Rare 2030

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

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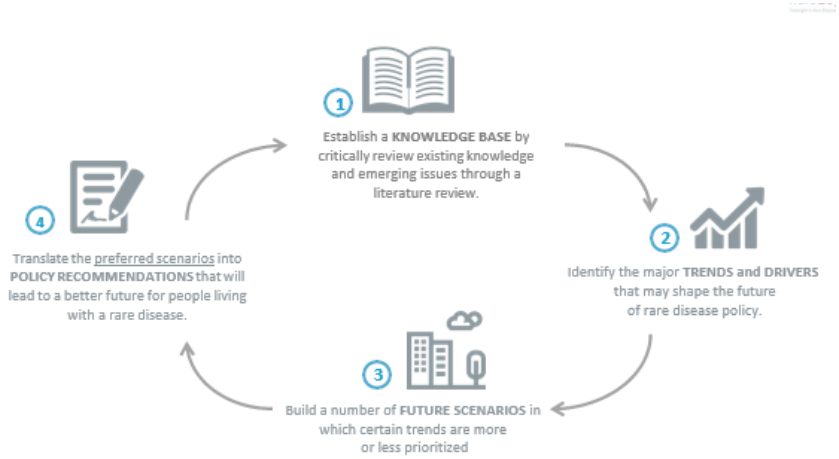
Executive summary

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 8 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 and the Research Advisory Board 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, represented by the core part "horizon scanning phase" of the report, the Consortia intended to investigate which changes have played a key role in shaping our present. In this regard, Rare2030 has consulted experts, including the member the Research Advisory Board, 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

Insights from the Research Advisory Board

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. In addition to conduct the desk research and consult the Panel of Expert, the project team has carried out eight semi-structured interviews with the representatives of the Research Advisory Board (RAB). The ideas behind was to complement subject-matter expertise from specialists with broader knowledge from key opinion leaders who are "intensely curious but sharp observers, who understand the way the world works and have their finger on the pulse of the change" (K. van der Heijden 2002)[1].

To gather strategic insights, ISINNOVA has adopted the 7 questions interview technique which originates in the work of the Institute of the Future and has further refined by Shell and ICL[2]. The interviews were held on-line by ISINNOVA and EURORDIS, took approximately 40 minutes and were composed by the following seven questions:

1. *Meet a clairvoyant*. If you could speak someone from the 2040 who could tell you anything about Rare Diseases governance and treatment, what would you like to ask?
2. *Optimistic but realistic outcome.* If things went well, how would you expect the governance and treatment of RDs to develop in the next 20 years and what would be the signs of success? what is your vision?
3. *A pessimistic outcome*. What are the dangers of not achieving your vision? How could the environment change to threaten RD governance and treatment?
4. *The internal situation.* From your knowledge of the RD system organization and resources, which are the priority changes to make your vision a reality?
5. *Looking Back*. Looking back at the past 10/20 years, are there particular lessons – successes, failures – we can learn from?
6. *Looking forward.* What major decisions with long term implications are faced at the moment? What needs to be done now to ensure that your vision becomes a reality? Please take into account the following PESTLE categories: Political; Economic; Societal – cultural; Technological Legal/Ethical; Environmental
7. *The Epitaph.* If all constraints were removed and you could direct what is done, what would you do?

After the calls, the interviews scripts were sent to the participants for final review. It is important to note that the work was direct to gather personal reflections from key opinion leaders that could offer interesting insights for enriching and validating the systematic analysis

[1] Van der Heijden K. et al (2002) "The six sense: accelerating organizational learning with scenarios". New York: Wiley
[2] Government Office for Science (2017) "The Futures Toolkit - Tools for Futures Thinking and Foresight Across UK Government"

conducted by the project team. Among the lessons learnt, the experts mentioned:

- "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"
- "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 patient"
- "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"
- "We have been able to create a great multidisciplinary collaborative spirit involving patient associations"
- "We 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".
- "ERNs was a success for RD community but the fact that the ERNs are divided by disease opens the doors to a possible competition for funding among disease's areas"
- "There have been action plans but, perhaps, there has been too little commitment to put them into practice and maybe too little oherence in the action plans in different countries. Also, there is not enough pressure from EU level. There are not enough checks on what is written in the action plans"

When asked to look forward, the experts highlighted the following trends and paradigm shifts as key for the future of RD policies and strategies:

The trend	Type of trend
Economy of well-being: healthy Europe – sustainable health system	Economic and political
Gene therapy and gene editing and correspondent ethical problem of "Super" Humans – human augmentation	Technological and Ethical
Moving from technology push to responsible innovation	Technological
Standardized data and data sharing	Technological and Ethical
Patient centeredness in health-care delivery	Socio-cultural and Political

Networks in Europe and at world level	Political
New ways and incentives collaboration between researchers	Socio-cultural
The need for new concept framework for RD	Political
New technologies, innovations , AI, Machine learning	Technological and Ethical
Solidarity as value is at risk due to the rising intolerance	Social and Economic
Increased inequalities in treatment	Economic
Stronger advocacy	Socio-cultural and Political
Aging population	Socio-cultural

The insights gathered in these conversations were all taken into account in the drafting of the factsheets contained in the following section "Rare 2030 Horizon Scanning – Emerging trends". In addition, The interviews – reported as confidential in the Annex I - are highly inspiring and will be used, in the course of the project, to illustrate the possible different perspectives on strategic issues and choices.

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*

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*

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*

Opportunities

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*

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.
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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*

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*

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/

Full reference available at:

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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*

Risks

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*

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*

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*

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 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*

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*

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*

<u>Risks</u>

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*

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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Annex I Key Opinion Leader Interviews

Terkel Andersen

Bios

Terkel Andersen was elected President of EURORDIS-Rare Diseases Europe in May 2003 and has been a member of the EURORDIS Board of Directors since 1997, when the organisation was founded.
A person with haemophilia himself, Terkel has broad experience in disability and health issues becoming involved in the rare disease field in 1983 when he joined a Nordic project on the mapping of problems related to rare diseases. Terkel served as president of the Danish Haemophilia Society 1985-2017. He was one of the founders of the Danish Alliance of Rare Disorders in 1986 and worked as the first Executive Director of the Centre for Rare Diseases and Disabilities of the Ministry of Social Affairs in Denmark from 1990 to 2001. From 1992 to 2002, he served on the executive board of the World Federation of Hemophilia; and from 1993 to 1999, he was chairman of the European Haemophilia Consortium. In his professional capacity Terkel worked with the Danish National Council for Volunteering until October 2018. Terkel represents EURORDIS at International Conferences throughout Europe and beyond.

Interview transcript 27 September 2019

1. **Meet a clairvoyant. If you could speak someone from the 2040 who could tell you anything about Rare Diseases governance and treatment, what would you like to ask?**

Well. I think one of the big questions that we would like to ask in the future would be, “whether inequalities have either been reduced throughout Europe or, if , on the contrary, the developments in science and therapies would have the consequence that inequalities in treatments would have increased?” So, more what kind of impact technology improvements have made and if they would be for the benefit of most or only to selected, more privileged part of the European population. Now this is that European perspective, of cause. That would be other questions if we take a more global perspective.

2. **Optimistic but realistic outcome. If things went well, how would you expect the Rare Disease Governance and treatment to develop in the next 20 years and what would be the signs of success? what is your vision?**

Well, 20 years is not such a long time… not when we talk about developmental therapies. So would probably be quite happy if we could say by 2040 that most significant proportion of people living with rare diseases would have access to therapies with a significant impact on the quality of life. At this point, I believe the general opinion is that it's around 5% of rare diseases which have access to any kind of therapy and treatment. Very few of them being curative. I would expect that number, that proportion would increase significantly over the next 20 years. But I think it's being too optimistic to believe that 20 years is enough to reach out to more than perhaps, 10 to 20% of rare diseases with therapies at that point. But it would be also a major step forward if we could have therapies at least for a large part of those, 390 rare diseases, which represent the 98% of the population of rare diseases. According to the recent study by Anna Rath (INSERM) and others, so, to triple or quadruple the number of diseases with access to quality treatment, with a significant impact on survival and on quality of life functionality, that would be a fairly ambitious undertaking but not absolutely unrealistic outcome.

3. A pessimistic outcome. What are the dangers of not achieving your vision? How could the environment change to threaten RD governance and treatment?

