many clinicians in the past were not interested in the conditions. • Technology advances: first telehealth solutions for home therapy (mainly through mobile phones) • Medical breakthrough: development of gene therapy, next generation gene sequencing, Increased international matchmarking (genomic discovery through the exchange of phenotypic & genomic profiles) yet in disconnected projects • Decreasing costs of genetic testing and genomic sequencing, including Direct to Consumer genetic tests • Emergence of precision medicine and precision health • Emergence and larger impact of new technologies in RD research (Artificial Intelligence, gene-therapy, next-generation sequencing) “Treatment Revolution” • Shift towards standardisation and sharing of information also regarding data standards • Grater tooling and resources to help doctors and researchers collect and use coded computable phenotype data • Transition of electronic health records (EHR) adoption, accelerated with beginning of ERN RD registries (2018) • More data collected creating possibility to link it with registries and do comparative analysis for member states • Emergence of medicines for secondary or accompanying conditions • Development in prenatal screening and preconception screening • Greater use of technology, especially of eHealth solutions, which have started to connect doctors and specialists virtually and remotely • Decline in number of products passing from designation to MA • Opportunity for trained patients to participate in therapy development process and to contribute actively e.g. by proposing PROMs (patient-reported outcome measures) • Emergence and growth of transnational medical research and transnational clinical trials

Lessons learnt

Looking back is more than a speculative exercise as the main aim is to identify what has made us change in a positive way and reflect to what extent the change is still on-going or is challenged by new events. Below are four quotes from the Research Advisory Board who recalled for us the lessons learned from the past that should not be forgotten while looking to the future.

"As for successes, I think the very fact that we had the opportunity to increase collaboration throughout Europe and also on the international level has been one of the major drivers of progress. And for rare diseases of course this is one of the key elements to explain why we have come to the kind of understanding of the issues that we have today. And the collaboration on smart ways to enhance development of therapies, diagnostics, et cetera. We also have a new wave of international understanding of where we could actually take our global community through embedding rare diseases into the policymaking around leaving no one behind is actually something which seems to be quite efficient. And of course, we were living in the very difficult and very challenging time. But I think the fact that we can actually see signs of international collaboration and solidarity in the move towards these sustainability goals is something that we should keep in mind and could make us keep up optimism around where we'll be. One thing is having a beautiful vision for people living with RD already around the globe. But we have to admit, that even at a European level, we struggle to make it possible for people in the different Member States to get to the point where public authorities actually take on the responsibility to make diagnosis and treatment available for all and provide support to a level where people at least can have better lives. Just imagine that we would have all around Europe resource centers, like Frambu or Agrenska. We have fine objectives to where we want to go, but at the same time we could end up having more divergence, more difficulties for people to actually obtain what should be available in some Member States". Terkel Andersen - Danmarks Bløderforening, EURORDIS

"I have been involved for 5 years in RD. There have been action plans but, perhaps, there has been too little commitment to put them into practice and maybe too little coherence in the action plans in different countries. This could be improved in the future.
Also, there is not enough pressure from EU level. There are not enough checks on what is written in the action plans. RD is very challenging and can be addressed well if addressed coherently and together at the EU level, what each country does separately it is not enough, more linkage is necessary.
Cross border healthcare should be still improved much, there are reimbursement mechanisms for emergency practice, but nor for treatment. It seems that it might be not so easy to be treated in another country, if it is not an emergency situation. It is matter of luck if you have a treatment for RD and if that clinician is part of ERN. It is about luxury whether you get good treatment or not, especially for patients who are less educated and less informed.
There is a lot of fragmentation between primary and secondary healthcare, even for people with chronic diseases. But what has gone very well in Germany is the establishment of Centres of RD, mostly because hospitals would get more funding if you call yourself "Centre for RD". That is why the number of Centres has increased a lot and this is very positive. We have seen a very positive development of this incentive and I think that is something that we can use in the future. We also have seen increased awareness of RD, that was going very well; because of the activities on the EU level, such RD days and events, awareness has increased, that is something that should continue". Tanja Bratan - Fraunhofer Institute

ERNs were created as a political instrument and the process leading to their creation, as well as their establishment, was a success for RD community.

European Commission Rare Disease Expert Group: It was a really multi-disciplinary, critical but constructive, Expert Group which was able to facilitate dialogue between stakeholders and suggest changes in critical areas (e.g drugs pricing). Then, after the approval of ERNs, all the attention has shifted to their structure and organization and the Expert Group was closed down through a short-sighted decision. The ERNs' Board has a representation of all MS but does not involve representatives or experts from different areas of RD and it is not interdisciplinary. All ERNs consult and involve patients' organizations but this is not organized in a way that is harmonized or systematic.
In addition, the fact that the ERNs are divided by disease opens the doors to a possible competition for funding among diseases areas as patients' representatives would naturally look more for advancement and funding for their own areas. Conversely, the Expert Group looked at the whole of RD". - Kate Bushby - Former EUCERD Joint Action leader and Vice-Chair of the EUCERD

"Some examples of successes were mentioned above; many of them have been put in place because of very dedicated people behind. Often patient organisations are in place. The lesson would be that we cannot develop good practices without patient organisations.
They are not only at the centre of caring for those being affected but they are also at the forefront of thinking of how this can be done, from the very beginning of research efforts until the very end of delivering new treatments to patients. Including elements and suggestions for a new regulatory structure as often what is important for the regulators is not necessarily important for the patients.
I give you an example, I remember a conversation about some novel gene therapies for cystic fibrosis, the risk and benefit being evaluated by regulators. The carers pointed out that getting the preparation time in the morning for a patient to about 10-15 minutes would improve their quality of life dramatically. So how you include these experiences in the regulatory processes, and product development plans becomes essential.
We can learn also from failures, or not very efficient processes. For instance, sometimes RD organisations work separately and focus on one disease only. In order to achieve these structural changes, all RD organisations need to work together. One has to have umbrella organisations that can help centralise the common needs to address the system change. Then the individual organisations can develop the thinking around implementing the change in what makes sense for each particular disease. I do see it as a tension, a lot of work needs to be done".- Ruxandra Draghia-Akli Merck (formerly DG RTD)

"Rare disease profiling and making RD an EU priority has accelerated research and results. Looking 10-15 years back we did not have a strong EURORDIS and RD, at least so visible at WHO level. This has drastically changed. Today the RD community has a very considerate voice that has raised concerns about some of the development that we have seen. This has been extremely helpful.
One success is the reputation gained in the community, which is very different to those who do interest lobbying, and this is not RDI at all. I just received an auditor's report that looked into detail about the structure of EURORDIS and RDI and everyone is very impressed. If only there were more NGOs like this who are committed, reasonable, but at the same time personally engaged. This is helping a lot because you are making a real case that everyone can understand.
The second success the way advances have been used for rare diseases and analysed. And that I don't think we at WHO would have been able to do.
And last but not least in terms of what could we do better, I'm not sure if that within your remit or whether this is from the broader environment, but the focus being on the big issues in the world, like cancers, cardio-vascular diseases, and preventable non-communicable diseases. All that take some of the attention away from RD, but this is beyond your remit. From overall public health perspective, we make huge advancement on health globally to concern toward RD. I would argue that we need to mitigate this risk and create instruments so that the attention can be put on RD. INSERM has been a big partner including other research centres that have of course committed to this". - Ruediger Krech – WHO

"In my opinion the positive lesson from the past is that we have been able to create a great collaborative and multidisciplinary collaborative spirit together with respective patient associations. I do not want to exaggerate but this is really a fantastic momentum, in that patients, researchers and doctors are now working together for a common goal! We all share same values and try to do our best on our "individual fronts". Moreover, we are vanguards for other fields of medicine, in that patients are our genuine partners. They are the experts in their diseases, they show us their real needs, and they taught us to look at care through their prism, i.e. beyond medical textbooks so to speak and utilise patient-reported outcomes, simply what they find most important and relevant! And this is, I would say, the baton which we shall pass to the younger generation, including the strong "collaborative mindset" in our field. In fact, this international collaborative mindset is in my opinion the major success of the rare diseases field compared to many other "competitive" fields of medicine, thus far.

Moreover, I would say let us nurture and expand this momentum by gradual involvement of our colleagues working in other, seemingly unrelated, fields of medicine into our multidisciplinary teams. We also made important inroads into social and palliative care and formed new working partnerships with them. Also improving awareness of rare diseases among public at large has been in principle achieved. Finally, gradually we are also discussing access to orphan medicinal products within a broader societal context, and giving patients appropriate expectations in this regard, as already discussed.

Well, as we all know with our own children, experience is often rather difficult to transfer, right. But I would dare to say, although this may sound like dad´s advice nonetheless, please continue working together; don't close yourselves within your own professional silos, continue working with patient associations and fight for balanced access to preconception reproductive options and treatment for those rare diseases patients which are already amongst us. Simply do not take what has been achieved for granted! Please work both at domestic and international levels, because, you know, none of us have sufficient expertise; we must learn from each other. Cherish European Reference Networks and fight for their better financing because, without them, we will be back again in a very difficult starting position.

Thus, in this regard I'm a true believer in international collaboration, in friendship, scientific partnerships, in open-mindedness and in higher level of tolerance, broad - yet responsible- solidarity. Please also be responsible in terms of your political choices - a functioning tolerant and highly interconnected society is of paramount importance for care, better quality-of-life and not just mere survival of people with rare diseases. Don't forget, that technology is not everything; technology is important, but it's not a "silver bullet". Only when working together at the European level we will overcome all the potential challenges which are waiting for us down the road
Prof. Milan Macek - Orphanet, Eurogentest, RD Connect

" I think yes, the first would be the work that, for example, EURORDIS did in Europe to combine the voice and at the same time convey knowledge about the huge variety of diseases, which are in the rare disease family. I think that there is a big return in this area where problems are little understood. There's a big return to an effort in educating the public. So that will be one success. Secondly, I think, if you look at the solution that is Mitochondrial transplant, and you look at the way in which engagement with public opinion enabled an a priori unfavorable ethical judgment about the deployment of

mitochondrial transplant to be reversed, certainly in the UK. I think the second lesson from success is we need to engage public opinion as well as science in the generation of an ethical framework for cutting edge cures and treatments.

Thirdly, I think if you look at the orphan drug regime, which is currently succeeding too well in Europe and is therefore being very much challenged by people who see it as now an excuse for pharmaceutical companies to gain disproportionate perhaps and protection. And I don't think that's a failure, but it's a lesson that when you succeed, when you create an orphan regime, you need to keep the proportionality of the relationship between the additional benefits and the evolving needs under review. And I think we could have perhaps with hindsight future-proofed the regime by enabling that question of, you know, what is enough protection to be mechanical is you managed by the different stakeholders collectively within the regime, rather than firing the regime up and sending it off and then having a controversy about whether or not it should be changed. So those would be three that I would offer as examples".

Robert Madelin - formerly DG SANTE, CONNECT)

Rare 2030 Horizon Scanning – Emerging trends

This list of trends below results from an iterative and highly participative process from January 2019 until Nov 2019 and represents the Knowledge generation but especially the HORIZON SCANNING phase of the Rare 2030 Foresight Study. Participants included in discussions leading to this synthesis include:

1. Project partners during PARTNER-WIDE meetings, monthly calls and reviews
2. Rare 2030 Patient Workshop @ EURORDIS membership meeting – May 2019, Bucharest.
3. The 186-person-strong Rare 2030 Panel of Expert Calls across 8 topic-specific working groups
4. Rare 2030 Research Advisory Board interviews
5. RD-specific and broader health care sector literature reviews

For more details around these reflections please visit the *Governance* and *Our Work* sections of the www.rare2030.eu website. The RD section of each factsheet was written by UNEW, and reviewed and revised (where necessary) by EURORDIS. ISINNOVA complemented this with the fruits of research and analysis of foresight studies on broader health and healthcare trends.

Overarching Trends in RDs	Specificities for RDs	Relevant Broader Trends in Health and Healthcare	Type of Trend
1. Rise of pan-European multi-stakeholder networks to advance diagnostics, treatment and care for rare diseases	Europe is now firmly in the age of the European Reference Network (ERNs) - networks of centres of expertise and healthcare providers organised across EU borders whose future depends on continued support. Multi-stakeholder collaboration is also becoming increasingly popular in the research and innovation sectors (e.g. European Joint Programme for Rare Diseases (EJP RD)). Stakeholders in the rare disease field are increasingly collaborating with actors from complimentary fields including social sciences, health policy, regulatory science, eHealth, big data, -omics approaches, bioinformatics, nanotechnology, etc.	Multi-stakeholder governance	Political
2. Strains on the health care budget and the emergence of new care delivery models	As healthcare budgets continue to strain and rare diseases "compete" with more increasingly prevalent non-communicable diseases, health care delivery models for people living with rare diseases become more person-centred and holistic to maximize impact	New healthcare delivery models	Economic