Development of therapies goes relatively slow. However, we can envisage that a large number of diseases can be diagnosed. What we would see probably in the next two decades would be an increasing frustration about the fact that you have more and more knowledge about individual rare diseases at hand but still a long way to access adequate support and therapies. The ability to diagnose which in itself is a positive thing, but also creating the sensation that it's going to be difficult to translate this knowledge into therapies.

The screening itself would mean that in some countries it might not be welcomed that people have children with rare diseases. There might be increased pressure on families to terminate pregnancies if at risk of having a child with a rare disease, perhaps mostly outside of Europe, but also inside Europe.

Giovanna Giuffrè: Yes, yes. Especially, there is a stress on a technology advancement in medicine, but also on social, how people react to. So how is the perception and ethical changing or how we will face the information we will be able to have in the future and how much our ethics is going, is growing or so. When they think that sometimes we have too much to deal with them. There is no so much growth in the social, the speed of technology. So there are these two aspects that can pose risk, can be opportunity but can be risk depending of what we'll do.

Terkel Andersen: Exactly. And in the years up till now, we have seen an increasing individualisation and I'm not so sure that we could not risk at some point to have rare diseases pinpointed as an individual responsibility. An increasing challenge but also problems to health care pockets. And that solidarity in health might be become an issue, increasing the pressure on families with rare diseases to try to avoid having children with the rare diseases, instead of pushing for a generalized access to those treatments, which gradually will become available.

4. The internal situation. From your knowledge of the Rare Diseases system organization and resources, which are the priority changes to make your vision a reality?

It requires that we invest much more in creating cross border collaboration on rare diseases. The European Reference Networks has of course become a major hope for realizing a vision of sharing knowledge and new improvements, as quickly as possible. And to develop even more knowledge about rare diseases through the sharing of data and case studies. So, no doubt that by this, that will mean a tremendous increase in the knowledge about rare diseases and to the understanding of the different phenotypes of individual rare diseases. The Reference Networks will give an enormous contribution to a more ready [inaudible] access to therapies and support. However, there is a need to invest in this infrastructure and to make it possible to improve it to the level where it actually is seen and considered as an assistance in daily care. And I think at this moment, that's one of the priorities of course, to make sure that that kind of support is provided in a collaboration between the European Union and Member States. It is essential for the Member States to really understand that they need to follow up on their national plans and to make sure that the infrastructures, which give so much promise, can actually become workable. That's one thing we need, The European Commission to push member States towards editing the national plans, and making sure that the national plans for rare diseases are also embedded into the national health strategies in general. And that probably means that we will have somehow to sort of reread the whole idea about how to change the rare diseases practice across Europe. So that's one of the things that we could hope for in the future, that we will have a multifaceted a new set of recommendation from the European Health Council to make sure that we create a common vision across Europe for policy development on rare diseases. Not only including the health issues, but also including social issues. How to create models to make sure that we actually can minimize the divergencies which would otherwise emerge between more wealthy healthcare systems and less fortunate member States with less funding for more new therapies.

We also see in these years tremendous partly patient led strive for more collaboration at the international level. And there is of course a lot to be gained from that. Taking advantage of the level of science in all the parts of the world. So increased international collaboration is of course important. And holds the promise of innovative approaches to data collection also on an international scale which could have promising perspectives and opportunities for future generations.

5. Looking Back. Looking back at the past 10/20 years, are there particular lessons – successes, failures – we can learn from?

Terkel Andersen: 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.

Giovanna Giuffrè: Yes. And the economic crisis, a lot of health care system in reducing some service that they mentioned can also impact. Looking back, just the question I want to ask especially to you for your experience and advocacy because something that was mentioned in different teleconferences was the change of generation. So, about the new generation of advocacy or person involvement, the rare disease fields, what you especially would suggest to them based on all your work and commitment. What do you think? Like if you could say some words for what they should be careful on what they should be more attentive. What, because it seems that there is a moment of change of somehow the working and the generic degeneration days come

Terkel Andersen: My hope would be that young people with rare diseases would get involved and voice their hopes for a better future living with rare diseases as we are seeing actually in many of the member States and the national organizations. So, the fact that actually patients with rare diseases raise their voice and use the tools that now becoming available for sharing knowledge on the internet, using social media, creating forums, where they actually not only contribute, but actually take possession of development of things. And I think one of the very important tools is to make sure that data collection is done with the active involvement of patients and in a way to demonstrate the impact and added value of this on implementing new therapies and new approaches. Also, psychosocial, in a way to improve quality of life. So, to improve our knowledge about how these things actually can make a difference for people, put faces to it and tell the stories is one of the ways to make sure that we do what is ethically correct.

6. Looking forward. What major decisions with long term implications are faced at the moment? What needs to be done now to ensure that your vision becomes a reality? Please take into account the following PESTLE categories: Political; Economic; Societal – cultural; Technological; Legal; Environmental

If I could start from behind the ethical and cultural aspects which are significant when we talk about rare diseases… People living with rare diseases as well as some groups have already experience in being first movers, you might call it, when it comes to integrating new technologies and new possibilities in medicine, and to deal with new difficult ethical choices. And I hope that in the years to come there will be a growing understanding of the fact that there is a great burden on the shoulders

of the community of people living with rare diseases to actually discuss among themselves and with society on how actually to both embrace what are the promising steps forward in science and technologies and also to make sure that this community has sufficient support and guidance and also room and time is given to the individual patients and their communities to grasp and cope with what will become very difficult issues when it comes to gene therapy and use of technologies which may not only impact your own generation, but also future generations. Like seen with CRISPR. And all the difficult choices about accessing knowledge at a point where you may not actually have access to therapies. But also, in the future that the right to know also means putting ourselves into very vulnerable positions where there will be a growing need to make sure that people are integrated into a peer networks to discuss and try to cope with such issues in the future. So not only for the reason of patient and patient communities being a strong advocates, but also strong innovators in health and social care as we have seen in the rare disease community, but also for the very basic fact that these communities actually play an important role in designing how we actually manage progress in science where we will always be the forerunners.

7. The Epitaph If all constraints were removed and you could direct what is done, what would you do?

Terkel Andersen: Well, I would certainly try to invite stakeholders to come together to make sure that we design sustainable pathways, with a good possibility to design both support systems but also scientific pathways to solve the challenges of rare diseases in a way where we do not only focus on the most common rare diseases, but also to find ways to create therapies for those who would otherwise be at risk of being left behind. We are now having the ability probably to develop therapies for monogenic diseases or a number of diseases counting for probably the major part of people living with rare diseases. But we'll also have to look into how we can manage more complex, rare diseases where the current status of science does not hold probably clear answers. And I think we have some challenges there. And that's on the scientific part and also how to organize signs and healthcare around that collection. However, there is also another aspect which is for the next two decades we probably have to realize that there will still be a number of issues which are more complex because they also comprise a political and cultural aspects. And where we at this moment are not doing well enough like the way we manage people who are living with a mental retardation, the way we reach out to subgroups and our populations, which may be a bit less easy to access, who have less easy access to healthcare systems. I think we may have neglected this to some extent. E.g. People living with rare diseases inside ethnic minorities

Natasha Azzopardi-Muscat

Bios

Natasha Azzopardi-Muscat, MD, MSc Public Health, MSc Health Services Management, PhD, FFPH, DLSHTM. Ms Azzopardi-Muscat is the President of the European Public Health Association (EUPHA). She currently works as a consultant in public health medicine at the Directorate for Health Information and Research in Malta, having previously held various senior positions in the Ministry of Health in Malta, including that of Chief Medical Officer. Since 1999 she has also been a resident academic at the University of Malta where she lectures on health systems and health policy. Her main research interests are European Union health policy and small state health systems. She has authored several publications on these topics.

Interview transcript- 14 October 2019

1. *Meet a clairvoyant*. If you could speak to someone from the 2040 who could tell you anything about Rare Diseases governance and treatment, what would you like to ask?

I think I would ask whether we would still consider RD as a different category of diseases. Because I think that our concept of common diseases would have to be changed. We will understand that some of the diseases which are considered today to be common are just not sufficiently well elucidated. Therefore, I think that in 2040 more and more of diseases would fall into today's definition of RD which will necessitate that we rethink the whole concept of RD.