3.	Greater variation in access to treatments and care resulting in more inequality across Europe for people with rare diseases	High market price of orphan medicinal products allows for return on investment and continued R&D in the sector but results in heterogeneous availability and accessibility across member states	Access to medical products	Economic
4.	Demographic change of RD patients introducing new challenges	As more people with rare diseases are living longer the RD population is faced with new challenges such as reproductive choices, transition into adolescent/adult care, comorbidities of ageing and age related disease and a better understanding of the natural history of many rare diseases	Ageing population in a changing family structure	Socio-cultural
5.	Threats to solidarity equity, and the prioritization of rare diseases	On the one hand increased threats to solidarity and (such as inequalities in access to care and treatments between and within countries in Europe) are anticipated. At the same increased efforts for solidarity and equity on the global scale are underway such as efforts for integration of people living with rare diseases and related disabilities in society	Increase inequality and threats to solidarity	Social and Economic
6.	Increasingly empowered rare disease patient and the patient advocacy evolution	Dynamics in patient advocacy and in the role of the patient in health care, research and innovation are changing due to a number of social, technological, political and economic drivers leading to a new era in patient partnership.	Advocacy evolution and patient empowerment	Socio-cultural and Political
7.	Rise in innovation-oriented, multi-stakeholder, needs-led (patient-led) research	The lack of disease-modifying treatments and devices for the vast majority of rare diseases suggests continued gaps in design, execution, delivery, and ultimately the outputs of rare disease research. A globalization of efforts; a rise in needs-led objectives and co-creation are a few of the trends filling these gaps.	Innovation in Healthcare Research	Socio-cultural and Political
8.	Facilitation of knowledge exchange and local care	A greater potential use of virtual care and *eHealth* technology to facilitate knowledge exchange and deliver care locally is being	Digitization of healthcare	Technological

	delivery through digital health	recognized though implementation remains heterogeneous across countries. Challenges and opportunities exist.		
9.	Increased potential for large sets of standardised and interoperable data	The potential to help advance understanding of RD and accelerate research (with coded and structured data) continues to be recognised as do the technical, legal, ethical, social obstacles in data collection and sharing (e.g. data donation, data portability, dynamic e-Consent control; threats: GDPR over interpretation) that require resolution.	Big Data	Technological
10.	Rise in the use of AI for diagnostics, treatment and care, opening-up the potential of 'big data'	A rise in the potential of AI for diagnostics, treatment and care, (via *eHealth*, codification of *eHealth* records, portable data, etc.) opening-up the use of 'big data' which nevertheless remains limited in the field of rare diseases and still requires significant regulatory attention and a clearer ELSI (ethical, legal, social issues) framework.	Big Data and Artificial Intelligence	Technological
11.	New technologies and advanced therapeutics	A better understanding of the mechanisms behind developmental, functional and degenerative rare diseases, new technologies such as gene editing and advanced therapeutics including precision medicine introduce breakthrough opportunities to improve the lives of people living with rare diseases but also potential undesirable consequences	Innovation in Medical knowledge	Technological
12.	Application of Whole Genome Sequencing from the research to the clinical sphere	With a great majority of rare diseases being genetic, advances in the technology around Next Generation Sequencing (NGS) offer significant promise for unravelling the epidemiology of rare disease, accelerating accurate diagnosis and better targeting treatments. These advances introduce a need for an updated ELSI (ethical, legal, social issues) framework.	Genomics	Technological, Ethical and Legal

Trend #1 : Rise of pan-European multi-stakeholder networks to advance diagnostics, treatment and care for rare diseases

Opportunities:

Europe is now firmly in the age of the European Reference Networks (ERNs) - networks of centres of expertise and healthcare providers organised across EU borders in a clear governance structure. Officially launched in 2017, the scope of the 24 ERNs collectively covers almost all rare diseases (along with highly specialised procedures and surgeries requiring a particular concentration of expertise). The first pan-European networks of their kind, ERNs are first and foremost expected to optimise access to high quality healthcare in specialised domains, addressing the current inequalities and gaps in care and treatment; however, they have strong research expectations too, and therein lies their major potential. By connecting centres of expertise (in the ERN vernacular termed HCPs or HealthCare Providers), ERNs offer the opportunity to bring research and innovation ever closer to care, which is essential for so many of the 6-8000 rare conditions (about which, overwhelmingly, knowledge and expertise are still scarce).

The future of ERNs depends largely upon the demonstration of their added-value across their first 5-10 years. Assuming they obtain continued European support, and a greater-than-hitherto level of support at the national level, the Rare2030 Panel of Experts identified the following future-facing trends:

- *ERNs will certainly continue to be important in future - their importance will grow as their impact is demonstrated**
- *ERNs will demonstrate the added-value of networking in rare and highly specialised communities, and will increasingly become beacons for investment and for a range of rare disease activities*
- *ERNs will lead to concrete improvements in the health and clinical outcomes of many rare disease patients, as well as accelerated diagnostics*
- *Virtual care for rare and specialised conditions will be more efficient and more accessible than it is today, via the ERNs' Clinical Patient Management System*
- *Prominence of ERNs will lead to more good practices being disseminated in national health systems*

Regarding the latter trend, particular opportunities are foreseen if ERNs and their constituent HCPs can embrace and help to spread good practices concerning data collection and sharing, codification of diseases, integrated and holistic care, etc.

Although the ERNs are now a major focus of rare disease activities in Europe, it should be noted that multi-stakeholder networking more broadly is becoming increasingly popular, as the benefits of collaboration are appreciated and more opportunities exist for multinational consortia (as evidenced for instance by the launch of the European Joint Programme for Rare Diseases (EJP RD)). Increasing, stakeholders in the rare disease field are collaborating with actors from complimentary fields including eHealth, big data, -omics approaches, bioinformatics, nanotechnology, etc.

Risks

The major risk here is that the ERNs will *not* receive the requisite support from competent national authorities and the European Commission in future; without this, it will be difficult for the Networks to fully demonstrate their concrete added-value in diagnostics, treatment, care and research. It is particularly important to note that impact in these areas is very difficult to assess over short periods of time – improving clinical outcomes for some

conditions, for instance, will take years to achieve: thus in assessing the value of the Networks, policy-makers will need to allow sufficient time for the ERNs to mature. An additional risk is failure for the ERNs to become fully integrated to national health systems. The Rare2030 Panel of Experts identified many concrete suggestions for 'next steps' to improve and optimise ERN operations (see full discussions here). In terms of specific risks to pan-European multi-stakeholder networking, however, a particular concern of the Panel of Experts stems from the recognition that the majority of ERNs were established by Coordinators who can justifiably be viewed as trailblazers in their field: and it may be that the rare disease community will struggle to attract individuals of the same calibre or level of dedication in future, and that the challenges of making a career in this field will be off-putting to the next generation.

- *Despite the boost to networking brought about by ERNs, access to care in the future could be made more challenging due to a shortage in people choosing to specialise in rare diseases*
- *There will be a shift away from the model in which particular rare diseases have a single champion: rare disease specialists and political champions will retire, and there is a fear that there may not be such a committed and passionate group coming up behind*

There is also a concern that medical teams are more used to competing than collaborating, which exacerbates the challenges posed by high workload and a lack of time for networking activities.

Furthermore, a lack of legal provision for the collaboration between ERNs and other stakeholders currently prevents full collaboration between ERNs and industry in improving the knowledge of rare conditions and developing diagnostics tools and therapies. In the meantime the Board of Member States (the formal body in charge of the approval and termination of networks and memberships comprised of representatives of the all EU and EEA countries) offers the following guidance.

Bullet points in italics represent specific future trends identified by the Rare2030 Panel of Experts

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Broader Health & Healthcare Trend: Multi-stakeholders governance

Trends	Drivers	Indicators	Time horizon	Outcome for the EU
Enhancement of EU multi-stakeholders governance on health issues	• Health systems reforms • Medical innovations	• Number of networks • Network accountability • Network effectiveness	Medium - short-time	• Greater coordination among health policies, and actions • Optimise access to high quality healthcare in specialised domains • Reduced inequalities and gaps in care and treatments

Table: Rare 2030 -own elaboration

Health care networks are inter-organizational collaborations among health care organizations or individual care professionals. Such networks are widely accepted and used as an organizational form that enables integrated care as well as the possibility to deal with complex matters in health care (Sheaff et al., 2010, Willem and Gemmel, 2013). Networks typically involve a wide set of actors ranging from governments (national or local), social insurance

funds and professions, private companies, NGOs, agencies and other entities, which are called to either formulate or accept a health policy strategy. In healthcare, the need and interest in an integrated and connected system of care arises from the aim to achieve person-centered, efficient and safe care. An integrated model of care can guarantee a continuum of care which overcomes the issues of fragmentation of services from different providers (EC, 2017).

The latest years have seen an increasing interest by the EU in the development of collaboration in the form of network creation through the set-up of new bodies with broad remits in the field of healthcare, such as the European Reference Networks (ERNs); the Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases (SGPP); the EU Health Policy Platform; the Expert Group on Health Information. Among these ERNs are particularly important for rare diseases. By connecting centres of expertise, ERNs offer the opportunity to bring research and innovation ever closer to care, which is essential for so many of the 6-8000 rare conditions (about which, overwhelmingly, knowledge and expertise are still scarce).
This framework does not only show the intention to develop a network of different stakeholders but also the aspiration for greater collaboration within the EU member countries on health issues (although the extent to which this is embraced by *all* member states is, at present, uncertain). Europe is characterized by significant diversity in the organization of health services among member states and by a great level of decentralisation of health care spending, with subnational governments, e.g. regions, increasingly becoming the main responsible subject for health care spending. This is particularly common in federal, quasi-federal and North European countries. However, the devolution of spending responsibilities is not always accompanied by an equivalent transfer of financial resources (EC, 2016). Paired with increasing health care costs, this has put pressure on sub-national government budgets over the last decade. In the medium-to-long term, this imbalance may pose a threat to the sustainability of public finances at sub-national level, and generate difficulties in public service provision (OECD, 2015) and not only that. How is network governance in healthcare going to function properly and reach the goal it is created for, if its (financial) pillars are undermined? And how a network where responsibilities and actions should be spread by definition can be implemented if its nodes are threatened by financial insecurity?

Accountability can be identified as the main key factor for a good network governance, as it is crucial to how a system performs. It translates into high quality in decision-making and in policy implementation, it shapes the incentives of governing bodies, which will ultimately be called to justify their actions to deliver the system's goals. Together with it, a high degree of transparency is crucial to support system's goals delivery against external pressures, especially in a highly fragmented and complex network (EC,2016).

Do you want to know more?
Have a look at : European Reference Networks (ERN) 2019, Continuous Monitoring Working Group of the ERN Coordinators Group & the Board of Member States, Set of ERN core indicators (18)V.2

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Trend #2 : Strains on the health care budget and the emergence of new care delivery models

When dealing with complex rare diseases, it is increasingly important to recognise that to achieve the best possible outcomes and quality of life for patients who overwhelmingly lack any dedicated treatment options, it is necessary to adopt an integrated, person-centred, holistic approach to health and social care. As systems are increasingly under pressure to ensure optimal use of resources and reduce waste, these sorts of care delivery models may become more commonplace. Patient reported outcomes on their health and well-being are an important emerging key to this transformation of care delivery.

Opportunities

The effective implementation of more integrated health and social services in part rests upon a greater understanding of the *impact* of rare diseases on patients and society at large, and of the benefits of a more joined-up approach to service delivery and holistic care. The Rare2030 panel of experts anticipates:

- *More research on the social impact and burden of illness of rare diseases**
- *More emphasis on understanding Health-Related QoL and on developing and utilising Patient Relevant Outcomes and Measures*
- *A growing realisation that even where there are no medicines or treatment options, integrated and holistic care can improve quality of life for people with a rare disease*
- *In the past, we have focused more on treatments - moving forwards, more attention will be paid to the disabilities/abilities side, the social side, and this will entail more collaboration with complementary fields e.g. disability forums*

In terms of the steps towards more integrated and holistic care, the PoE identified the following trends:

- *There will be more emphasis on integrated care and we will see the realisation of this in countries*
- *There will be a better diffusion of knowledge on integrated & holistic care, accelerated by resource centres for RD*

- *There will be an increasing tendency for more general professionals to evolve into complex care and case coordinators for RD*
- *There will be a greater drive towards implementing case management for rare diseases*
- *We may see more focus on patient 'trajectories' for rare diseases that target the natural history of a disease and turning points in its treatment and care process.*

Digital health tools (such as machine support and assistive technologies) mean that Independent living is a reality for people living with a RD, while eHealth tools offer major potential to provide high quality care for patients closer to home

Risks

Despite the benefits, not all experts are convinced of the inevitability of a stronger paramedical and holistic focus for people with rare diseases; for some, in order to accommodate the rising costs of OMPs

- *Centres may actually be forced to reduce their focus on paramedical and holistic care*

An additional risk is that Integrated care is not being fully included in the ERNs' realm, and a political will is necessary to fill the gap between healthcare and social and paramedical care, otherwise this is left to the patients themselves. Furthermore, true implementation of patient-reported outcomes in care and follow up may take time. And once again there is a 'personnel and skills-related' risk associated with this trend:

- *As more people live longer with better outcomes (from more and better treatments), there will be increased demand for specialised services for which the workforce is not yet in place*

Bullet points in italics represent specific future trends identified by the Rare2030 Panel of Experts

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Broader Health & Healthcare Trend: New delivery models and healthcare sustainability

Trends	Drivers	Indicators	Time horizon	Outcome for the EU
Development of new sustainable healthcare delivery models	• Social values • Cost containment and avoiding waste of resources • Advances in technology and availability of data	• Healthcare expenditure over GDP • Sustainability Index	Medium-long term	• Improved level of patient centredness • Reduced inequality in healthcare • Value-based healthcare

Table: Rare 2030 - own elaboration

Ageing population, biomedical advances, new technologies and medication, the increasing prevalence of chronic diseases and long-term conditions all represent huge challenges in delivering high-quality, accessible, and affordable care (Splaine Wiggings, 2008). Advances in technologies, in particular, both in terms of new technology and rapidly increasing use of existing technology are considered to be a major driver of increased costs in health care

delivery (Bryan et al., 2014). In the OECD countries, the average healthcare expenditure rose from 8.2% GDP in 2001 to 9.3% 10 years later (OECD, 2013). According to World Bank figures, public expenditure on healthcare in the EU could reach 14% in 2030 and go even far beyond in the future. In addition, the latest global financial crisis has had a direct impact on the size, quality, reliability and population coverage of health services through the rapidly changing dynamics of public financing, and the need to protect and balance health spending (WHO). Since 2010 many countries have cut public spending on health (Harris et al., 2017). This has directed attention towards the need for new sustainable healthcare delivery models, which are achieved by delivering high quality care and improved public health without exhausting natural resources or causing severe ecological damage (SDU).

Several countries have tried to fight the effects of the global financial slowdown through extensive reform of their respective healthcare sectors, but none of these efforts has yet proved successful, despite the involvement of the best expertise on healthcare. Europe is currently characterized by two main types of healthcare systems. The tax-funded model, which can be found in the UK and Scandinavia, is a single-payer, predominantly public, system with salary, where patients have a choice of providers and specialist access is regulated through General Practitioners. The social insurance model (e.g. Germany, Netherlands, France) has both multiple payers and owners of provider assets with fees being charged for services, where patients have a choice of insurers and direct access to specialists (UCL). These systems present both different opportunities for change. For instance, recent health reforms in the UK have focused on increasing patient choice of provider, because there is no choice outside private insurance of payer; while in the Netherlands, the emphasis has been on patient choice of insurer within a system in which insurers compete with one another on rate of return.