2. *Optimistic but realistic outcome.* If things went well, how would you expect the Rare Disease Governance and treatment to develop in the next 20 years and what would be the signs of success? what is your vision?

I think success would be if people with RD would be linked globally, virtually, both the patients and the providers. Expertise would become more shared between the providers and the patients, because nobody has a full ownership of expertise, particularly if the condition is a chronic one. We would have an optimistic outcome if people with the same disease for which an effective treatment is available could have access to the treatment irrespective of where they live, through a totally different mechanism of funding, pricing and distributing of medicines and treatment and through a global extension of the European Reference Network (ERN) concept where is expertise to travel as far as possible, rather than patients.

3. *A pessimistic outcome*. What are the dangers of not achieving your vision? How could the environment change to threaten RD governance and treatment?

A pessimistic outcome would be to remain with the current mechanisms of pharma access and reimbursement, which provides support only to a small proportion of persons around the globe and those persons have even less access to treatment because of the higher costs. Such model is unsustainable and industries stop developing research and innovations because nobody can buy them at the current prices, this would be a decline instead of the era of progress. This means that the progress continues, more effective treatments are discovered, but they are available to fewer and fewer people.

4. *The internal situation.* From your knowledge of the Rare Diseases system organization and resources, which are the priority changes to make your vision a reality?

First priority is represented by medicines, especially by the price transparency negotiations. The second is how we can exchange data, and make it available in a safe way.

5. Looking Back. Looking back at the past 10/20 years, are there particular lessons – successes, failures – we can learn from?

I think the RD lobby is extremely successful in capturing a lot of the EU agenda. So, it is an example, how to lobby could be considered a success to learn from. In term of policy failures, I think that the Orphan medicines regulation was a step in the right direction but has now become problematic.

6. *Looking forward.* What major decisions with long term implications are faced at the moment? What needs to be done now to ensure that your vision becomes a reality? Please take into account the following PESTLE categories: Political, Economic, Societal – cultural, Technological, Legal, Environmental?

I think that on EU level, what is very important is to pay attention to the ethical -legal -social implications., because not every country can work it out for itself. I think

all these innovation topics are posing big dilemmas from this perspective, and I think this area is not sufficiently well regulated from a policy perspective. The second thing is that health systems are under a lot of pressures. At EU level we keep pretending that we should not have any mandate to interfere into the health systems. But we work better together. A lot of challenges that we work on, we overcome so the second policy change that I would like to see is that the Ministries of Health are becoming a bit braver and acknowledging that we need to do more together.

As we have the European Medicines Agency (EMA) today that has a centralized procedure for licensing, I think for RD we need central procedure even for access and procurement. It is a big policy leap but I think it needs to happen. I mean, the question is to what extent the solidarity model will be able to prevail. It is under pressure. Do we have the right politicians in the right places, that will continue to privilege, the value that Europe has given to access to health services for all? Or we will end up having systems that leave people who are at risk of certain diseases, and who to a larger extent learn of this earlier, to make their own way just "everyone being left to his own devices".

7. *The Epitaph.* If all constraints were removed and you could direct what is done, what would you do?

I think I would try to fix the access to medicines to make sure that the pricing model is fixed. I will also try to push EU member states to come together, also with the neighbouring countries, showing that we can be very large markets and that we can go for something such as GDP index linked pricing, just to make sure that we make these effective treatments available for everyone who can benefit from them.

At the moment, most of the very expensive medicines are somehow for conditions that would fall into the definition of RD and rare cancers. I think that is the place to start in terms of putting together forces to generate economies of scale, reliability for costing in the area of RD and in the area of infectious diseases and vaccination. Second thing, it is really central to enable professionals and experts to work together, so that a patient can access the best, not only as the best medicines but also the best expert opinion.

Tanja Bratan

Bios

Tanja Bratan Fraunhofer ISI, Coordinator of Business Unit Innnovations in the Health System. Between 1999 and 2002 Dr Tanja Bratan studied Communications and Multimedia Systems at London Guildhall University, UK, and graduated with a Joint Bachelor of Science degree (BSc Hons). In 2003, she received her Master of Science (MSc) degree in Telemedicine and e-Health Systems from the Department of Information Systems and Computing at Brunel University, London. In 2007 she was awarded her PhD by Brunel University, based on her thesis titled "Design of a generic system architecture for remote patient monitoring". Between 2007 and 2010 she was a Research Fellow and Lecturer at the Department of Medical Education at University College London, UK. In August 2010, Tanja joined the Competence Centre Emerging Technologies at Fraunhofer ISI, Germany, as a Senior Researcher and Project Manager. She has been coordinating the Business Unit Innovations in the Health System within the Competence Center since June 2013.

Interview transcript - 15 October 2019 -

1. *Meet a clairvoyant. If you could speak someone from the 2040 who could tell you anything about Rare Diseases governance and treatment, what would you like to ask?*

I would like to ask: which new approaches ultimately have proven to be beneficial? Which role has gene therapy, gene editing, and AI? How those played out? There are lots of question I could ask… Something what can be also interesting is to ask whether if the number of RD has gone up a lot in these 20 years by segmenting common diseases into variants, which are rare diseases?

2. Optimistic but realistic outcome. If things went well, how would you expect the Rare Disease Governance and treatment to develop in the next 20 years and what would be the signs of success? what is your vision?

I think there would be a clear policy commitment to improve research for RD and treatment for RD at EU level and National Level, that should be a long-term commitment. Strategic approach could be through further action plans and other means. At National level there would be adequate reimbursement of treating patients with RD, because, as we know, it is very time consuming, there is lot back and forth, much less established pathways, that often does not get covered, generic reimbursement, payments. And if there would be adequate reimbursements there would be more centres for RD being established. For now hospitals provide services, but they often have to find other funding, since it does not get fully covered. If we have more centres for RD, there would be much more networks in RD, individual collections, depending on how people already network with each other. There is a need of more formal collaboration, because formal means also are being reimbursed.

If we go beyond the centres themselves, it is important to have RD incorporated at primary care level. It will be impossible to educate all general practitioners, but what is important is that they see "red flags", when they see patients with unusual symptoms, and they have clear pathways of what to do with this patient. For some RD there are pathways, for others not. We need to have RD better integrated in medical education and at the moment this is not the case, at least in Germany. When doctors confront with RD they are not sort of prepared for that. Also, we would have more investment into infrastructure for example through registries and biobanks to sharing patient data and patient records and to have more research, including on genetic mutations and spontaneous mutations as well.

Regarding the signs of success, a soft indicator could be identified in "red flags", if clinicians could recognise the red flags mentioned earlier, this would be a very positive sign because, in this way, they could send the patient on the right pathway, rather than keeping them in primary care. A harder indicator could be considered in patients that receive the diagnosis more quickly and, other indicator, if patients could be treated easily in any country across Europe, that expertise from other EU

centres could be sort (spread?). And, obviously, the ultimate indicator would be the improvements in quality of life of RD patients.

3. A pessimistic outcome. What are the dangers of not achieving your vision? How could the environment change to threaten RD governance and treatment?

This has a lot to do with the performance of healthcare system, a system which is already underperforming as we see, for example, in several eastern EU countries, but also in other healthcare systems. Such system is not working well for patients with RD because there is already lack of funding, stuff shortage, doctors emigrating to other countries, primary care is not well linked, there could be lack of good practice and evidence. So such healthcare system is sort of a guarantee for pessimistic view.

Also in a research system which focus only on areas where you can publish more easily, as on cancers, cardio-vascular diseases, where you do not get recognition if you work on RD, sort of exotic topics are not going to perform as well. In Germany, if stockholder groups mainly follow their own interest, so university, hospitals, have their own interest and insurance companies have their own interest, that is not going to be a favourable environment for people with RD, because they do not have such a strong representation of their interests.

4. The internal situation. From your knowledge of the Rare Diseases system organization and resources, which are the priority changes to make your vision a reality?

Between all stakeholders the key is a shared vision and shared goal. It is crucial also to have framework conditions which favour to follow that vision, which means funding, knowledge, incentives, rewards for doing what is good for patients RD, it has to be easy for them to do that. It is important that politics comes into that because it has a big influence on this.

What we see in Germany is that one of the big problems is a slowdown progress, that stakeholders who follow other interests, they have other topics, that can even go against interest of RD. For example, if there is a Health insurance system and putting more resources into RD can increase costs, they have less interest in RD. So, in this way, they will prevent progress for RD or slow down a lot.