The Expert Panel recently gathered by the DG Health and Food Safety has identified reallocation of resources as the most urgent need for sustainable and resilient European healthcare systems: resources need to be freed and reinvested from low to high value care according to the system of *value-based healthcare* (VBHC). But what is that? *Value-based healthcare* (VBHC) can be defined as a comprehensive concept built on four value-pillars: appropriate care to achieve patients' personal goals (*personal value*), achievement of best possible outcomes with available resources (*technical value*), equitable resource distribution across all patient groups (*allocative value*) and contribution of healthcare to social participation and connectedness (*societal value*) (EXPH, 2019). Thus, if on the one hand values and in particular social values are identified as key drivers for new sustainable healthcare delivery models, on the other hand Europe must take advantage of the technological and data driven revolution that we are currently living. Instead of looking at what individual countries do, it is important to compare their different performances and assess how and why different systems achieve different levels of success. This can be achieved through the use of real-life, free-flowing data and the construction of indexes which could help institutions to evaluate their outcomes and to future proof healthcare systems (FPH, 2019).

Embracing more comprehensive and integrated patient-centered delivery models could help to ensure a high quality and high-value care, improving health outcomes, patient satisfaction and quality of life and reducing healthcare costs. A holistic healthcare approach intended as care that considers the physical, emotional, social, economic, and spiritual needs of the person, his or her response to illness and the effect of the illness on the ability to meet self-care needs (Ventegodt et al., 2016), could perform well in this direction, especially for multi-morbid and long-term patients. An integrated care should be centered on the needs of individuals, their families and communities and should be delivered by a coordinated multidisciplinary team of providers working across settings and levels of care (WHO, 2016). The adoption of this cultural and organizational approach, that must be encouraged in healthcare, rely on the reshaping of health systems organization and the ways of different professionals to work and interact.

Do you want to know more?

Have a look at: Future Proofing Healthcare FPH 2019, The Sustainability Index: https://futureproofinghealthcare.com/sites/default/files/2019-01/FINAL_FPHI_European_Report.pdf

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Trend #3: Greater variation in access to treatments and care resulting in more inequality across Europe for people with rare diseases

Risks

Many factors influence the accessibility of treatments and care for rare disease. Only ca. 5% of rare diseases have a dedicated therapy. The medicines which *do* have a marketing authorisation in Europe tend to be clustered around particular therapeutic areas (leaving many others without any disease-modifying treatments in the R&D pipeline). The Rare2030 Panel of Experts envisages this to continue:

- *Areas already attracting OMPs will continue to be the focus of pharma R&D, thus increasing the gap between disease areas with therapeutic options and those without*

Following authorisation, multiple factors determine whether or not a marketed medicinal product is actually accessible (i.e. it can be accessed and reimbursed) to patients in each individual country. This results in a very heterogeneous picture of OMP access across Europe, a 'geographical lottery' of

sorts, which leads to inequalities for patients (see forthcoming outputs of WP5). The cost of OMPs (though not always exceeding the average cost of medicines for non-rare indications) is often viewed as a barrier to access, and as national budgets are placed under increasing pressure, there is a concern that access will become more restricted. A similar heterogeneity can be observed concerning access to specialist rare disease care more broadly, encompassing issues such as existence of centres of expertise for particular conditions, access to integrated social and holistic care, access to medical devices, etc.)

The Rare2030 Panel of Experts identified a number of specific trends here:

- *The prices of OMPs will continue to rise until we have a 'disaster' of sorts or there is a critical turning point e.g. where patients really struggle to access their medicinal products*
- *As healthcare resources continue to shrink -and society becomes less-caring- expensive treatments for rare diseases are less and less likely to be made available*
- *Public support not always guaranteed for rarity over high unmet need.*
- *The gap between public and private care and services will probably increase*
- *Some of the disparities in terms of RD diagnostics, treatment and care might get bigger between countries and within countries*
- *Migration from other world regions to Europe means more people unable to access any health and social services*
- *(In consequence of having to pay increasing costs for OMPs), centres may be forced to reduce their focus on paramedical and holistic care*

<u>Opportunities</u>

An important trend is that stakeholders are *recognising* the costs of OMPs more and more, and are analysing the strengths and weaknesses of existing legislation pertaining to rare disease medicines. The differences between countries are also more publicised than ever before. Many believe that greater collaboration across borders in the health technology assessment (HTA) domain (particularly for OMPs and devices intended for use in rare disease patients) is key to ultimately reducing variation and eroding inequalities: particular opportunities here include the proposal for an EU Regulation on HTA, and regional collaborations for HTA and pricing negotiations. The Rare2030 Panel of Experts identified several future-facing trends concerning HTA:

- *There will be more regional and cross-country collaboration in discussions between HTA bodies and payers*
- *HTA considerations will continue to be introduced earlier, closer to the regulatory discussions*
- *There will be a greater drive towards performance-based approvals and access models, with reimbursement based on clinical outcomes*
- *There will be growing transparency in the HTA process - better educated/more capable patient advocates will participate more in HTA*

This last trend illustrates changing perceptions of the value of patient involvement in the HTA process (which today is certainly variable between EU countries): whilst this is perceived as a positive development, it will likely result in a higher level of awareness of the inequalities that *do* exist, as practices in different countries are increasingly exposed.

Activities which ultimately make OMPs and other types of treatment and care for rare diseases more affordable would foreseeably help to reduce the variation observed today. Various trends could contribute to this, involving the following:

- *Reflections that public money (Universities, government grants) has been used to instigate the R&D development of orphan drugs is not taken into account adequately yet - this should be addressed as part of the incentives / pricing when available on the market*
- *Less-traditional technology companies are going to enter the rare disease therapy space more and more, which may see new approaches to bringing drugs to market* [with the expectation that prices would become lower]

Bullet points in italics represent specific future trends identified by the Rare2030 Panel of Experts

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Broader Health & Healthcare Trend: Access to medical products

Trends	Drivers	Indicators	Time horizon	Outcome for the EU
Ensuing accessibility to medicines	• Increased cost of new medicines • Increase demand of medical products for ageing population • Search for financial sustainability of healthcare sector	• Cost of medicine • Time between market authorization and patient access	Medium-long term	Higher level of human health protection

Table based on WHO (2015), Vogler et al., 2015, Deloitte UK (2019)

According to the Charter of Fundamental Rights (Art. 35) of the EU on Health protection "Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices. A high level of human health protection shall be ensured in the definition and implementation of all the Union's policies and activities". Ensuring access to medicines is crucial for turning this principle into reality. Although EU aims at ensuring that all European citizens have equal access to appropriate and high quality healthcare, government budgets of EU Countries are subjects to a growing burden due to the increasing expenditure on health care. Across 16 of the 28 European countries, GDP spent on health care has increased from 9.5% in 2010 to 9.7% in 2016 (Deloitte UK,2019), while 20% of Member States' average health budget is spent on medicines (European Parliament 2017). Both Europe's ageing population and the increased cost of new branded medicines pose a major social and economic challenge for Europe and open up the debate of healthcare sustainability (Medicine for Europe, 2017; OECD, 2015).

One of the main barriers to ensuring accessibility to medicines is represented by the price of necessary medications, especially in low and middle income countries. Because of high prices, approximately one-third of the global population is unable to obtain the necessary medications (Vogler et al.,2015). Unaffordability of medications may lead to the patients' non-compliance and to increased direct and indirect costs of treatment. Given this, the WHO

recommends that healthcare decision-makers come up with solutions to administer pricing policies (WHO 2015). Affordable prices are designated by WHO as a determinant of access to medicines – together with rational selection and use, sustainable financing, and reliable health and supply systems (WHO, 2015). In this regard, global differential pricing across countries has been suggested as one of the possible solutions. In this scenario, it is necessary to find a balance between gaining the health benefits of innovation while maintaining a sustainable health system by defining a stable and predictable intellectual property and regulatory framework, as well as proper and timely implementation for supporting patient **access to innovative and effective treatments** (European Parliament, 2017). In fact, in Europe pharmaceutical products are struggling to reach patients quickly, as a result of the wide gap between market authorization and patient access. Upon an analysis conducted on data collected by the EFPIA (European Federation of Pharmaceutical Industries and Associations), in Europe the average number of days from market authorization to patient access (essentially to **reimbursement**) has increased from 233 days in the period 2007-2009, to 318 days in the period 2014-2016 and it is heterogeneous between countries (Deloitte UK, 2019). Moreover, the lack of political commitment due, for example, to conflicting industrial or trade policies, can act as a barrier to the adoption of strategies to reduce the price and improve the availability of medicines (Cameron et al., 2011). Aware of all these challenges, **payment models for medicine are called to satisfy several objectives** as ensuring affordability of new products to institutional payers and patients, reward innovation, cover costs of companies, promote efficient use and efficient production. Higher affordability to institutional payers can be achieved shifting costs to patients through higher cost sharing rules, which in turn decreases affordability and financial access to patients. On the other hand, affordability to institutional payers may be achieved by limiting the volume of patients to be treated, which however results in access issues and eventually too much rationing in access to treatment. Thus, a balance between affordability to institutional payers and to patients needs to be achieved. The innovative payment models have to contribute to achieve this balance (EC,2018). For OMPs in general, an accurate regulation of pricing and reimbursement rules, ideally, shared between all EU countries, would be beneficial, especially if addressing the fast reimbursement of treatment by national health care payers.

Do you want to know more?

Have a look at: "EU Commission. Innovative payment models for high-cost innovative medicines.2018. https://ec.europa.eu/health/expert_panel/sites/expertpanel/files/docsdir/opinion_innovative_medicines_en.pdf

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Trend #4 : Demographic change in rare diseases patients is introducing new challenges

More advanced therapies, better targeted to individuals' genotypes and phenotypes and better standards of care means that patients are surviving for longer, wither fewer complications, and are encountering a new range of challenges and opportunities.

Opportunities

Greater understanding of the natural history of diseases and a stronger emphasis on understanding patients' daily realities results in more tailored, person-centred care, with better outcomes for patients and fewer complications. Co-morbidities will be better addressed, as part of a stronger emphasis on healthier ageing. For rare diseases, the secondary and tertiary symptoms of complex conditions will receive more attention, and healthcare services will begin to focus more and more on the pre-symptomatic carriers. One consequence of this demographic shift will be greater reproductive choice, as people who in years gone by would not reach adulthood, become able to have families of their own. For example, as pre-implantation genetic diagnosis continues to advance, and becomes more available, patients and carriers will be able to make more informed reproductive decisions.

- *The mean age is growing - for humans living in our part of the world generally but also for conditions where better care and treatment mean longer lives**
- *More patient registries, collecting broader datasets and QoL information, will illuminate more clearly the problems and needs of people living with RD*
- *The rise in assisted technology and supportive devices (particularly through Artificial Intelligence), will improve the quality of life for people with disabilities*
- *More people with rare diseases will live increasingly independent lives, administering their own care*
- *New therapies will not replace the need for holistic care for RD; however, the emergence of new therapies will change the way PLWRD actually live with them, and we will adapt our approach to how people live with those*
- *Emergence of therapies for the secondary or accompanying conditions*
- *Preventative, pre-symptomatic therapy will become more commonplace*
- *Care will not only focus only on patients but also increasingly on healthy mutation carriers*

- *Prenatal screening and pre-conceptional screening will continue to become more popular and widespread, resulting in more disease prevention ('Comprehensive' prevention would actually require genetic screening of the general population, including newborns and health adults; however, this raises even more ethical questions)*

Risks

Reproductive planning for people with rare diseases often entails challenging ethical considerations, and requires specialist genetic counsellors (which may not be available in the numbers required). Preventative medicine, in all of its forms, incurs difficult ethical discussions on the value of human life. From a practical perspective, as people live longer, more services will need to ensure a smooth transition of care between paediatric and adult stages: this has traditionally been viewed as a challenge for rare diseases, but becomes arguably even *more* difficult in the case of conditions for which adult services have never been in place (due to the life-limiting nature of the diseases). As patients live longer, and with a better quality of life, more and more will seek independent lives: whilst a positive development, this will require a larger number of specialists able to provide appropriate social and holistic care, and could exert more pressure on overstretched health and social systems.

The Rare2020 Panel of Experts discussions identified the following specific future trends in this area:

- *As more people live longer with better outcomes (from more and better treatments), there will be increased demand for specialised services for which the workforce is not yet in place*

Bullet points in italics represent specific future trends identified by the Rare2030 Panel of Experts

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Broader Health & Healthcare Trend: an ageing population in a changing family structure

The table below presents the key trends in demography level at EU and global level.

Trends	Drivers	Indicators	Evidence base (0/+/ ++/+++)	Time horizon	Outcome for the EU
Global population growth (driven by middle-income and lower-income countries)	High fertility in developing world, declining mortality (due to medical improvements), empowerment of women and changing values	Fertility rates, life expectancy at birth, 'ideal' family size across various countries	+++	Medium long (10-50)	Global strain on natural resources and food supplies, migration flows

Population ageing in high- and middle-income countries	Increased life expectancy, declining fertility (due to economic, developmental and value-related factors)	Old-age dependency ratio, average life expectancy, healthcare costs as a proportion of GDP	+++	Short to long (5–50 years)	Financing welfare state models with a shrinking workforce, managing healthcare and pension costs, challenges in provision of services (e.g. elderly care)
Changing family structures and sizes in Europe	Increase in the number of elderly citizens, increase in single person and single parent households, changing family formation patterns (cohabitation, etc.)	Proportion of single parent households, average household sizes, divorce rates, at risk-of-poverty rates by household type	++	Short to medium (5–10 years)	Ensuring adequate housing supply, adaptation of family support systems, managing risk of poverty and social exclusion
A youth bulge in parts of the developing world	Past high fertility rates in the developing world, improving maternal and neonatal health, improved sanitation, declining under-5 mortality, declining prevalence of infectious diseases	Total fertility rate, birth rate, neonatal/child/ under-5 mortality rate, proportion of 15–24, total population, number of hospitals per 1,000 capita, prevalence rates of infectious diseases (diarrhoea, malaria, etc.)	+++	Long term	Effects of population growth on migration flows to the EU, possible societal unrest or pressure for democratic reform, potential sources of radicalisation.

Table 1 Matrix for key trends in demography . Based on RAND 2015

Across the world, the basic determinants of population size and structure — fertility, mortality and migration - have been fundamentally shaped by the processes of social and economic development. As a result, **the global population doubled to 7 billion in the last half century and will continue to grow to between 8 billion and 9.6 billion by 2050** (United Nations, 2013). However, regional trends differ markedly and in EU-27 population is expected to be 5% lower in 2030 than in 2010.

One of the determinants to demographic change in EU countries is that the life expectancy is constantly **increasing and ageing** is projected to affect all EU countries and most policy areas. In the next few decades, the proportion of elderly persons is set to rise fast, while that of working-age people will fall significantly. By 2025 more than 20% of Europeans will be 65 or over, with a particularly rapid increase in the number of over-80s (European Commission Ageing Policy website, 2013). As old-age dependency ratios increase, the social contract may come under strain. Public finances could worsen as a smaller, economically active population is relied upon to provide for pensions, health and long-term care and other needs of the elderly. Ageing trend is connected with the rise of Non Communicable Diseases – now accounting 90% of the disease burden for the over-60s in low, middle and high-income countries (WHO). Furthermore, ageing is also associated with an increased risk of a person having more than one disorder at the same time (multi-morbidity). In a period of financial constraints, the rise of chronic diseases and multi-morbidity requires health care systems to reorient and integrate their services.

Two recognized demographic uncertainties over the next 50 years in the EU are the size and **structure of families** and the **international migration** (Cohen, 2013). In the EU, OECD projects the rise of single adult households, an increase of single parent families, and a rising number of childless

couples (OECD, 2012). Parenthood seems to begin at a later average age than before and marriage appear to be less stable, while new family structures (single parent households and step parenting) are increasing (RAD, 2012). Some studies investigate the complex range of factors affecting the declining fertility trends in the EU drawing correlations between the increased women's enrolment in education and access to the labor market as drivers for birth postponement. Generally, the mean age of couples at the birth of the first child has steadily risen across EU over the past decade, while the gap between desired and actual fertility at specific ages has also increased (Rita Testa, 2012).

With over a million refugees arriving on Europe's shores in 2015 alone, according to the UNHCR, **migration** has become a top priority in the EU political agenda. In 2011, around one out of ten residents in the EU was born in another country (Eurostat,2013). High numbers of immigrants, typically combined with their younger age structure and often with higher fertility rate, could contribute significantly to the number of births in the EU country. On the other hand, the permanent settlement of immigrants with different socio-cultural backgrounds demands policies and actions aimed at appropriate integration without which societies run the risk of cultural crash and social unrest (FRESHER, 2014).

Do you want to know more?

Have a look at A growing and ageing population Global societal trends to 2030: Thematic report 1

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Trend #5 : Threats to solidarity, equity, and the prioritization of rare diseases

The rare disease field may be facing substantial threats in the face of growing indifference or even antipathy from wider society, alongside an increasing awareness of the need to maintain a strategic and ethical focus on what makes people living with rare diseases unique and equal members of society.

Opportunities

Globally, the rare disease 'cause' is arguably gaining traction: patient organisations and research initiatives are increasingly global in their membership and outlook. Many aspects of living with a rare disease are bound-up with fundamental rights and concepts of equity and solidarity; for instance, recent

years have seen the creation of IRDiRC (the International Rare Disease Research Consortium), Rare Diseases International, and the emergence of RD at United Nations level (NGO Committee for Rare Diseases and a UN Universal Health Coverage Political Declaration that includes people living with rare diseases). 'Rare diseases' as a concept is also becoming more prominent in countries and regions world-wide which hitherto lacked any significant awareness. Alongside this, there is a growing awareness of fundamental human rights, and this is very complimentary to the increased emphasis on the importance of integrated, social and holistic care. People living with rare diseases are supporting each other in new ways, as evidenced by the rise of peer-to-peer work enabling people to exercise their rights and live their lives. The Rare 2030 Panel of Experts perceives also a greater potential to strengthen collaborations and build solidarity with other groups of patients:

- *In the past, we have focused more on treatments - moving forwards, more attention will be paid to the disabilities/abilities side, the social side, and this will entail more collaboration with complementary fields e.g. disability forums**

Rare diseases continue to pave the way, in some cases now moving away from being 'therapeutic orphans' and instead paving the way for personalised treatments (which can go beyond medicines). Rare diseases will be more often diagnosed and thus more common overall, whereas more common diseases will become more rare because of precision medicine. Rare diseases can help anticipate many of the challenges of precision medicine. They represent an experimentation platform for the health care systems of tomorrow.

Risks

There is a growing concern that rare diseases will struggle for continued prominence in the face of social and economic change and external challenges.

- *Progress made over the past 20 years in rare diseases was partly driven by a general trend towards fairness and equality; unfortunately, however, there has been a recent backlash to this trend with the rise of more selfish attitudes, typified by the rise of nationalism*

There is a sense that rare diseases will increasingly have to compete with other conditions and causes, and that their particular needs are less likely to be met in a more cash-strapped, less caring society:

- *As healthcare resources continue to shrink and society becomes less-caring, expensive treatments for rare diseases are less and less likely to be made available*
- *Public support will not always be guaranteed for rarity over high unmet need [in other areas]*
- *"Compassion fatigue" may be setting in: as rare disease patient organisations become better organised and raise awareness, there is a risk that the public can become disengaged.*

The threats are not only external – challenges may also come from *inside* the rare disease community

- *There will be increased competition and tension between patient organisations*

Precision medicine and the reduction of common conditions to rarer subtypes is viewed as a particular threat in this respect:

- *The market for targeted therapies and precision medicine will expand, which will usher in competition between rare diseases and subtypes of more common diseases, to become quite blurred*
- *We may see a growing dilution of the concept of a 'rare disease' as common conditions are broken down more and more and personalised medicine becomes more popular and widespread*
- *As we see a trend towards development of precision medicines, rare diseases as a field could lose its identity: there will be less distinction in terms of the types of approaches, the types of trials, the types of data packages that come with OMPs*

All of this, coupled with the threat of shrinking health budgets, may impact on rare diseases nationally, at the strategic and political levels:

- *As RD fall off the national agenda, National plans and strategies (NP/NS) may see less funding for rare disease activities*
- *Countries will move away from NP/NS for RD specifically and will instead go for broader health strategies/plans: perhaps with merely chapters dedicated to subjects such as RD, cancer, genomics, etc.*

A final threat here concerns the attractiveness of the RD field, for would-be specialists:

- *We are seeing a shift away from the model in which particular RD have a single champion: RD specialists and political champions who build these communities will retire, and there is a fear that those coming up behind may not be as committed and passionate as their forerunners*

Bullet points in italics represent specific future trends identified by the Rare2030 Panel of Experts

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Broader Health & Healthcare Trend: Increased inequality and threats to solidarity

The table below presents the key trends in inequality at EU level.

Trends	Drivers	Indicators	Time horizon	Outcome for the EU
Increase in socio-economic inequality and health inequalities	● Growing difference between low and very high earnings; ● Increasing importance of unevenly distributed capital income; ● The emergence of long-term unemployment ● Economic crisis and cut of resources ● Healthcare systems reforms (lack of)	● The Gini coefficient ● The income quintile share ratio ● Health system coverage ● Availability (health workforce, distance from point of care, waiting time)	Short - Medium	Effects of population health and well-being in terms of exposure to Non Communicable Diseases and access to medical advances.

Table 1 Matrix for key trends in inequality (FRESHER, 2015)

EU members have witnessed a long and sustained period of improvement in the lives people are able to lead, based on socially cohesive societies with developed welfare states, high-quality education and health services (Marmont et al., 2012). The result has been a remarkable health gain: Europe include countries with some of the best levels of health and the narrowest economic and health inequalities. However, **inequality** has increased on average across the OECD countries during the period 1980-2010, with the *Gini coefficient* being at a higher level at the end (from 0.228 to 0.373) than it was at the beginning (from 0.20 to 0.33). In particular, since 2008, the economic crisis and the consequential increased in unemployment rate have exacerbated this trend and exposed stark social and economic inequalities within and between countries.

In turn, the rising socio-economic disparities have affected **population health and access to care services**. Gaps in health are complex and involve a wide range of factors that can be summarized as follows (Xavier et al., 2009): i) living conditions; ii) health-related behaviours which are themselves influenced by socio-economic and cultural factors; iii) employment and working conditions; iv) income (or its absence and thus financial distress); v) education; vi) access to social protection including access to quality health care and disease prevention interventions. Inequalities based on income have become particularly important in the aftermath of the crisis. In the period 2008–2013, 9 countries recorded an increase of 1 percentage point or more in the share of the population reporting unmet needs for care and only 3 countries registered significant improvements in access (Social Protection Committee, 2014). **Unmet health needs disproportionately affect people of lower socio-economic status**, those with greater healthcare needs in general or those who belong to a specific disadvantaged ethnic minority, as well as homeless people and migrants. Moreover, the crisis has resulted in the emergence of new groups that were not previously considered vulnerable due to increased unemployment, especially among young men, and increased household debt problems, particularly for young couples facing housing and job insecurity. (EUROFUND ,2014). For instance, in Greece ESPN experts report that unmet needs for medical examination increased dramatically from 2010 to 2016: by 26.2 %, i.e. from 9% in 2010 to 35.2% in 2016 for the lowest income quintile (EC, 2018). In addition, health inequalities share two basic risk-full traits: persistence and self-reinforcement. Health inequalities start at birth and tend to persist into older age. The combination of poverty with other vulnerabilities, such as childhood or old age, disability or minority background, further increases health risks. Moreover, poor health for those more vulnerable further enhances social exclusion and socioeconomic inequalities, contributing to sustain a negative loop.

The economic crisis and the rise of inequality might also pose threats to the fundamental value of solidarity defined as "*shared practices reflecting a collective commitment to carry 'costs' (financial, social, emotional, or otherwise) to assist others"* (Prainsack and Buyx, 2011). "In circumstances of weak social mobility, growing income inequality can seriously endanger the cohesion of societies, undermining mutual trust and limiting the capacity and readiness to change. Combined with the demographic profiles of many countries, these developments will place a strain on social protection systems and demand significant efforts in the area of social innovation"(ESPAS,2015).

Even though persistent, health inequalities are not inevitable; public policy actions can tackle those factors which impact unequally on the health of the population (EC, 2009).

Do you want to know more?

Have a look at: "Shaping EUROpean policies to promote HEALTH equitY" http://www.euro-healthy.eu/

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Trend #6: Increasingly empowered rare disease patient and the patient advocacy evolution

Rare disease advocacy is evolving, accelerated by a growing awareness of civic rights, of the benefits of patient-centred (indeed person-centred) care, and myriad changes to the way in which advocacy happens in the era of social media.

Opportunities

There is an increasing awareness on the part of citizens that they have the *right* to participate fully in society, despite having a rare disease. The Rare 2030 Panel of Experts proposed specific future-facing trends highlighting the shift towards increasingly informed and assertive patients, willing and able to drive forwards aspects of their own care; in particular, patients and citizens have more opportunities to evaluate the quality of their care and services, and to seek redress when things go wrong:

- *Growing importance of civic society and shared collective identity for advocacy**
- *The changing roles of patients and families and patient organisations to drive health literacy and enable navigation of complicated health systems will open up access to some health services*
- *There will be a continuous drive towards more patient-centred care*
- *Patient democracy will continue to rise, with patients becoming more informed, and more able to access information and make decisions on care*
- *More opportunities for patient participation to some aspects of the ERNs' virtual reviews and consultations is envisaged*

The number of rare disease patient organisations is expected to continue to rise, with more conditions gaining an organisation of their own (and/or more cross-disease alliances). In some countries, however, there may be a move away from a purely 'RD' focus, to instead unite patients with a broad range of conditions: this could be envisaged if countries seem unlikely to be able to develop a RD-only alliance, but equally could be a way to avoid the issues raised by shifting parameters of which conditions are officially classed as 'rare'. Some also point to the benefits of embracing non-RD actors, creating new opportunities to learn from each other:

- *There will be an increase in the number of patient organisations in the RD field, and in their organizational capacity*
- *The scope of patient organisations may broaden, and there will be more collaboration with other advocacy groups, such as disability organisations*

The nature of advocacy –and the way in which organisations operate- is also envisaged to change, in some ways connected to the rise in use and prominence of social media:

- *There will continue to be a shift in the way in which patient organisations come together: for some, physical meetings are increasingly becoming replaced by virtual communications*
- *The nature of advocacy will change, as will the methods for engaging younger demographic*

Significant opportunities are foreseen for patients to lead more independent and autonomous lives, through increased opportunities (e.g. via social media) to connect with others in similar situations, but also as the concept of integrated and holistic becomes more embedded:

- *There is a growing realisation that even where there are no medicines or treatment options, integrated and holistic care can improve quality of life for people with a rare disease*
- *Rise in peer-to-peer work will enable people with rare diseases to exercise their rights and live their lives*
- *More people with rare diseases will live increasingly independent lives, administering their own care*

Several specific trends under this heading concern 'data': data is particularly important in rare diseases, as patients are often perceived to have particular expertise in their conditions, an expertise which typically is *not* shared by general health and social care practitioners (a major difference between rare and common diseases). Collecting and pooling as much data as possible on the cause, course, and effects of a rare disease is the only way to advance diagnostics, treatment and care. The Rare 2030 Panel of Experts envisages *more* data, and specifically, more directly-patient-generated data in future:

- *Increase in volumes of Patient Generated Data*
- *Increased portability of data and opportunities for people to access and maintain their own data and determine who can access is*
- *Continuation of the use of apps, mobile devices, and PROMs*

As the volumes of patient data increase (both clinician-entered and directly-patient-reported data), the expectation is that there will be a greater emphasis on collecting the 'right' sort of data: data on the burden of illness and societal impact of rare diseases is often considered to be lacking, for instance. Many agree on the need to select more patient-centric outcomes for clinical trials, and to improve the HTA process, particularly as the concept of value-based healthcare becomes stronger (the reasoning here being, to show the true value of an intervention, it is necessary to monitor outcomes that actually matter to patients):

- *Continued emergence of outcome-based healthcare*
- *Continued growing emphasis on collecting Patient-Relevant outcomes for studies*
- *More specific development of PROMs for RD: of disease-specific Patient-Centred Outcomes*
- *More emphasis on understanding Health-Related QoL and on developing and utilising Patient Relevant Outcomes and Measures*
- *Growing transparency and better educated/more capable patient advocates will participate more in HTA*

Another angle to the citizen empowerment trend concerns diagnostics. Rare disease patients have traditionally faced a 'diagnostic odyssey', and often encounter misdiagnoses. Although next generation sequencing technologies are becoming more available in the clinic, this is not happening at the same pace everywhere.