5. Looking Back. Looking back at the past 10/20 years, are there particular lessons – successes, failures – we can learn from?

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.

6. Looking forward. What major decisions with long term implications are faced at the moment? What needs to be done now to ensure that your vision becomes a reality? Please take into account the following PESTLE categories: : Political, Economic, Societal – cultural, Technological, Legal, Environmental?

Political categories might be a key to long term commitment towards RD. And it is not only a health issue, but research has to come in there as well, especially in the linkage between ministries. Of course, putting money into RD research is going to take a lot of time.

It is necessary getting a better understating of reasons of RD. This should not be seen as a charity towards RD, but also majority can benefit from this.

Pharma is not very interested in developing drugs for RD, because it is a small market. This can be improved through Off-label and an easier market approval, but incentives are needed. Funding for the centres is needed. Also, more orientation toward patient needs would improve the situation, more equal relationship between patients and health care system would be great, because RD patients know a lot about their disease.

Other focal point is the social aspect of collaborating and reaching decision together. Also, the DATA argument is very important. The question of sharing data is very sensitive for health care provider side and for the patient side, to what extent we are ready to share data? And also, linked to that, the acceptance of gene therapy and gene editing is central, there is a debate about this, but this is a huge hope for RD cause, for example, for cystic fibrosis there is no treatment now and gene therapy could fix the problem. Regarding the technological environment: regulatory framework for technology development is needed, and the acceptance as a society, how much do we allow interference on people genome? This is also an ethical and legal question.

7. The Epitaph If all constraints were removed and you could direct what is done, what would you do?

I think I would include more research on RD, I would include existing treatment options to everyone who needs them, improve medical education, improve awareness, improve acceptance and knowledge about RD. I think I would do those as a major mission.

Katie Bushby

Bios

Professor Kate Bushby is a clinical academic with joint appointments between Newcastle University and the NHS. She is a member of the Neuromuscular Research Group within the Institute of Genetic Medicine and plays a leading role in the National Commissioning Group (NCG) for rare neuromuscular diseases. Professor Bushby has a long---standing interest in the molecular genetics of the limb---girdle muscular dystrophies and related disorders and is interested in the best possible development and implementation of care guidelines as well as clinical trials. Her team has developed an extensive programme of research in NMD from basic molecular pathology to clinical studies. In November 2014, Kate Bushby along with Volker Straub and Hanns Lochmüller launched the John Walton Muscular Dystrophy Research Centre. The Centre will focus on three key research areas: translational research, innovative clinical trials and international networking. Prof Bushby has been actively involved in many European projects including being a founding co-ordinator of the TREAT---NMD Network of Excellence whose objective is to ensure that the most promising new therapies reach patients affected by neuromuscular diseases as quickly as possible. Kate has played a leading role in the European and national rare disease policy area, acting as vice chair on the European Union Committee of Experts on Rare Diseases (EUCERD) from 2010 to 2013, mandated to assist the European Commission in the implementation of rare disease activities in all member states, and the led the EUCERD Joint Action on Rare Diseases. She also acted in the capacity of expert on the Commission Expert Group on Rare Diseases until 2017 and was one of the key experts spearheading the development of European Reference Networks.

Interview transcript- 25 July 2019

1. *Meet a clairvoyant. If you could speak to someone from the 2040 who could tell you anything about Rare Diseases governance and treatment, what would you like to ask?*

Having people work together to find common solution to data registry and data gathering. In particular, I would ask how the question of avoiding data fragmentation and the efforts against duplication has been solved and the way in which the respect of patients' privacy has been ensured.

Which solutions have been elaborated to ensure that RD drugs could be equally accessible to patients in the different countries?

2. *Optimistic but realistic outcome. If things went well, how would you expect the governance and treatment of RDs to develop in the next 20 years and what would be the signs of success? what is your vision?*

That Brexit has not happened.

That ERNs have pushed beyond the boundaries of being an EU bureaucratic structure and has become a center of knowledge that have the power, with mandate and competences, for organizing an EU RD data registry structure and for negotiating with pharmaceutical companies.

ERNs have now a real-life impact in patients and have a key role in shaping EU RD policies. All RD patients know about the ERNs and are able to access them automatically from their national health care system.

Two milestones have made this vision possible. On the one hand, patient organizations had increasingly a voice in ERNs aims and works. On the other hand, national healthcare institutions have embraced the model and included it in their healthcare systems.

ERNs have been able to coordinate efforts for gathering data in a consistent way, guaranteeing that no money and time was wasted in 'reinventing' the wheel for organizing, each time, data registry for different diseases at different geographical level or for new research projects.

3. *A pessimistic outcome. What are the dangers of not achieving your vision? How could the environment change to threaten RD governance and treatment?*

ERNs are not being able to evolve and to become those networks able to make a difference for a patient's life. Rival networks/structure could be created for certain countries – with an increased risk of inequality for accessing treatment and cure within EU countries. Nationalism and policy fragmentation are on the rise.

Threats for RD:

- Political williness (EU level)
- National governments: risks of discontinuity on integrating RD policies into national healthcare systems
- Bureaucracy: how to ensure that the systems will not get too complex to be effective?
- Less liberal EU: nationalism and budget constraints could lead to the reduction of welfare services and to a wave of increase of inequity and RD patients could likely suffer from discrimination.
- Unified or fragmented EU policies

4. *The internal situation. From your knowledge of the RD system organization and resources, which are the priority changes to make your vision a reality?*
   - *Sort out the data*. Currently there are too many registries but not a common platform, not standards, and even if long discussed, this situation has not been solved. New registries are still being created from the scratch with wasteful of resources. After such long discussion, there is the need for a top-down plan on what is needed and how to proceed. The plan should come from a powerful coalition involving patients' organizations and some big company able to provide the knowledge and the infrastructure for such paradigmatic change.
     - There will be the need to build trust on how the data will be used and it could start up as a philanthropic action. After so many years, efforts are too slow and it makes no sense to continue investing on single registry project/call, there is a urgent need for a big/significant answer able of setting a common platform and for tools able to capture a large amount of data from genomics to imagining.
   - *Drugs pricing*. We need to find new ways and different methods for bargaining with pharmaceutical companies and "red tape" (see the paper)
   - *Rare cancer.* The specificities of rare cancer are poorly understood, maybe because they are being at the cross between cancer and rare, but more efforts are needed in this area.

5. *Looking Back. Looking back at the past 10/20 years, are there particular lessons – successes, failures – we can learn from?*
   - Rare disease profiling and making RD an EU priority has accelerated research and results.
   - ERNs was created as a political instrument and the process leading at its creation, as well as at its 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 experts group was close down with a short sighted decision. 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 disease's 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.

6. *Looking forward. What major decisions with long term implications are faced at the moment? What needs to be done now to ensure that your vision becomes a reality? Please take into account the following PESTLE categories:*
   - Political - More or less liberal EU?
   - Societal - cultural – risk of loosing emphasis on RD or RD remain in the policy agenda as a priority (e.g rare assimilated to all disabilities)
   - Technological – to what extent new technologies, devices and advances are accessible to all
   - Legal/Ethical – how long does it how long does new technologies take to be available?
7. *The Epitaph. If all constraints were removed and you could direct what is done, what would you do?*
   - Reinstating the RD Committee of Experts with a clear definition of tasks to be accomplished
   - Investigating to what extent ERNs are able to make a difference for patients' life. An institution at its infancy needs to evolve and grows
   - Reaching an agreement on data infrastructure
   - Streaming a decision for making an agreement on drugs policies and costs

Ruxandra Draghia-Akli

Bios

Dr Ruxandra Draghia---Akli is currently Vice President Public Health and Scientific Affairs at Merck Global Vaccines. Prior to this position she served as Director of the Health Directorate at the Research and Innovation DG of the European Commission, where she initiated the International Consortium for Rare Disease Research (IRDiRC) along with her counterpart at the NIH (US) Francis Collins. She also initiated or provided support for legislative, regulatory and policy issues in the area of health research and innovation, and established, in consultation with stakeholders, research priorities for the Health Research Programme of the EC. Previously, Dr Draghia---Akli served as Vice---President of Research at VGX Pharmaceuticals (now Inovio) and VGX Animal Health. Her research activities focused on molecular biology, gene therapy and vaccination. She is a global leader in the field of nucleic acid delivery for therapeutic and vaccination applications. She is an inventor on more than a hundred patents and patent applications. Dr Draghia---Akli received an MD from Carol Davilla Medical School and a PhD in human genetics from the Romanian Academy of Medical Sciences. She also completed a doctoral fellowship at the University of René Descartes in Paris, supported by the rare disease association "Vaincre les Maladies Lysosomales", and a post---doctoral training at Baylor College of Medicine (BCM), Houston, Texas, USA, and served as faculty at BCM. In 2012, she became an honorary member of the Romanian Academy of Medical Sciences.