- *Patients will increasingly take a more hands-on role in the search for a diagnosis*
- *DTC (Direct To Consumer) testing will become more commonplace, which will impact strongly on the wider field of genetic testing for people with RD*

The Rare 2030 Panel of Experts also predicts a more proactive role for patients in developing therapies and devices (both directly, and by partnering with stakeholders such as Industry and academics), whilst also driving forwards and shaping research at all levels:

- *Patients will continue to drive innovations in rare disease devices, therapies, and aids to everyday living*
- *Increasing prominence of the concept of co-creation and development of innovative funding models to advance rare disease causes*

<u>Risks</u>

The Rare 2030 Panel of Experts anticipates some potential risks around the changing face of patient advocacy. As more patient organisations appear, competition for the same roles and grants may intensify: particular for conditions which are traditionally better networked, and for which many groups exist (not always in harmony). There are also concerns around the nature of the advocates participating to meetings, projects and events, in terms of their realistic ability to represent diverse diseases and different economic and literacy levels. As long as patients are not reimbursed for their time and energies to undertake advocacy work, the pool of those able to take on these roles will remain limited, potentially skewing the perspectives they are sharing:

- *There will be increased competition and tension between patient organisations*
- *The 'divide' between the roles of 'patients' and 'patient advocates' will likely increase*

There are concerns that the very identity of 'rare disease advocacy' may come attack, for various reasons. For instance, there is a fear of 'compassion fatigue', which, if materialising, will affect advocacy and empowerment significantly. A lot of successes in the RD field have been facilitated by a general trend towards fairness and equality over the past couple of decades, but some sense that society is becoming increasingly self-centred and less philanthropic, which could fundamentally damage the future rare disease cause:

- *"Compassion fatigue" is setting in: as rare disease patient organisations become better organised and raise awareness, there is a risk that the public can become disengaged*

- *Public support will not always be guaranteed for rarity over high unmet need*
- *The market for targeted therapies and precision medicine will continue to expand, which will usher in competition between rare disease and subtypes of more common diseases to become quite blurred*

There are numerous risks on the data side: set against the opportunity to have *more* data (and more interoperable data), illuminating patients' needs and realities, are the concerns around data ownership, transparency, and consent:

- *Patients may be less willing to donate /share their data if they are not certain who will own it and who will use it*
- *Lack of regulation in genetic testing will continue to place sensitive data in the hands of big companies*

Another risk, of quite a different nature, is that despite the opportunities brought about by more integrated health and social care leading to improved outcomes and longevity for children and young people with rare diseases, the current generation of parents and carers will not always be there to provide the care and support they have delivered hitherto. This is naturally a major concern for many people.

Future-facing specific trend identified by the Rare2030 Panel of Experts

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Broader Health & Healthcare Trend: Patients empowerment and advocacy evolution

Trends	Drivers	Indicators	Time horizon	Outcome for the EU
Patients empowerment and advocacy evolution	● Shared decision making ● Health literacy ● Self-management ● Technological development	Health Care Empowerment Questionnaire the Patient Enablement Instrument the Patient Activation Measure	Short-medium term	● Better connection between public spending on healthcare and population health needs ● Improved health in terms of quantity and quality ● Lower use of drugs ● Improved clinical outcomes

Table: Rare2030 Own elaboration

Patient empowerment can be broadly defined as a situation in which "citizens are encouraged to take an active role in the management of their own health, transforming the traditional patient–doctor relationship and providing citizens with real management capabilities" (Calvillo et al., 2015). This involvement does not only concern the treatment, but all stages of the medical process: prevention, diagnosis and treatment.

The driving forces for patient empowerment can be identified in:

Shared decision making: The principles of share decision making are well rooted among doctors, with their first mention dating back to 1982 (Elwyn et al.,2012). According to these principles, the clinician should support and inform patients about their condition and the treatment options to reach a consensus about the optimal course of action, taking into account patients' condition, life circumstances and personal preferences.

Health Literacy: Health Literacy is defined as "the capacity to obtain, process and understand health information and to use it to make decisions about health and healthcare" (EPF, 2015) and represent a necessary condition for patients' empowerment. Indeed, the new huge amount of information that is now available to citizens through the internet and social networks raises the need for citizens to be able to handle it with the risk of misunderstanding and wrong decisions. Therefore, the access to high-quality information is a key facilitator of empowerment. In order to promote health literacy, clinicians and public authority should on the one hand educate patient to think critically while on the other hand provide themselves the correct information.

Self-Management: Most people cope and manage minor illnesses without recourse to professional help because they know what to do and are confident in taking action. Supported Self-Management could be the key to change the way healthcare is provided, especially for those affected by chronic disease. Indeed, on the one hand clinicians have a limited time to dedicate to patients, while on the other hand it may be the case that the objectives of patients are not always aligned with the objective of the clinician. Patients should therefore be helped to manage their conditions in a more independent way. This can be achieved through a combination of two instruments: i) Technological innovations: smartphone applications if designed to meet the need of patients would be powerful instruments to monitor their health, enabling patients to take corrective measures without relying on the clinicians. Moreover, they can increase the capability of patients to better self-monitoring all the environmental factors affective their disease such that diet, physical activity etc. ii) Personalized care planning: it is defined as a "collaborative process used in chronic condition management in which patients and clinicians identify and discuss problems caused by or related to the patient's condition, and develop a plan for tackling these" (Coulter et al., 2015).

The three factors described undoubtedly share a common denominator: technological development. For Calvillo et al. (2015) technology is in fact the main factor contributing to patient empowerment, allowing patients to obtain information much more quickly and to form networks, which are particularly important when dealing with chronicle or rare diseases (see the example of ERN 2019). If technology is the common line for the driving forces of patient empowerment, one could expect a fast progress of patient empowerment in healthcare in the future, happening at the pace of the quick developing technology. Nevertheless, it is not easy to find a measure for patient empowerment. A universally accepted measurement instrument for patient empowerment does not exist yet (Castro et al., 2016) and most of the existing measurement scales are specialised, focusing only on particular conditions such as diabetes (Anderson, 2000) or cancer (Bulsara et al., 2006).

Do you want to know more?

Have a look at EMPATHiE (2014) 'Empowering patients in the management of chronic diseases: Final Summary Report', available at: http://www.eu-patient.eu/contentassets/543c15ed8f8c40f692030a0a0d51b8e2/empathie_frep_en.pdf

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Trend #7 : Rise in innovation-oriented, multi-stakeholder, needs-led (patient-led) research

The lack of disease-modifying treatments and devices for the vast majority of rare diseases suggests room for improvement in the overall research and development process. The Rare2030 Panel of Experts identified numerous trends to improve the design, execution, delivery, and ultimately the outputs of rare disease research. One fundamental issue is the extent to which current research addresses the realistic needs and challenges faced by patients: this entails a robust understanding of what those needs and challenges actually *are*, which in turn requires a willingness to recognise the unique experience and expertise of rare disease patients, families and carers. This is an area in which co-creation is essential - patients must be able to help shape research from the outset, elaborating relevant and appropriate research questions.

Neglected areas of research require specific attention in order to fully understand the needs of the target population; for instance, the Rare2030 Panel of Experts anticipates that:

- *There will be more research on the social impact and burden of illness of rare diseases**

The needs of patients can also be elucidated through greater volumes of (ideally poolable/queryable) patient-generated data:

- *We will see an increase in the volume of patient-generated data*
- *There will be a greater use of surveys to understand the needs and realities for rare diseases patients, to drive research*
- *Patient-led registries will be a profound driver for the development of patient reported outcomes and also for attracting the interest of developers. They will help to fill some of the gaps around epidemiology, natural history and relevant measures etc.*

A better understanding of the epidemiology, natural history and daily impact of rare diseases supports the selection of more relevant and feasible outcomes for clinical research (and increasingly also for health technology assessment (HTA) purposes, as well as decisions on pricing and reimbursement). The Rare2030 Panel of Experts anticipates the following specific trends here:

- *There will be a continued, growing emphasis on collecting patient-relevant outcomes for studies*
- *There will be more specific development of Patient Reported Outcome Measures (PROMs), and more agreement on disease-specific Patient-Centred Outcomes*
- *More emphasis will be placed on understanding Health-Related QoL and on developing and utilising Patient Relevant Outcomes and Measures*
- *There will be an increasing volume of healthcare data collected directly from electronic health records and an increased integration with other health-related data in national data hubs and EU digital space.*

In fact, the design and execution of clinical trials and studies at large is expected to change:

- *The model for clinical trials in rare diseases will change, in favour of decentralised trials on a smaller scale, which are conducted quicker*
- *We will see the emergence of new methodologies for clinical trials in rare diseases and other small populations*
- *More agile personal health records or health apps will result in more data on rare diseases, whilst reshaping the design of clinical trials and studies*

Meanwhile, the trend for patients to fund and shape research projects more proactively is expected to continue:

- *We will see increasing co-creation and patient partnerships to develop registries and conduct research*
- *Patients and patient organisations will drive the research agenda more and more in future, by funding and shaping research*
- *Patients will continue to drive innovations in rare disease devices, therapies, and aids to everyday living*

The last point incorporates the trend for some patients and families to actually design and conduct various types of R&D activity single-handedly.

Considering research more broadly, the Rare2030 Panel of Experts proposed that to address the perceived shortcomings of the traditional model of rare disease research, a significant paradigm shift will be necessary:

- *There will be a rise in translational research enabled through academic-initiated and multi-stakeholder collaborations*
- *We will see increasing collaboration with actors from 'external' but complimentary fields including eHealth, big data, omics, bioinformatics, to explore new avenues for research*
- *Development of a more cohesive and comprehensive RD Research Ecosystem across EU but also within the different Member States, a sort of one stop shop for access to data and resources, funding, training etc.*
- *Less-traditional technology companies are going to enter the rare disease therapy space more and more, which may see new approaches to bringing drugs to market*

Future-facing specific trend identified by the Rare2030 Panel of Experts

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Broader Health & Healthcare Trend: Innovation in Healthcare Research

Trends	Drivers	Indicators	Time horizon	Outcome for the EU
Innovation in Healthcare Research	• Sharing of large-scale clinical dataset • Participative approaches in research	Global Innovation Index (2019)	medium-long	• Innovation and advancements in research approaches • Treatment evaluation and drug development • Economics returns

Table: GII(2019); SPH (2016, 2018); Glover et al. (2018); Marjanovic et al. (2017); Wooding et al. (2011)

Health research holds a crucial role in informing and driving health care and health policies. Research can find solutions for existing problems, through discovery and validation, and these solutions can be performed by the health-care system to provide the best possible care to patients. Moreover, researchers scanning the health care system can have information on the quality of the solutions implemented, and research on these outcomes can drive new discoveries, which in turn can lead to new solutions. (SPH, 2018). Overall, **health research benefits society**. Research can foster innovation and advancements in healthcare that help people with rare diseases, chronic diseases and disability to live a more active, healthy and long life, to be capable of working and be productive, contributing to society (SPH,2016). Studies have demonstrated that there is also an economic return on research investments for a variety of diseases (e.g. Glover et al.,2018; Wooding et al., 2011). In particular, large-scale linkage of international clinical datasets could lead to unique insights into disease *aetiology* and facilitate treatment evaluation and drug development. Multi-stakeholder consortia are currently designing several disease-specific translational research platforms to enable international health data sharing (Kalkman et al., 2019). The chain from exploratory research to innovation and implementation involves **multiple stakeholders** with different goals and expectations, including scientists and health care professionals, governments and public funders, private enterprises, patients and society at large (SPH, 2016). Among the range of stakeholders, consumers, patients, caregivers and patient advocacy organisations are playing an increasing role in the dialogue with healthcare professionals. **Their growing involvement in research** is mainly due to a higher health literacy of Europe's citizens, who use data themselves to help self-manage their condition, modify their behaviour, and engage in decisions about their care (Stakeholder Guide 2014; The European Group on Ethics in Science and New Technologies,2015). The use of health data empowers patients to be more engaged with healthcare decision making, supporting health professionals and policymakers in clinical and policy decision-making, enabling researchers and academics to enhance research quality and to undertake new types of analysis, research and innovation (Marjanovic et al., 2017).

This creates potential for improved preventative approaches and tailored treatments aiming for precision medicine, which represents a major opportunity for health research and health care (Nimmesgern et al.,2017). Health service can be improved becoming more sustainable by transforming the competencies of patients in participation behaviors of health value co-creation (Russo et al., 2019) and the early involvement of patients and patients organizations in research processes, could also avoid the development and market access of drugs useless for patients . More recently, **experience-based**

co-design (EBCD) has been used to enable patients, families and practitioners to co-design improvement initiatives together, in partnership. EBCD allows participants to share their experiences of care through in-depth interviews, observations of group discussions. In this method of data collection patients, family members, and healthcare providers are brought together to explore the findings and identify areas for service improvement (Fucile et al., 2017).

A participative approach and the active engagement of patients and patient associations is central not only in the research process, but also in the therapeutic alliance. In precision medicine, and in many cases in RD management as well, treatment is recommended according to molecular markers, which predict efficacy before drug consumption, most of the time in the absence of population-based evidence. Consequently patient adherence implies the understanding of the biological evidence and of their implications and the acceptation to participate to a process which could be considered very similar to clinical research. This approach, which has higher chance of success and reduces the costs as compared with the traditional approach, faces the challenge of patient trust and attitude towards **risk aversion**. Patient, and more generally consumer , engagement is mandatory to overcome risk aversion and could be also mediated by patient associations. However, trust will be gained only if all other stakeholders are also engaged in the process, health care providers bringing relevant, understandable and unambiguous information, pharmaceutical companies transparently accounting for patient's needs and expectations for their R&D and pricing strategies, and payers being well aware of the social and individual actual values of new therapies.

Therefore, an adaptive legal and ethical framework is needed to allow research to **ensure the safe development of discoveries** without hindering their implementation. EU programmes should be coordinated with national priorities of national governments, setting out a joint strategy and action plan in consultation with all stakeholders (SPH, 2016). Such comprehensive research policy requires scientific leadership, continuity and broad consultation at a scale that takes full advantage of the European Research Area. A European Council for Health Research could be the next step in building health research for the next era. This Council would connect several European bodies with national bodies across ministries of health, science and innovation, with representatives of citizens and patients, and with public and private actors to solve existing fragmentation issues and optimize resource allocation (SPH,2018).