Interview transcript-30 September 2019

1. *Meet a clairvoyant. If you could speak to someone from the 2040 who could tell you anything about Rare Diseases governance and treatment, what would you like to ask?*

First and foremost, by 2040 I do hope that in Europe, US, all around the globe and every single country would have a RD plan. It took a long time to get here and work is still to be done (to the point where many countries have a plan in Europe).

I would like the clairvoyant to tell me that this is the case, that most countries have one. In terms of governance, in order to be able to address the needs of people living with rare diseases (PLWRD), governments need to do more in terms of diagnostics. Without having a correct diagnosis and identifying the appropriate treatment(s), you cannot make a plan.

And then, after receiving a proper diagnosis, I would like to know which percentage of these RDs have treatment. Even knowing that many of them may not be treatable by 2040, but I would like to know what progress we made, and how many are treatable.

Again, first have a plan. After, I think it depends from disease to disease. If you cannot diagnose something you don't know what kind of treatment you need. Sometimes the treatment can be easy and sometimes very complex.

2. *Optimistic but realistic outcome. If things went well, how would you expect the Rare Disease Governance and treatment to develop in the next 20 years and what would be the signs of success? what is your vision?*

Diagnostics is one of the big problems. By definition, RDs are rare, thus many clinicians do not have the occasion to see them. Today getting a correct diagnosis takes years and years, and sometimes visits to 10-15 clinicians in order to arrive to a diagnosis. One of the current goals of the international rare disease research consortium (IRDiRC) is that a patient should be diagnosed within one year of the presentation to a medical professional. A real sign of success would be achieving this ambitious goal. There is such a multitude of ways (artificial intelligence tools, exon sequencing is more accessible for example) that this may happen. A corollary to this

outcome, would be for these diagnostic means to be available for the majority of PLWRDs around the globe, not only in EU or in the US. .

A Chief Executive Officer (CEO) in a big pharma company once shared with me that "25 percent in the next 10-15 of future therapies of pharma companies could include cell and gene therapies". If I am an optimist, in the next 20 years you will have a therapeutic solution for many of these rare diseases including those based on advanced therapies, such as cell and gene therapies or novel small molecules better targeted and designed for specific patients.

3. A pessimistic outcome. What are the dangers of not achieving your vision? How could the environment change to threaten RD governance and treatment?

Healthcare systems are under a lot of pressure with current regulatory environment, financial situation, pressure due to the coming up with innovative treatments which will be extraordinary expensive even if they are for very limited number of patients. The risk is that, if we take into account only the financial hurdles, we will never get beyond the place where we are today. We need to come together, as a community, to discuss comprehensive solutions not just the one-off innovations that are too often taken as examples and made a focus.

4. The internal situation. From your knowledge of the Rare Diseases system organization and resources, which are the priority changes to make your vision a reality?

I do believe that the UN resolution is a good step forward. We need also to build onto the political good will and build a practical plan of how to move forward. How to modernize regulation addressing advanced therapies? How are we recognising the leadership of Europe while creating a global community? How are we going to move forward on all of these practical aspects? How are we going to put forward a regulation for advance therapies to decrease the cost of innovation and facilitate the bringing of these treatments to the market? We have discussed about the timely diagnosis. But as one knows, diagnosis is part of a continuum of care, and we cannot change the system overnight. We need to take it from the theoretical to a workable strategy.

Some of the models I have in mind are examples from IRDiRC and can be transferrable to the healthcare system. Example: 1. sharing of resources in rare diseases. How we identify the cause or genetic component of a given condition? We gather patients with similar symptomatology and possible diagnosis. We unified those resources around the globe, create specialised centres. 2. Treatment should be available for people around the world at the same time. Every healthcare system currently decides on reimbursement models which makes for a very unequal playing field. Even for a simple medication it creates a situation where a molecule that is introduced in certain markets such as the US or EU is not accessible for another 8-10 years in other countries. This is a hyper inefficient process for rare diseases. Is it logical to go through this complicated process for such a small number of patients per continent? As a community, as soon as a treatment is available, we need to find a way to make it available around the world at the same time.

We need to have a solution similar to IRDiRC in which we share knowledge to accelerate this process. Digitalization can help us enormously. Think out of the box for the solutions, because current model is not only too expensive, but also unpractical.

Role of the EU? Europe has always been a lead in this effort. We are already well-placed to come up with a common mechanism, we have the legislation underpinning to make it happen, we have the Cross Border Health Care (CBHC), we have EUnetHTA, we have cross boarder directives. Rare diseases can be at the forefront of pricing and reimbursement policies.

We have opportunities further upstream and they should be operational almost immediately. You have a lot of efforts in Orphanet. We can build a model which is operational.

5. Looking Back. Looking back at the past 10/20 years, are there particular lessons – successes, failures – we can learn from?

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.

6. *Looking forward. What major decisions with long term implications are faced now? What needs to be done now to ensure that your vision becomes a reality? Please consider the following PESTLE categories: Political; Economic Societal – cultural; Technological; Legal; Environmental*

First, collaboration and partnership are needed at every single step of the ecosystem. We really need to decide that we will work together around the globe in order to avoid that every single country is coming up with its own solutions. In order to avoid that every country work with its own processes. We should avoid fragmentation.

Second, research and innovation costs a lot of money. We cannot be in the model of a new molecular entity costing a few billion to bring it onto the market. We really need to be in the framework of cluster therapies. Example: therapies based on a particular gene therapy platform. If we move from looking at each disease and each treatment in isolation and looking at them as clusters and develop processes that are based on the cluster, I actually think that we will be able to move significantly, avoiding fragmentation. Let's think out of the box, let's think on HOW WE STREAMLINE PROCESS.

As a cultural change, I would emphasize "sharing". Sharing is not what researchers used to do. Conversely, patients with RD are much more willing to share information, including their valuable personal data. In a sharing model, work can be performed properly, respecting the highest ethical standards and very consistently. As soon as you have issues or questions about data sharing, one will have a lot of regulatory questions.

7. *The Epitaph. If all constraints were removed and you could direct what is done, what would you do?*

I would not try and reinvent the wheel. There has been an enormous amount of good work and I would capitalise on the existence of IRDiRC and many other similar global initiatives and take it to the next level. We need to ask ourselves what do we need to do as a community, from early discovery to access. We need to change the focus from research to focus on the patient. We need to focus on how to make sure that we are bringing diagnostics and treatments to patients. I would use existing structures to push the agenda forward.

Ruediger Krech

Bios

Dr Rüdiger Krech is currently the Director, Health Systems and Universal Health Coverage at the World Health Organization (WHO) covering WHO's work in the areas of integrated people---centered health services, safe and effective medicines, health workforce, financing and health governance. He also facilitates coordination and coherence between the health systems work of the Organisation and other areas of public health. Prior to that he was Directors of the Department of Ethics, Equity, Trade and Human Rights also at the WHO from 2009 to 2012. In this capacity, he was also responsible for WHO's work on Social Determinants of Health and Health in All Policies. Before joining WHO, he was in charge of German International Cooperation's (GiZ) work on social protection from 2003---2009 both in its Headquarters in Eschborn near Frankfurt and in India. He has also held various management positions at the World Health Organization (WHO) Regional Office for Europe in Copenhagen in the fields of health systems, health policies, health promotion and ageing between 1992--2 003. Dr Krech has studied educational sciences, medicine and public health and holds a doctoral degree in public health.

Interview transcript 2 October 2019

1. *Meet a clairvoyant. If you could speak with someone from the 2040 who could tell you anything about Rare Diseases governance and treatment, what would you like to ask?*

I would like to ask how the development of Centers of Expertise (CoE) on a global level for rare diseases has actually changed the way we treat people around the world today and how this has helped make sure no one is left behind? 20 years ago, a lot of people were not diagnosed and treated, how it will change, it would be my question. In 2019, we still have unequal diagnosis and treatment for people living with rare diseases (PLWRDs) across countries. So (I would ask) to what extent the clustering and new technologies have increased the opportunities for correct and speed diagnosis and treat the patients with dignity.

2. *Optimistic but realistic outcome. If things went well, how would you expect the Rare Disease Governance and treatment to develop in the next 20 years and what would be the signs of success? what is your vision?*

First of all, I think what we are seeing on the horizon is good news for PLWRDs and their families. We see a lot of technologies that can help to detect early and treat RDs that could not be treated 10 years ago. We see a lot of technological advances in stem cell research, gene therapy etc. that actually help us to revert some of the rare diseases (not all) but some. I would expect the ever-quicker cycles of innovation to allow to detect and treat rare disease even quicker and even more of them. RDI, EURORDIS and many other actors in this community have helped identify many more of the rare diseases identified in the ICD 11 (2018-19).

The optimistic scenario is really that we are using this technology and disseminating the knowledge globally and analysing the experiences of caring for PLWRDs if we cannot treat them. But that we are analysing these experiences so that patients and their families can actually use that knowledge for their own treatment.

With regard to the knowledge hubs, I think it's ever so important that we are creating these global CoE. There are many top-notch hospitals that are very good in doing this. But, as we have a small prevalence and incidence in RD, we need to globalise them. It's not good enough to count incidence and prevalence rates at the national level. So that we will need to account them at the global level. And then create CoE for clusters of RD that specialise in them. In a globalised world, let's use the advantage of this globalisation. In centralising the knowledge in treatments and care standards/techniques such as surgery, we can also inform people outside of

the CoE on the use these technologies. I am referring to e-health technologies that allow specialised experts to be in real time in touch with the physicians in other places to advise them what needs to be done in a time of crisis: peer to peer online counselling of doctors and medical personnel in order to deal with acute crisis.

And that will help because, as you know, RD are not diagnosed early so they are often appear in critical medical scenarios. So then when you are a doctor faced with a patient you are often in the dark and playing with trial and error at a critical moment for a patient. And global knowledge hubs will then advice on what you should do under certain circumstances. The idea that we've developing comes from emergency care in rural areas. You also have specialists in emergency care that advise them what to do.

For the longer-term care, (the optimistic scenarios) is to also advise on the medium and long-term care to maintain the best level of autonomy for patients and their families.

I can only see lots of advantages in clustering the expertise, bringing them together and use this central hub for the good of patients in the whole world. This is how I would see the optimistic side in terms of treatment. If the resources are made available for these efforts.

3. A pessimistic outcome. What are the dangers of not achieving your vision? How could the environment change to threaten RD governance and treatment?

The risks are real. There is a risk in industry and there is a risk in "professional conduct", if you will. On the commercial side, the way we see medical and medical technological research advances is made in terms of return on investment. So, either we see one strand in medical research which is personalised medicine in which we will be creating medicines for the rich, in which you will be asked to pay 300-500.000 dollars for a treatment. We are moving away from a strategy to care for all to one where you rather care for those who can pay. This is a real risk, because if you have RD and go through individualised therapy, the family will be put immediately in poverty, because no insurance in the world will pay for this. For many PLWRDs you will put families who seek treatment in poverty.

Another risk is a professional conduct risk. If you look at how medical research is undertaken today, it is extremely competitive. The way you promote your personal professional career is all based on personal remit, not team work remit. This creates a danger. If you are dealing with physicians, medical doctors who are not used to socialization and who are not used to work in teams and share the knowledge, then just put the wellbeing of the patients in the centre of their thinking, because the environment in which they work does not incentives these behaviours. This is a real second risk because it creates an environment where you do not share your knowledge.

There are ways out of it: to establish solidarity mechanism is RD policy development, in terms of a financial resource. You would create a reserve fund for paying for certain expenses while being in a very transparent dialogue with industry on the costs of treatments. Which for the moment is in the dark. We have established a dialogue with pharma industry on the pricing of medicine. Some years from now , we could also include RDs in this discussion.

In the personal conduct issue – this is a bit more difficult because doctors are educated for many years until they arrive at working in a CoE for RDs and creates years of socialisation and mentality. That is more difficult, but you could reward "good" behaviour through financial benefits or professional advancement. If you had a project where you could exchange experts around the world, you could create a research "in-group", where you could change the incentives towards team work and reward knowledge sharing by creating exchange programs between global CoE, create alumni networks with that and financial incentives that go beyond the usual practice. So there are some ways how we could mitigate this issue.

4. The internal situation. From your knowledge of the Rare Diseases system organization and resources, which are the priority changes to make your vision a reality?

There are global tendencies. If you look at the WHO, in our internal organisation, is moving away from individual disease management. What we are looking at overall patient safety, patient management, client services, we are moving towards patient centred services. Our main priority are the 80% diseases that can be easily clustered. And then we can focus on the "margins", this is where we face a huge problem. Because in most countries we have an essential set of services that need to be put in place if we want to meet universal health coverage for 1 billion more people in the next coming years. I think it's my duty to really flag this risk and propose how we can make this narrative of leaving no one behind a reality and this includes of course how to make this a reality for people living with rare diseases.

But realistically we cannot ask countries, that are just putting in place health insurance programs, to cover all diseases for all their population. This is why we need to supplement with an external financial platform.

In the last 15 years, there were hundreds of countries which couldn't cover their own health care systems. Today 15 years later we have only 35 countries. We have made a big progress in 65 countries, we worked with them, so they can finance their own health systems, adapt to their environment and social- economic realities. Therefore, we would like to ask regional bank to focus on these 35 countries; and expand the development work on the other 65. I would then add that in order to really meet the goal of leaving no one behind, one would need a reserve fund for the low incidence, low prevalence but huge number of different diseases.

And that is something, where we would need a lot of support of the RD community because this is a political choice and it is not a technical one. What Member States and what heads of governments could do is to have supporters such as the European Commission or the World Bank, regional banks, like the Islamic and Asian development bank, this would be very useful to lead these discussions with them and see whether this is politically feasible.

5. *Looking Back. Looking back at the past 10/20 years, are there particular lessons – successes, failures – we can learn from?*

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.

6. *Looking forward. What major decisions with long term implications are faced at the moment? What needs to be done now to ensure that your vision becomes a reality? Please take into account the following PESTLE categories: Political; Economic; Societal – cultural; Technological ;Legal; Environmental*

I would look at the interdependence of the P-E-S-T-L-E approach. If you look at politicians, they work and think about "what I can do". Policy makers would give a

"Sunday speech" about leaving no one behind, but they would not be able to work and act upon it. But if you can give concrete solutions, political commitment will be stronger. And one of the big challenges will be the financing of the therapies. If you (1) look at the technological advances and (2) empower politicians to accurately negotiate with producers or manufactures of health technologies or medicines to have a realistic price. I would strongly suggest not to play the game around charity - where pharma give drugs out for free. This must be a part of an overall system able to guarantee access for everyone. The reason behind is that if you have built it on a charity approach then if you have a disengagement of certain individuals and then you may fall backward. This will not happen if you integrate your approach in the system that leaves no one behind.

Looking at the economics of it: the economic case made by EURORDIS makes a lot of sense in terms of burden on families. But if you bring it to the individual level you will always find huge costs attached to RD and so therefore here again the argument needs to be at the global level and needs to be linked to an ethical approach. Yes, while there is an economic argument for somethings, it remains a fundamental ethical approach – right to health and a fundamental ethical right. This is definitely something I would bring to the floor when talking about the economic burden.

I have also mentioned, social environments that are conducive to new approaches to treatments and adapted care.

What I haven't touch yet is the legal aspect. There are few countries that have put in their constitutions the right to health, for example, Brazil. What is included in this right to health and what is not included? Because the link is the trigger, there is a political way out and financial instruments that can be put in place in order to implement this right for everyone. So, my argument is to look coherently and comprehensive at all aspects in PESTLE approach, and the interlinks between them because that is how you could put things in motion.

7. The Epitaph If all constraints were removed and you could direct what is done, what would you do?

Again, I really think beyond the political practice that we have at the WHO on a daily basis. I think the right thing to do is to create these global centres of excellence. That's where you have the best "buy for the buck" but also the best way to advance agendas.