Do you want to know more?

Have a look at: Scientific Panel for Health (SPH). Building the future of health research. Proposal for a European Council for Health Research. 2018https://ec.europa.eu/programmes/horizon2020/sites/horizon2020/files/building_the_future_of_health_research_sph_22052018_final.pdf

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Trend #8: Facilitation of knowledge exchange and local care delivery through digital care

Digital health could optimise knowledge exchange and improve care delivery for rare diseases by allowing the pooling and combination of different types of data, from various sources and across countries. Rare disease populations tend, by definition, to be fragmented geographically. Patients very often live far from an expert in their disease, and whilst in the past this 'geographical lottery' has led to patients travelling (or even relocating permanently) to be closer to centres of expertise for their conditions, advances in digital solutions and e-Health are facilitating virtual care. The complex nature of rare diseases also often requires multidisciplinary expertise for optimal diagnosis, care and treatment.

Opportunities

A wider deployment of increasingly sophisticated eHealth tools will increase opportunities for expertise to travel rather than patients, wherever possible. It will also help accelerate diagnosis of rare and complex disease across national boarders by allowing experts from multiple disciplines to contribute to e-consultations In particular, the success of the European Reference Network's (ERNs) system for virtual consultations and review of complex cases – the Clinical Patient Management System (CPMS) – is anticipated to accelerate virtual knowledge exchange. The Panel of Experts identified the following trends:

- *Virtual care for rare and specialised conditions will be more efficient and more accessible than it is today, via the ERNs' CPMS and similar models**
- *Telemedicine tools will become more widely used and more important. The CPMS could be an inspiration for international eHealth and even involve AI, in time*
- *More opportunities are envisaged for patient participation to certain aspects of the ERNs' virtual reviews and consultations*

Complimentary to the wider use of e-Health tools to facilitate virtual care, experts predict more favourable digital healthcare *environments*:

- *There will be an increasing drive towards interoperable e-Health systems*
- *More potential to extract data from electronic health records*
- *There will be an increasing volume of healthcare data collected directly from electronic health records and an increased integration with other health-related data in national data hubs and EU digital space.*

A greater emphasis on the standardisation of different types of rare disease data will increase the power of that data exponentially, as data becomes more syntactically and semantically interoperable:

- *Greater tooling and resources to help doctors and researchers collect and use coded, computable phenotype data, leading to more accurate and more numerous diagnoses*
- *We will see a greater harmonisation in use of coding ontologies and more strategic and widespread use of standards and ontologies which are NOT specific for rare diseases.*

Additional opportunities stem from a greater volume of patient-generated (and citizen-controlled) data, which can be used to support more streamlined and personalised care. Rare disease patients visiting a range of specialists or non-specialists in their local care environments will foreseeably be able to provide more immediate access to their own health records, and share data from their personal health-related apps with practitioners:

- *E-health tools, such as personal health records, will lead to greater cooperation and more personalised local care*
- *There will be an increase in the volume of patient-generated data*
- *We will have more (and better) data on complex rare diseases, facilitated by medical devices (including tech, e.g. wearables)*
- *Increased portability of data and opportunities for people to access and maintain their own data and determine who can access it*

To fully realise the opportunities afforded by digital health, however, certain legal and policy-oriented challenges will need to be addressed:

Risks

A lack of interoperability in the data collected through different health systems could be a barrier to the wider exchange of this data for patient benefit. The rise in popularity of mobile applications and personal devices should result in a larger pool of health-related data, whilst making data more portable (particularly as more technology companies enter the digital health arena); however, concerns remain around ownership and access:

- *Patients may be less willing to donate /share their data if they are not certain who will own it and who will use it*

This risk could be alleviated somewhat if all data producers and publishers (patients, researchers, clinicians, companies, etc.) could commit to FAIR Data Principles: meeting standards of findability, accessibility, interoperability and reusability. Legislation and policies around the capture and use of data are also unlikely to be harmonised across countries, notwithstanding the General Data Protection Regulation (GDPR): for instance;

- *Countries will continue to diverge in terms of models of consent for clinical data sharing*

If opportunities are to be pursued and risks addressed, more human, technological and financial resources will need to be invested. The European Court of Auditors' recent evaluation of the implementation of the Cross Border Healthcare Directive suggests that better management is needed to deliver on the ambitions of this directive, which includes facilitating the exchange of patient data across borders.

Future trends identified by the Rare2030 Panel of Experts

Broader Health & Healthcare Trend: Facilitation of knowledge exchange and local care delivery through digital care

Trends	Drivers	Indicators	Time horizon	Outcome for the EU

The rising growth of digital health tools and market	• Exponential growth of IT Solutions and digital health tools • Opportunity to store, share and work on huge quantity of data	WHO "Monitoring and Evaluating Digital Health Interventions", 2016	Medium-long	• Speeding up research, increase treatment effectiveness and quality towards a more personalized approach • Increasing cross-border sharing of data and disseminating knowledge • Increasing patient empowerment and engagement in co-production of health • Redirecting interventions from hospital settings to people's homes • Improving processes of care and evaluation in healthcare • Reducing inefficiency and waste

Digital health and care referring to tools and services that use information and communication technologies (ICTs) to **improve prevention, diagnosis, treatment and management of health**. It encompassed several applications as **mobile health (m-Health), wearable devices, tele-health and tele-medicine, e-Prescription, Electronic Health Records (EHRs) and Personal Health Records (PHRs)**.

Digital health (or e-Health) is considered a worldwide **disruptive innovation** in healthcare aimed to improve **effectiveness, efficiency, accessibility, safety, and personalization** in healthcare services and systems. Its enormous potential could be seen at **health systems level** (i.e in supply chain management, priority setting and evaluation of programmes), **provider level** (i.e in supporting the decision-making process) and **patient level** (adherence to care, empowerment and self-management) (WHO, 2016).

The opportunity to collect and store a huge quantity of data as in the *European Platform on Rare Disease* (EU RD Platform) could help to **speed up the pre-clinical and clinical research**, to **develop diagnostic algorithms** (further helped by AI) and to deliver standards of care in a timely, "ready to use" way. Innovation as **Blockchain** as a way to safely share data between stakeholders could further aid the full realization of the potential of sharing health data allowing national and international medical consultation and avoiding the duplication of exams and procedures.

Digital tools can connect highly isolated patients, increase the sharing of workforce expertise as in the *European Reference Network (ERN)*, facilitate the access to specialized and high quality care in different settings, easing the effective development of the home-based care in a more integrated patient and person centered model of health service delivery.

Focusing on the m-Health, the mobile-health application (m-Health app) market has seen a remarkable increase in the last decade with over 100 000 m-Health apps estimated on the market in 2017 (European Commission, 2017) and 3.7 billion m-health app downloads worldwide (FDA, 2019). M-Health apps, texting with healthcare teams and the use of wearable devices could promote the **engagement of people** in the process of care and their **health self-management**. The support of m-Health in **behavioral change** and in the **adherence to therapy** is being widely tested in the management of chronic disease as cardiovascular diseases. Social media could also help to **identify risk behaviors** and could represent a useful tool to **promote health**.

Nevertheless this potential is strictly influenced by the **digital health literacy** of the users and by the appropriate training performed by healthcare professionals.

The fulfillment of digital health potential is strictly related to the **adequate planning** of e-Health policies and to the **availability and implementation of infrastructure** and technologies that allow to safely share useful digital health information. Appropriate and widespread (i.e both in urban and rural areas) **information systems** and **skilled personnel** able to safely manage data are crucial to ensure safety, efficacy, efficiency and equity in digital health opportunities.

Compliance with recent **data protection regulations** remains a central issue, especially in healthcare. Adding to this, collecting a huge quantity of **useless** data could **undermine trust of users** and patients posing relevant ethical and legal implications. Shaping digital health on users' needs strengthening their engagement in e-Health development could represent a relevant paradigm shift in the **e-health development: moving from technology-lead to citizen and patient-centred e-Health**. (ESPON, 2019)

The **costs of the implementation** of e-Health services and systems (not covered in the short-time) and the **lack of well-defined monitoring and evaluation approaches and tools** in the **analysis of the impact** of **digital health** are some of the most reoccurring issues in the field. Digitalized healthcare evaluation systems are insufficiently developed or non-existent often focused on analyzing changes in governments, providers and patients' healthcare expenditure (ESPON, 2019) and not in the efficiency of processes, access and quality of healthcare and life of users.

According to a recent public consultation on digital health conducted by the European Commission in 2017 in the framework of the *"Digital transformation of health and care in the context of the Digital Single Market"*, 81% of respondents believe that "sharing of health data could be beneficial to improve treatment, diagnosis and prevention of diseases across the EU" and 64% of respondents are in favor of developing a "cross-border infrastructure to pool access to health data and scientific expertise more securely across the EU" (European Commission, 2019). Since e-health legislation is not defined at the EU level, the cross-border application of e-health has to face with relevant heterogeneity in e-health policies, EHR systems and implementation stages in EU MS. EU policy has strongly increased policy attention aimed at support national and international actions that foster e-Health in EU MS and promote cross-border integration.

To enable the progress of e-Health across the EU, the European Commission has supported two relevant platforms: the *eHealth Network* and the *eHealth Governance Initiative* (eHGI) to provide coordination, structure and guidance on e-Health across the EU (ESPON,2019). The *e-Health Network Multiannual Work Program 2018-2021* has identified the empowerment of people in the management of their health, the appropriate use of health data to develop knowledge for healthcare policies and stakeholders, the continuity of care, the improvement of cross-border e-Health services and the implementation challenges as some priority areas to address. Another central initiative aimed at **facilitating digital standardisation and cross-border exchange** of healthcare data in EU is represented by *eStandards*, a collaborative project funded by the EU under Horizon 2020. *EStandards* produces guidelines for standardising EMR in EU helping in aligning and **improving interoperability** of data progressing the fulfillment of the digital health potential.

Do you want to know more?

Have a look at : ESPON 2020 Cooperation Programme "eHealth – Future Digital Health in the EU" Final Report Version 25/03/2019 Available at: https://www.espon.eu/eHealth

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WHO "Monitoring and Evaluating Digital Health Interventions", 2016

Trend #9: Increased potential for large sets of standardised and interoperable data

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, the range of symptoms observed, the development of the disease over time, and the likely outlook for newly-diagnosed patients. Therefore, the ability to share, pool, or at least query data from disparate resources, ideally across borders, is essential.

Opportunities

Rare disease patient data, especially if collected in a standardised form, takes on greater power to serve what may loosely be termed 'secondary purposes'. Therefore, the ability to pool or somehow link data from disparate resources -for instance registries, biobanks, electronic health records (EHRs) or diagnostic-related databases- is vital in order to advance knowledge, improve diagnostics, promote better care, and -crucially- stimulate and streamline research. The Rare 2030 Panel of Experts predicts several positive trends here, around understanding natural history and advancing diagnostics:

- *Greater tooling and resources to help doctors and researchers collect and use coded, computable phenotype data, leading to more accurate and more numerous diagnoses**
- *More widespread and pooled data from genome/phenome correlation studies will accelerate the pace of genetic diagnostics*
- *Better understanding of natural history of more rare diseases via global federated registries and from better use of unstructured data*

This last trend relates specifically to patient registries, which (depending on scope and design) can be an essential tool for epidemiology, natural history, comparing clinical outcomes, trial feasibility studies and planning, research, regulatory purposes, and more. More registries are anticipated in future, with greater disease coverage, and will foreseeably be implemented more strategically than in the past:

- *There will be more patient registries, collecting broader datasets and QoL information, which will illuminate more clearly the problems and needs of people living with a rare disease*
- *There may be a move away from centralised vast 'mega-registries' – we are more likely to see registries sitting within a wider data ecosystem of sources able to 'speak' to each other somehow*
- *We will see real and intensive use of data searching/finding via the EU RD Registry Platform*

One concept growing rapidly in prominence and importance in the rare disease field (and far beyond) is that of FAIR data: FAIR is an acronym for Findable, Accessible, Interoperable, and Reusable data (and metadata). Numerous activities and approaches contribute to making data more FAIR – two important pillars here are the use of syntactic standards (for data capture, structuring, transfer, etc), and the use of semantic standards (including ontological standards) to support greater semantic interoperability of data (in a nutshell, making sure that computers can *understand* the meaning of the data they receive, and can recognise synonyms for diseases and symptoms, for instance). As more data sources embrace the FAIR principles (or certain aspects of them at least) and health systems develop more interoperable, standards-based health records, many opportunities should emerge:

- *We will see a greater harmonisation in the use of coding ontologies and more strategic and widespread use of standards and ontologies which are NOT specific for rare diseases [this is important, to allow 'our' data in the rare disease field to 'speak' to data from the broader eHealth field]*
- *There will be more potential to extract data from EHRs*
- *There will be an increasing drive towards interoperable e-Health driven systems*

The developments predicted above will entail more collaboration with different communities. There should be greater opportunities for collaborative working via searchable aggregate data resources (or at least searchable metadata catalogues):

- *Increasing collaboration with actors from complimentary fields including eHealth, big data, omics, bioinformatics*
- *Open platform research (open science principles) could change the medicines development game significantly*

<u>Risks</u>

The Rare 2030 Panel of Experts anticipates larger quantities of patient-generated data, specifically:

- *Increase in volumes of Patient Generated Data*
- *We will have more (and better?) data on complex RD, facilitated by medical devices (including tech, e.g. wearables etc.)*
- *Continuation of the use of apps, mobile devices, and Patient Reported Outcome Measures (PROMs)*
- *Increased portability of data and opportunities for people to access and maintain their own data and determine who can access is*

These specific future-facing trends all represent ***opportunities***; however, to obtain full value from these sorts of data sources, some degree of interoperability with resources such as registries, biobanks, and EHRs will be necessary, which is an extra layer of complexity. The potential for data directly generated by patients to be able to 'speak' to broader sources is perhaps dependent (on some level) on the confidence of rare disease patients in the future use of their data:

- *Patients may be less willing to donate /share their data if they are not certain who will own it and who will use it*
- *Countries will continue to diverge in terms of models of consent for clinical data sharing*

Furthermore, despite the greater collaboration between different fields, a move towards more standardised and interoperable datasets will pose challenges in terms of skills and resources

- *There will likely be a shortage in data experts able to read/interpret/manage large quantities of data (requires a multidisciplinary knowledge)*

Future-facing specific trend identified by the Rare2030 Panel of Experts

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Broader Health & Healthcare Trend: Big Data

Trends	Drivers	Indicators	Time horizon	Outcome for the EU
The rising growth and importance of Big Data	● Exponential growth of digitised information ● The technological development of cloud-based IT solutions ● Opportunity for personalised diagnosis and treatment	The Data Monitoring tool	Medium-long	● Increasing treatment effectiveness and quality ● Widening possibilities diseases prevention ● Improving pharmacovigilance and patient safety ● Predicting outcomes ● Disseminating knowledge ● Reducing inefficiency and waste ● Improvement of cost-containment.