From a public health lens, you have to deal with the nature of RD and use the globalisation in which we live and use them to you advantage. I would acknowledge them by WHO. Have high recognition and high rewards on those in terms of how you treat, care, innovate, research and how you finance. You could create a reward system that acknowledges the personal engagement of people, who are so dedicated to move agenda forward in RD, so that there are a lot of advantages in creating those.

The glass is half full. I see a lot of opportunities politically but also in terms of social advances and with the whole environment of Sustainable Development Goals, there is a shift now towards inclusion. All that plays in your hand. Keep up your good work and I am glad to contribute as much as I can.

Milan Macek

Bios

Professor Milan Macek Jr. MD, DSc is the chairman of the Department of Biology and Medical Genetics at the Charles University in Prague --- the largest academic medical and molecular genetics institution in the Czech Republic. He was a past President of the European Society of Human Genetics (ESHG), currently a board member of the European Society for Human Reproduction and Embryology and of the European Cystic Fibrosis Society (ECFS). His institute contributes to dissemination of knowledge in genetics gathered within various international European projects, such as CF Network, EuroGentest, EuroCareCF or Techgene, to Central and Eastern Europe.

Prof. Macek did his postdocs at the Institute of Human Genetics in Berlin and at the McKusick---Nathans Centre for Genetic Medicine, Johns Hopkins University in Baltimore. During that time, he was also a fellow at Harvard School of Medicine in Boston. Prof. Macek is national coordinator of Orphanet, active member of Eurogentest, has been the chief advisor of the Czech EU Council Presidency under which the "EU Council recommendation on an action in the field of rare diseases was adopted in June 2009. He also serves at the EUCERD committee on rare diseases and is involved in the rare disease---focused initiatives EURenOmics and RD-Action.

Interview transcript 3 October 2019

1. *First question, meet a clairvoyant. If you could speak to someone from the 2040 who could tell you anything about Rare Diseases governance and treatment, what would you like to ask?*

Well, the best predictor of the future is past performance, things which have a proven track record and which have been around for quite some time have also the highest potential to be also successful in the future. However, we are a rather young interdisciplinary field of medicine, starting with the orphan drug regulation in year 2000, so we are still building our own foundations and establishing our own "tradition". Hence, I would like to paraphrase what the Yann Le Cam as CEO of Eurordis.org has been saying for some time, that "we now have the pipes, but we don't have the water in them". We have achieved a lot, but still this is only the beginning of our field, which will make predictions very difficult for even a very talented clairvoyant.

Let us rather look a positive and negative aspects through an informal SWOT analysis. Thus, I can only underscore that the main strength that we have achieved at the European level, is that we really have a well-established structure. We now have European Commission and European Council communication / recommendation which should be updated though as proposed by the 2017 Maltese Presidency, we have operational European Joint Program on Rare Diseases, we have many registries, JRC is involved, Horizon 2020 program has put forward many dedicated calls in the field, we have the Crossborder Directive, recent important report from the European Court of Auditors, and most importantly we now have European Reference Networks.

However, we all see at the moment, and it is in my view currently one the main weaknesses - is that majority of European national plans, including the 1-3rd Czech national plans, mainly represent a "nice piece of paper", of course with several exceptions like France or Germany. They were approved by respective EU governments, often with substantial public relations spin, but in reality there is very limited funding available to implement them. Therefore, we have created a strong momentum, which is also the main opportunity in such a SWOT analysis. But the main threat is that this momentum could slowly fade away.

There are multiple reasons, for instance our "founder" generation is quickly reaching its retirement age, and we may not give our successors a strong "running baton" to carry forward. This is not a "defeatistic" statement, rather we now urgently should fill in the pipes with water – that is with appropriate funding in order to

consolidate our activities in the field. For us it who have witnessed that there had been almost nothing in place more than a decade ago, and when even few people knew what rare diseases represent…, then the current status represents a truly remarkable achievement. Thus, from this point of view our generation still retains such an optimistic view, while our younger colleagues, who may not have witnessed all such gradual developments are now often confused and can become demoralized in the absence of dedicated and meaningful funding. Hence, my main concern is how could we assure long-term sustainability?

We also ought to realize that we compete with other fields for health care funding. Even within rare diseases themselves, rare cancer therapies are treated differently by health care systems compated to life-long therapies, and so on. Rare diseases are also highly "politicized" given the increasing costs / budget impact of orphan medicinal products, including most recent "one off" gene therapies. Essentially, it is really tall order in front of us, since we are dealing with marginalised populations, whose care reflects the overall equity and solidarity within European health care systems, which are increasingly financial stress.

In addition, since we are dealing with marginalised populations, we must realise that with the aging of the majority of European populations, with the emerging problems in the elderly, and with the decreasing of birth rates in most European countries, we may have a problem to receive sufficient political attention in the future Please do not get me wrong I am already reaching the age of sixty and naturally I have nothing against the elderly! However, I've witnessed such a change of "philosophy" in the views of the Council and at the European Commission or when studying call structure at European of national research funding agencies. It is as if they "unisono" indicate between the lines, okay, in the last decade we gave to rare diseases "sufficient attention", whilst now it is the time to do something else, to do something new or to do something more relevant for the mainstream population etc. As if rare diseases became as they say in the US "dad's old car", indicating that we had our peak and fair share, and now came the time to move on. This issue could be exemplified by the current discussion where we are almost desperately trying to assure continuation of Orphanet funding.

Another issue, which in my opinion is quite challenging, is how could we sustain the momentum in terms of the implementation of the orphan drug act. Because, as we all see, there is a gradual "push back" against orphan drugs in many European health care systems and since their budget impact, albeit in single digit numbers, is slowly growing. Also we are currently spending vast sums on medicines, while other aspects of comprehensive care in rare diseases may be lagging behind, or even remain underfunded. Hence, such internal disparities within health care funding for rare diseases themselves are growing, as is the nervousness of health care payers reflected by sometimes hectic/uncoordinated activities of patient support groups fighting for access. I am a bit worried that the rare disease field becomes fragmented again. Patient groups where orphan medicinal products are already available primarily concentrate on access to care, while the majority of other rare diseases groups without targeted therapy struggle with more basic issues, or require improved social- and palliative care. This could undermine our joint stance, so to speak. Here I mainly hope in the stewardship of Eurordis and their close collaboration of European national alliances, to reduce the current "cacophony".

For instance, in Czechia, orphan medicinal products represent about 4% of the overall health care budget. This is an issue; now even augmented by a situation when health care funding is stagnating, or merely covers inflation costs. As young field we are somehow viewed by our medical peers as "new kids on the block", implying that the established fields like oncology, cardiology, diabetology and so on, are also fighting for their piece of the healthcare "pie", and we find it increasingly difficult to find good arguments for ourselves. Intriguingly, when one fights for rare diseases, often they are suspected as being those who are indirectly "fighting" also for high-cost orphan medicinal products. This is not the case, we are primarily striving to consolidate genomic diagnostics and complex multidisciplinary care, including social care, palliative care and so on, whereby orphan medicinal products represent only a very small part, albeit important, of the overall interdisciplinary – multimodal therapeutic portfolio, so far.

Moreover, we aim to establish a nation-wide rare disease centre structure linked to European Reference Networks, implementation of palliative care, facilitating social care, setting diagnostic and therapeutic standards, and so on. In fact, Czech is now "first" in terms of European Reference Network coverage from all EU 13 "New" Member States, and 8th in the entire EU, which is great, but we need to expand coverage of ERNs through the ongoing second expansion call.

Another issue we are facing are times of economic transition and uncertainty, not only in Europe of course. Luckily post-2008 austerity is fading away, but there seems to be a new, let's say, an economic crisis on the horizon. Look at for instance the current Deutsche bank issues, the uncertainty of Brexit, problems within the Eurozone in balancing national budgets deficits etc. I am not an economist, but these issues are well known in the public domain. Thus, any major future economic crises can also threaten the rare disease "movement". In a time of crises one can envision that rare diseases could represent a "luxury leftover" from good times. I am personally worried that health care systems will have to rationalise on expensive life-long therapies within this context. I would hate to see a situation when patients on life-long therapies will be discontinued for economic reasons, mainly in cases where it is essential for patient survival, such as in lysosomal storage diseases, cystic fibrosis, or in neuromuscular disorders. Again I do not want paint negative scenarios, but as with Black Swans one should be ready for the unexpected.