Table: based on Habl et al., 2016; Accenture, 2018

Big data can be described referring to the 3V model, which expresses the dimensional increases in data Volume as the quantity of data gathered, Velocity in relation to the time to be processed, and Variety as the type of data included (Beyer and Laney 2012). Further features as Veracity have been added, referring to the accuracy of data (Bellazzi, 2014). Specifically for the healthcare sector, big data involves collecting large datasets from various healthcare organizations followed by storing, managing, analyzing, visualizing, and delivering information for effective decision making (Senthilkumar et al., 2018). From the Digital Single Market strategy (2015), different initiatives took place till measuring the European data market (http://datalandscape.eu/). Moreover, different projects based on big data techniques have been founded, as in cancer, paediatrics and anesthesia (EC,2017). **Healthcare data is**

predicted to grow by 300% between 2017 and 2020 (Accenture, 2018). Researchers are dedicating attention to big data to translate findings into healthcare practices (EC ,2014). Indeed, the use of big data could reduce healthcare costs while improving disease management. The McKinsey Global Institute estimated that if US healthcare were to use big data creatively and effectively to drive efficiency and quality, this would reduce US healthcare expenditure by about 8%, saving nearly $200 billion each year (Manyika et al., 2011). Some emphasize that big data has the potential to improve disease management by delivering personalized diagnosis and treatment (Chawla and Davis, 2013).

Even if Big Data in healthcare could lead to many benefits as summarized in the introductory table (Habl et al., 2016)**, the exploitation of Big Data holds three main challenges.** First, shortage of people with the skills to take advantage of the insights coming from datasets (Manyika et al., 2011). Second, the fragmentation of the four categories of health data sets (Accenture, 2018): i) *Clinical Data*, including Electronic Health Records (EHRs), introduced by many EU countries, providing an abundance of data with potential value to clinical medicine; ii) *Self reported-data; iii) personal wellness data iv) Proxy data* ranging from Facebook likes and Instagram comments to location and environmental data. The integration of health data is further hindered by the lack of funding for data standardization, the unwillingness of healthcare organizations to share data between them, the poor harmonization and standardization of data and lack of methods for integrating high quality medical information with low quality self-reported data (Accenture, 2018). Third, there is a growing concern ***around privacy and security regarding sensitive personal health data and about the threat of an uncontrolled large scale commercialisation.*** As health data grows, so does the number of actors collecting, accessing and using information (eg. national governments, care providers, manufacturers, payers, patients and external innovators). Patients may fear that misappropriation of their health information could have negative consequences (Feldman et al. 2012).

The EU regulators will have to define who should own, access and use health data, and how these actors should be held accountable (Accenture, 2018). The EU has started to address both technical (harmonization and centralization of data) and ethical (confidentiality and security) challenges (Salas-Vega et al.,2015). Further, the EU data protection rules have changed in each country since the implementation of the General Data Protection Regulation (GDPR) of 2016, supported by the AEGLEs platform enabling business growth in big data analytics for healthcare http://www.aegle-uhealth.eu/en/aegle-in-your-country/the-campaign.html.

Do you want to know more?
Have a look at : "Digitalisation and Big Data: Implications for the health sector", held on 19 June 2018 at the European Parliament.

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The AEGLEs platform http://www.aegle-uhealth.eu/en/aegle-in-your-country/the-campaign.html
The Data Monitoring Tool http://datalandscape.eu/

Trend #10 : Rise in the use of AI for diagnostics, treatment and care, opening-up the potential of 'big data'

Artificial Intelligence (AI) holds potential to improve rare disease diagnostics and care, but also to accelerate and optimise therapy development (for instance by screening and selecting appropriate molecules to act upon specific biomolecular pathways and processes). One important question is what constitutes 'big data' in the rare disease field. Generally speaking, individual records (even clusters of records) relating to patient registration or electronic health records would fall short of the usual definitions. However, *linked* datasets, allowing federated access to many individual records or data entries, will hold more potential for analysis through AI. Other sorts of resources, such as sequencing datasets (for instance –omics data), next generation phenotyping techniques and compound screening databases, are more in-line with the classic definitions of big data.

Opportunities

The Rare 2030 Panel of Experts anticipates several specific future-facing trends of relevance here:

- *Increasing use of AI on datasets, for clinical care and research**
- *Artificial intelligence will enable rapid access to all types of information by non-experts (doctors will be able to access all relevant information at the click of a mouse - no misdiagnosing or inappropriate treatments)*

- *Artificial Intelligence will free-up doctors' time by handling routine activities, which could leave more time for specialists to develop knowledge and expertise*
- *We will see increasing collaboration with actors from complimentary fields including eHealth, big data, omics, bioinformatics*
- *Better digital biomarkers / endpoints / outcomes measures and real-time analytics (supported by machine learning)*

The potential for AI to support the identification of target compounds for rare diseases may be enhanced by the entry of less-traditional, 'disruptive' actors to the orphan medicinal product development space:

- *Less-traditional technology companies are going to enter the rare disease therapy space more and more, which may see new approaches to bringing drugs to market*

The Rare2030 Panel of Experts identified a particular benefit of AI, namely supporting more independent and autonomous living for people with rare diseases, through increasingly sophisticated aids:

- *Rise in assisted technology and supportive devices generally, particularly through Artificial Intelligence, to improve the quality of life for people with disabilities*

The potential of AI is dependent not only on computing power, but on the size of the dataset: the larger the dataset, the better the chances of detecting patterns and making accurate predictions. As data on rare disease patients is collected in a more systematic, standardised and interoperable manner (see separate trend 'Increased potential for large sets of standardised and interoperable data') the pool of data available for AI analysis will presumably grow:

- *We will see an increase in the volume of patient-generated data*
- *We will have more (and better) data on complex RD, facilitated by medical devices (including technology e.g. wearables etc.)*
- *There will be more potential to extract data from EHRs*

A related opportunity here could be the likelihood for data to become more portable, as citizens increasingly access -and indeed control- their own health records, and collect data through mobile health-related applications:

- *Increased portability of data and opportunities for people to access and maintain their own data and determine who can access is*

Such data could be pooled and become subject to AI analysis.

Risks

Data privacy concerns have traditionally been particularly relevant in the rare disease field. The use of AI in diagnostics, treatment and research is not widely understood by the general public, and it will be important to reassure citizens that contributing their data to any resource likely to undergo AI analysis (assuming these emerge) does not leave them vulnerable to exploitation or abuse. The Rare2030 Panel of Experts cautioned that:

- *Patients may be less willing to donate /share their data if they are not certain who will own it and who will use it (the concept of data ownership is difficult in the health sphere – perhaps 'lending' data is a better term)*

There is also a concern in some quarters that many rare disease datasets will remain too small or unconnected to allow AI to provide significant added value. Erroneous results (false positives and negatives) also raise obvious concerns.

Future-facing specific trend identified by the Rare2030 Panel of Experts

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Broader Health & Healthcare Trend: Big Data and Artificial Intelligence systems

Trends	Drivers	Indicators	Time horizon	Outcome for the EU
Rise in the use of AI and Big Data	Technological advancements	AI Watch, monitors AI as an emerging techno-economic segment (TES) based on capturing the entire emerging ecosystem	Medium-long	• Project: predict disease, identify high-risk patient groups, and launch prevention therapies • Produce: automate and optimize hospital operations, automate diagnostic tests, and make them faster and more accurate • Promote: predict cost more accurately, focus on patient risk reduction • Provide: adapt therapies and drug formulations to patients, use virtual agents to health them navigate their hospital journey

Table: based McKinsey Global institute Analysis (2017); Annoni et al. (2018)

Presented by the European Commission (EC) as one of the most strategic technologies of the 21st century, AI refers to systems that mimic intelligent behavior by analyzing their environment and taking actions with some degree of autonomy to achieve specific goals. AI-based systems can be software-based, acting in the virtual world as in the case of voice assistants, image analysis software, search engines, speech and face recognition systems, or be embedded in hardware devices, including advanced robots, autonomous cars, drones or Internet of Things applications (EC, 2018a). Given its capabilities, AI has been applied in medicine since 1950s when physicians made the first attempts to improve their diagnoses using computer-aided programs (Frankish and Ramsey, 2014). Nowadays, AI devices for health care fall into two major categories. The first includes machine learning (ML) techniques that analyse structured data such as imaging, genetic and EP data to cluster patients' traits, or infer the probability of the disease outcomes. The second category includes natural language processing (NLP) methods that extract information from unstructured data such as clinical notes or medical journals to supplement and enrich structured medical data (Jiang et al., 2017). In this regard, the data mining of the electronic medical records could led to the automatic creation of disease registries, raising questions about the future of the current traditional registries.

Many activities related to AI are taking place in the EU under the Digital Single Market Strategy. In April 2018, the EC put forward a **European approach to AI** in its communication "Artificial Intelligence for Europe" (EC, COM(2018) 237 final). The communication is **based on three pillars**: i)Being ahead of technological developments and encouraging uptake by the public and private sectors ii) Prepare for socio-economic changes brought about by AI iii) Ensure an appropriate ethical and legal framework. Overall, the EC is developing strong approaches in AI, high performance computing, data analytics, which can help design and test new healthcare products, provide faster diagnosis and better treatments (EC, 2018b). Even if AI is applies to almost all economic sectors, no official statistics are available, escaping traditional industrial and product classifications. However, The EC through the AI Watch, monitors AI as an emerging techno-economic segment (TES) based on capturing the entire emerging ecosystem. As presented in the EC report on Artificial Intelligence of Annoni et al. (2018), EU is among the geographical areas with the highest number of players active in AI (25%), just behind US (28%) and ahead of China (23%).

AI has the potential to transform health care by performing clinical and business tasks currently carried out by humans with greater speed and accuracy using fewer resources. AI expected to improve the accuracy, precision, and timeliness of patient diagnoses, which could increase therapeutic success rates and decrease unnecessary medical interventions (Deloitte, 2016).

According to LEK Consulting (2018), Europe has **to overcome six barriers** before exploiting AI: i)Support to practitioners - AI companies need to recognize that practitioners will have more leveraged, demanding and tiring roles and have to help providers offer support to practitioner; ii) Demonstrate the clinical and economic benefits before deployment of AI technology; iii) Identify and secure access to core data sets; iv) Promote compliance with data protection and privacy requirements; v) Co-develop tools with clinician leaders to avoid regulatory pitfalls in the future – Developers need to avoid that AI technologies become a "black box" resulting in key algorithms not being subjected to rigorous peer review or scientific scrutiny; vi) Work with regulators and payers to develop liability management frameworks. The assignment of legal responsibility when an AI application in healthcare and in all industries is still a novel concept to address. If a patient is incorrectly triaged by an AI system, who is at fault? The developer, the partner provider or the AI system? The EU should have a coordinated approach to make the most of the opportunities offered by AI and to address the new challenges. In this sense, EU can leverage on World-class researchers, labs and startups, Digital Single Market and its common rules and on the wealth of industrial, research and public sector data (EC, 2018a).

Do you want to know more?

Have a look at: Jiang F, et al. (2017). Artificial intelligence in healthcare: past, present and future. Stroke and Vascular Neurology doi: 10.1136/svn-2017-000101

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Trend #11: New technologies and advanced therapeutics

Given the fact that only ca. 5 % of rare diseases have any dedicated therapeutic intervention, there are high hopes for technological advances and the launch of advanced therapeutics (with potential to actually become curative, in some cases). Technologies such as CRISPR and Gene Editing hold particular potential for the rare disease field, given the fact that approximately 85% of all conditions classed as rare have a genetic origin.

Opportunities

The Rare 2030 Panel of Experts anticipates a definite trend in terms of the *volume* of new technologies and therapies for rare diseases:

- *We will see more launches of advanced therapies and devices**
- *Increasing emergence of gene therapy and advanced therapies*

An important precursor for the future availability of new technologies and the development of advanced therapeutics in the rare disease field is an increased understanding of the conditions themselves. It is necessary to understand the mechanisms behind developmental, functional and degenerative rare diseases better than hitherto, to be able to develop more personalised therapies demonstrating greater efficacy and fewer side effects. Understanding of the pathology and of the natural history increases the likelihood of selecting appropriate candidate molecules and therapeutic interventions to act upon the pathways responsible for the patient's particular presentation : hence the crucial importance of stimulating basic research.

In this respect therefore, the anticipation of a greater volume of more interoperable (e.g. FAIR-compliant) rare disease patient data should be considered a facilitator for this overarching trend:

- *Better understanding of natural history of more rare diseases via global federated registries and from better use of unstructured data*
- *Greater tooling and resources to help doctors and researchers collect and use coded, computable phenotype data, leading to more accurate and more numerous diagnoses*

When it comes to searching large volumes of data, for instance when screening for potential compounds, Artificial Intelligence (AI) may hold particular benefits for the rare disease community. Indeed, the Rare 2030 Panel of Experts predicts that even for conditions which will *not* benefit from advanced therapies such as CRISP and gene therapy, future technologies could support assisted living:

- *Increasing use of AI on datasets, for clinical care and research*
- *There will be a rise in assisted technology and supportive devices generally, particularly through Artificial Intelligence, to improve the quality of life for people with disabilities*
- *We will continue to see limitations in the interventions we have for RD - some conditions will never have a gene therapy. There will be more emphasis on creating smarter technological tools and devices to alleviate disabilities and support patients*

To develop new technologies and advanced therapeutics will likely entail greater inter-sectoral collaboration:

- *There will be increasing collaboration with actors from complimentary fields including eHealth, big data, omics, bioinformatics*

Specific trends identified by the Panel of Experts concerning innovative ways of conducting and funding research should also create new opportunities here, and support a 'paradigm shift' around therapy development:

- *Open platform research could change the medicines development game significantly*
- *Less-traditional technology companies are going to enter the rare disease therapy space more and more, which may see new approaches to bringing drugs to market*
- *Patients will continue to drive innovations in rare disease devices, therapies, and aids to everyday living*

However, it is likely that new technologies and advanced therapies will need to demonstrate their value more clearly than ever before:

- *There will be a drive towards performance-based approvals and access models, with reimbursement based on clinical outcomes (clinical and social values)*

<u>Risks</u>

Despite the promise of technologies like CRISPR and gene editing, the ethical concerns for the rare disease community are significant (e.g. human augmentation, as opposed to treatment or prevention of disease).

Despite the expectation of more advanced therapies in the future, the Rare 2030 Panel of Experts identified concerns that without significant external intervention (for instance a dramatic change in the Orphan Drug legislation):

- *areas which already attract pharma attention will continue to be the focus of R&D, thus increasing the gap between disease areas with therapeutic options and those without [leading to greater inequalities for patients]*

There are also risks that as advanced therapies target specific mutations and pathways, the orphan medicinal product concept will become increasingly irrelevant and investments will focus more on the rarer indications of more common conditions (for which there are likely many licensed therapies already)

- *We may see a growing dilution of the concept of a 'rare disease' as common conditions are broken down more and more and personalised medicine becomes more popular and widespread*

At the same time, of course, there should be an opportunity to show that rare diseases can pave the way for a new management paradigm of common diseases through personalized medicine

Future-facing specific trend identified by the Rare2030 Panel of Experts

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Broader Health & Healthcare Trend: Innovation in Medical Knowledge

Trends	Drivers	Indicators	Time horizon	Outcome for the EU
Innovation in medical knowledge	New technologies	R&D investments	Medium-long term	Better, safer and more sustainable health

Table: Rare2030 Own elaboration

The development of new technologies as biotechnology, nanotechnology, combined with exponentially growing ICTs (NBIC) would become the major driver of 'socio-technological paradigm shift', described as the shift from ICT (1970-2010) to intelligent technologies (2010-2050) (Finland Futures Research Centre - 2012). In line with this, the EC working document "Preparing the Commission for future opportunities" contains the identification of six potentially transformative trends in health and bio-tech, resulting from nanotechnology, biotechnology and life-science, ICTs, cognitive sciences and neuro-technologies:

- *Personalised medicine*: it is defined as a medical model using personal health data and molecular profiling to "tailor the right therapeutic strategy for the right person at the right time, and/or to determine his or her predisposition to disease and/or to deliver timely and targeted prevention". The BOHEMIA Scenario "Precision medicine" describes a likely future scenarios and identifies associated priority directions for EU research and innovation.
- *Regenerative medicine and tissue engineering*: is a new approach, developed from the discoveries in the stem cell field, to offer treatment based on replacing damaged or diseased tissue or on stimulating the body's own regenerative capacity. The BOHEMIA Scenario "Human Organ Replacement" describes a likely future scenarios and identify associated priority directions for EU research and innovation.

- *Prosthetics and body implants* concerns the opportunity opened by knowledge on tissues, biocompatibility of materials, biological processes and IT to create prosthetic implants for more human body parts. The EC report foresees that by 2030 more than half of the body can be replaced.
- *Human enhancement (HE):* it relates to the use of prosthetic implants or medical devices that performs more than natural organs. As example, the connection between nerves-IT-interfaces could allow to develop "augmented reality".
- *Synthetic biology* aims to "deliberately design and construct novel biological parts, devices and systems to perform new functions, e.g. new microorganisms to produce antimicrobials and other pharmaceuticals or fine chemicals". The EC report estimates that by 2030 globally around 50% of all pharmaceuticals will be produced on basis of biotechnology/synthetic biology approaches for a global market value of more than € 500 billion.
- *DNA fingerprinting and personal genomes DNA sequencing*" is projected to increase either in combination with, or as a replacement for non-sequencing techniques like traditional DNA fingerprinting techniques.

The development of this knowledge opens a world of opportunities and promises to deliver better, safer and more sustainable health and care to European citizens. The convergence of new health technologies and new analytical tools of information technologies is held by some to be transforming our current 'reactive model of medicine' (the cure and care of the patient), based on limited data, and 'population-based' statistics and averages to a preventive, predictive, personalised, and participatory medicine.

On the other hand, such medical advances raise questions of ethics and fairness and it is now the time for governments to commission the development of ethical guidelines with input from scientifically and medically trained professionals as well as ethics experts and citizens (STAC, 2014). The above mentioned discoveries if not properly regulated can exacerbates the existing tensions regarding class disparities, privacy protection, and cultural threats (Anton, Philip S., 2001). In addition, from a global perspective, health care systems in high income countries make extensive use of technologies, whereas people in the world's poorest countries often lack of the most fundamental drugs and devices (FRESHER, 2014). Medical innovations is one of the key drivers of healthcare spending and the economic crisis urges health systems to look for those disruptive innovations and frugal technology able to make health care effective and sustainable. In 2009, total global investments in health R&D (both public and private sector) reached US$240 billion. Only about 1% of all health R&D investments were allocated to neglected diseases in 2010. Diseases of relevance to high-income countries were investigated in clinical trials seven-to-eight-times more often than those neglected diseases whose burden lies mainly in low-income and middle-income countries. (Røttingen J.A., 2013). The burden of chronic diseases is raising very fast in low income countries too. Since the low and middle income countries represent the majority of the world population, a main issue will be how to spread the benefits of the new technologies in the low and middle income countries too.

Do you want to know more?

Have a look at : "Preparing the Commission for future opportunities" https://ec.europa.eu/digital-single-market/en/news/looking-future-digital-technologies

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Trend #12: Application of Whole Genome Sequencing from the research to the clinical sphere

Given that the vast majority of rare diseases are genetic in origin, advances in the technology around Next Generation Sequencing (NGS) offer significant promise for unravelling the epidemiology of these conditions. Obtaining an accurate diagnosis has traditionally been very challenging for many people with a rare disease – but as the science advances, and the *accessibility* of techniques like Whole Genome Sequencing (WGS) increases, more patients will receive accurate genetic diagnoses. Traditionally, WGS was available only through research projects and innovative funding streams; increasingly, however, it is being applied to more routine clinical practice, as a diagnostic tool but also as a route to more personalised and targeted medicine and treatments. As WGS develops, it is likely that the number of RD will continue to rise significantly, particularly as collaborative (European and global) initiatives seeking to diagnose the undiagnosed reach full strength. It is likely that this will deeply impact our perception of the field and the disease management approaches, raising new challenges, especially with regards to the organization of health care pathways.

Opportunities

The emergence of WGS as a diagnostic tool has had a particular impact on the rare disease field. The ability to sequence the human genome has led to the 'discovery' of new diseases, which were previously undiagnosable. An important prerequisite for the diagnosis of many rare conditions is the ability to link large scale -omics (e.g. genomics or metabolomics) data with 'deep' phenotype data. As clinicians, researchers, bioinformaticians and data experts collaborate more closely to make -omics and phenotypic data shareable, the future seems positive for diagnostics: the Rare2030 Panel of Experts highlight the continued boost to genetic diagnostics in the RD field:

- *More widespread and pooled data from genome/phenome correlation studies will accelerate the pace of genetic diagnostics**
- *Greater tooling and resources to help doctors and researchers collect and use coded, computable phenotype data will lead to more accurate and more numerous diagnoses*

- *We will see a greater harmonisation in the use of coding ontologies and a more strategic and widespread use of standards and ontologies which are NOT specific for RD*

A greater application of WGS to the clinical sphere is anticipated (although the Panel of Experts does not expect a complete overhaul of the traditional system of diagnostics in all European countries over the next decade or so):

- *Decreasing cost of genetic testing/genomic sequencing*
- *Next generation sequencing will increasingly be utilised for diagnostics, but it will not become truly 'frontline' [not everywhere, at least in our timescales]*

A major opportunity associated with this trend is the growth of personalised medicine. As a patient's unique genotype and phenotype are better mapped and understood, the hope is that not only will treatment plans become more tailored (with fewer side effects), but more emphasis will be placed on *preventing* symptoms from developing at all (for instance in the case of asymptomatic carriers or people genetically predisposed to develop a disease in future):

- *Preventative, pre-symptomatic therapy will become more commonplace*
- *Care will not only focus only on patients but also increasingly on healthy mutation carriers*

NGS techniques also have a major potential in the field of preconception and prenatal diagnostics and screening: as WGS is increasingly introduced into the clinic, would-be parents will foreseeably have greater reproductive choice than ever before (raising a host of complex ethical, legal and social issues):

- *Prenatal screening and preconceptional screening will continue to become more popular and widespread, resulting in more disease prevention*

Risks

The Rare2030 Panel of Experts is somewhat sceptical about the prospects of embedding NGS seamlessly into the clinical sphere, at least for most European countries:

- *Clinical services for next generation sequencing diagnostics will continue to be underfunded for the roles they are increasingly expected to play, especially compared to research*

One key challenge is the perceived inadequacy of the skills and training of the current diagnostics workforce to cope with the increasing application of NGS to the clinical sphere:

- *There will likely be a shortage in data experts able to read/interpret/manage large quantities of data (which requires a multidisciplinary knowledge)*

For example, one of the most difficult aspects of utilising WGS for diagnostic purposes is the ability to interpret the findings and determine which variants are pathogenic etc. There is little expectation that these challenges will vanish in the near future:

- *The accuracy of diagnosis and interpretation of findings resulting from next generation sequencing will remain challenging*

The ethical, legal and social issues associated with NGS make it essential for those seeking and obtaining a diagnosis to have access to specialised professional support, for instance in the form of genetics counselling. Again, the likely shortfall in such expertise could pose challenges to the application of sequencing to the clinical sphere. More broadly, however, a robust ELSI framework to support this change is absent in most countries. Logistically and operationally speaking, countries are likely to implement NGS to the clinic at varying paces, which could adversely affect many patients:

- *Some of the disparities in terms of RD diagnostics, treatment and care might get bigger between countries and within countries*

Moreover, this heterogeneity in ability to access NGS through mainstream health services may lead to more patients contacting sequencing companies and private laboratories directly:

- *Patients will increasingly take a more hands-on role in the search for a diagnosis*

This could place people at greater risk of exploitation, but could also deprive vulnerable individuals of the need for expert counselling and support to help them deal with the results they receive.

- *Lack of regulation in genetic testing will continue to place sensitive data in the hands of big companies*

All text in italics represents specific future-facing trends identified by the Rare2030 Panel of Experts

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Broader Health & Healthcare Trend: Genomics

Trends	Drivers	Indicators	Time horizon	Outcome for the EU
Genomics potential and applications	• Technological advancements in genomic sequencing • Application of big data in genomics	• Cost of genome sequencing • Value market for Next Generation Sequencing (NGS)	medium-long	• Better prevention, diagnosis management of genetic diseases and other medical diseases • Higher rate of treatment success • Access to personalized treatment • Cost savings

Table based on: Stark et al. (2017); Calzone et al. (2013); PWC (2019); Cardon and Bell (2001)

According to the World Health Organization definition, Genomics is the study of genes and their functions, and related techniques in order to identify their combined influence on the growth and development of the organism. Since many diseases are caused by alterations in genes (Jackson et al., 2018), completing DNA sequences and performing genetic mapping can help understand them by spotting abnormal alterations in genes (Koboldt et al., 2013). Genomic information and technology are recognized to have the potential to improve healthcare outcomes, quality, and safety, and result in cost savings (McCormick and Calzone, 2016). Various **EU countries have plans to sequence the genomes** of large numbers of their citizens, as they are launching

national personalised medicine programmes or initiatives based on genomics to improve the diagnosis and prevention of human diseases, from (rare) monogenic syndromes to cancer (EC ,2018). This effort is confirmed by the Declaration of Cooperation "Towards access to at least 1 million sequenced genomes in the European Union by 2022", signed by 13 European countries, underlining their commitment to share and combine this accumulated knowledge on genomic information. Thus, its integration into population-level health initiatives requires a strategic approach for ensuring efficiency, effectiveness, ethics, and equity. Therefore, there has been a call for the cooperative development and harmonization of policy on genomics in healthcare between 28 of the EU member states and Norway (Mazzucco et al., 2017).

Moreover, it is necessary to consider that the **cost of whole-genome sequencing has fallen** in the last years with evidence of cost-effectiveness compared to that of traditional care (Stark et al. 2017). The Europe market of the Next Generation Sequencing (NGS), which is a novel procedure for sequencing genomes at low cost and high speed, is expected to reach US$ 7,685.4 Mn in 2025 from US$ 1,633.4 Mn in 2017. The market is estimated to grow with a Compound Annual Growth Rate of 21.4% from 2018-2025. The growth of the NGS market is primarily due to technological advancements in sequencing and an extensive use of genomics for medical applications (Insight Partners, 2019). **Information generated by genomics can provide benefits in the prevention, diagnosis and management of communicable and genetic diseases** as well as other common medical diseases, including cardiovascular diseases, cancer, diabetes and mental illnesses (Cardon and Bell, 2001). Early diagnosis of a disease can increase the chances of successful treatment, and genomics can detect a disease before symptoms present themselves. This opens to new possibilities in clinical diagnostics and other aspects of medical care, including disease risk, therapeutic identification and prenatal testing (Calzone et al., 2013). Moreover, advanced research into genomics together with proteomics, the study of the proteins that genes create or express, has accelerated the understanding of individual differences in genetic makeup, opening the door to a more personalized medicine, as "the right treatment for the right person at the right time" (PWC, 2009). Medical research on genomics is based on the **analysis of big databases** containing medical data on people, as electronic health records (Korane, 2011). However, these datasets are often fragmented between different countries and institutions. Therefore, aggregating data could develop knowledge databases, and in turn improve diagnosis and treatment (Global Alliance for Genomics and Health 2016). In the EU, large-scale data sharing of genomic health data is not yet allowed due to strict national regulatory frameworks, calling for solutions to enable federated data analysis (Lawler et al., 2017). Other challenges relate to the lack of competences of health professions. For this matter the European Society of Human Genetics has agreed on a set of competences for practitioners providing a framework for genetics education of health professionals (Skirton et al., 2010).

Do you want to know more?

Have a look at: "Birney E., Vamathevan J. and Goodhand P. (2017). Genomics in healthcare: GA4GH looks to 2022, https://www.biorxiv.org/content/biorxiv/early/2017/10/15/203554.full.

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