In this regard we see when we work with non-European populations in the field of rare diseases and when we deal the respective Ministries of Health in countries with emerging economies that their eventual support for a selected group of more common rare diseases has a strong "PR component". They often view them as a prestigious showcase; as if they would like to say, "look how good we are - we care about our marginalized citizens". However, when confronted with the lack of comprehensive care for all rare diseases they tend to look the other way… Moreover, and frankly, beyond Europe, there are still pressing concerns with communicable disorders, diseases strongly associated with poverty – like tuberculosis, AIDS, etc., these represent really "burning health care issues" that must receive priority. One should always remember yow privileged we are in the EU, and how societies couple of hundred kilometres apart from us are faced with a completely different, dire reality, in their everyday lives.

We don't know what will happen with population migrations. Intra-European migration is approximately ten times larger than the extra-European migration, which however receives most of the attention by press and politicians. A lot of Baltic, Polish or Ukrainian, mainly young, people are moving to Germany or to Scandinavia and Romanians to Italy according the recent United Nations report. And these are the people who will also require in the end medical care. Therefore, this may create political tensions in that those citizens who have paid their health care taxes throughout their entire working lifetime, now expect decent care in their retirement. Nonetheless, European solidarity-based health care budgets will have to cover care for new immigrants who did not have the chance to contribute to the health care "pot" in the long-term. We see first examples for such tensions in Denmark, and not only populist parties raised this issue. Also the high degree of consanguinity in Middle Eastern and North African populations is related to increased prevalence of recessive rare diseases which may require life-long treatment. We all know that despite having a dedicated "Crossborder Directive", legal cross-border care for European Union citizens is still not functioning up to its full potential, there are many administrative hurdles, yet immigration establishes new status quo which needs to be dealt with. Do not get me wrong, this is not a negative statement, rather we need to face this developing reality and proactively try to deal with incoming demographic trends, before some shrewed technologists of power would attempt to misuse them, with rare diseases being one of the victims of their restrictive policies as one might envision. In this regard the principle of EU "subsidiarity" in terms of national health care, i.e. the regulatory power of the European Union which "stops at the hospital entrance", creates unnecessary boundaries for true transnational "medical" collaboration in our field.

Hence there will be an increasing need for a strong intergenerational solidarity. This may be particularly challenging for us in the rare disease field since a large part of "our mission" is to also create exactly this type of solidarity. Here kids with rare diseases are not- let's say- "responsible" for their illness, compared to heavy smokers. Rare diseases are different, they occur essentially out of the blue in various families, rich or poor, and reflect various historic carrier advantages that are no longer necessary for our postnatal survival due to modern paediatric and adolescent medical care. Through rare diseases, mainly those which are caused by ancestral variation, not de novo mutations, we "repay" our increased historical survival, like in cystic fibrosis through resistance to enteral infections causing excessive electrolyte loss.

We also should closely collaborate with pharma in this regard and find novel business models for them based e.g. on increasing value of real-life data generation for

their products and sharing costs for post-marketing clinical research. We ought to be fair with patient representatives and show that most orphan drugs have been developed based on well-selected but rather confined clinical trial outcomes, which may be appropriate to get the novel drug through the regulatory process on the market, but they may not cover the entire spectrum of rare disease-associated pathology. Hence, we should promote utilization of patient reported outcomes by the industry during drug development. These aspects do not make headlines, but sometimes pharma creates exaggerated expectations with respective rare diseases patient groups, which may or may not work out based on real-life evidence. Importantly, please let us try to avoid marketing hype as much as possible, we should rather properly manage patient expectations! The same happened in the nineties with early forms of gene therapy and I'm worried a geneticist that the same kind of overselling is now happening with the CRISPR-Cas9-based gene editing. Safety issues related to gene therapy are of course another domain which has not received sufficient attention thus far.

For instance, there is a blurred border between research and therapy, between research and diagnostics in rare diseases, both represent specific aspects of our field which did not receive much business attention thus far. Look how for instance micro-attribution or nanopublications in multicentre papers changed crediting in academic promotion and facilitated large-scale collaborative projects. Similarly, microattribution of provision of clinical data by rare disease patients to pharma within real-life data gathering business models could be one of the way how the society, i.e. taxpayers and industry could work together to improve orphan medicinal products access, yet still generate a decent profit for the industry and meaningful impact for given rare disease based on e.g. patient reported outcomes, which in the end really matter. Blockchain could enable such nanopublication approaches for provision of precise clinical data by patients within drug development and post-marketing studies, importantly within a European-wide manner. There is a wealth of literature how to “democratize” medical research and drug development in this regard. Only when we will get sufficient data whether a given orphan drug “really” works on a broad spectrum of disease symptoms and how it positively changes the natural history of a disease, we might justify the higher societal investment in targeted therapies. Naturally, we also know that pharmaceutic innovation is important for our economies and my stance is clearly not against business *per se*, rather we should find better and innovative / sustainable models for rare diseases and utilise their model potential for their common disease counterparts! Finally, mind that orphan medicinal products are currently usually being applied “on top of” other standard therapies, so it is sometimes difficult to argue with payers that they represent the “only option” in terms of an efficient therapy. Of course there are exceptions, of course there are clear successes stories, but we also have to monitor patient adherence, which is still underestimated within this context. Here the role of patient associations is crucial.

It has to be noted that there is an increasing number of rare diseases patients reaching adulthood, and from specialised paediatric care they are transferred to generally unprepared health care personnel dealing with adults, this is a major challenge on its own, again rather complex and beyond the scope of this interview. We should carry out more training, more education, commit more resources, centralise care where paediatricians and adult physicians could interact –e.g. within European Reference Networks, but this requires change of reimbursement models, promoting collaboration and reaching out of our professional specialty “silos”. Indeed, European Reference Networks started to tackle this problem!. It is difficult, but doable with lots of good will. In our country, we also try to teach medical students about the specifics of rare diseases within genetics courses, and together with patient associations present various rare disease patients and their families to them. These courses are highly regarded by our students and represent “eye openers” in terms of future multidisciplinary medical care for them, not only in rare diseases, but in entire medicine I dare to say.

We should not forget that increasing utilisation of voluntary preconception screening offers couples efficient reproductive choice. In some instances, such as cystic fibrosis its birth prevalence is even gradually decreasing. On the other hand with increasing parental age, mainly of fathers, the de novo variation burden and thus related monogenic, often dominant diseases, are on the rise. Unfortunately, these types of monogenic disorders cannot be screened for at the preconception level and we need to raise awareness with the public at large, that both genders should consider earlier reproduction. In genetics we see an increasing uptake of

preconception screening programs when people learn that orphan medicinal products for many rare diseases are in place, but access to them is limited. Thus, many campaigns which are conducted by rare diseases patient organisations aimed at assuring access / reimbursement of orphan medicinal products make others seriously consider their reproductive options. Simply, all this means that there is a changing epidemiology of rare diseases and it is likely that their structure and distribution may also change both due to improved care, detection of more severe cases at the preconception or early postnatal phases. Unfortunately, this approach will not solve ultra-rare diseases, e.g.with prevalence lets say between 1:500,000 – to - 1,000,000; here EU-wide action is of paramount importance and these need urgent attention. We ought to consider the demographic effects of migration, role of various public health screening programs, and their socially or culturally driven acceptance. This brings us to the domain of "Big Data" analysis, where specific artificial intelligence may help in their analysis and identification of future trends.

Many neonatal screening programmes enable earlier medical interventions, thereby overcoming the proverbial Diagnostic Odyssea and improving the overall quality of life in cases were therapy was applied early. All these preventive measures should consider different cultures in Europe, including their development, which influences utilisation and acceptance of various public health approaches, rare diseases notwithstanding. Fragmentation of our society, as we see e.g. in social media where specific "tribes" have been established, represents another challenge to broad society-wide solidarity and compassion. Thus, the clairvoyant you mentioned in your question should have a broad team of advisors, right (?); that is to feed their "intuition" with key-emerging trends. We are entering a rapidly changing world with many uncertainties, with different societal and/or economic "vectors", which hopefully will be in the end positive and move the field of rare diseases forward.

2. *I have two points for you that are interrelated because I think you somehow expressed the danger and the risk, and the question are concerning these. One, what do you expect if on the one side everything went well and if you could just give us help to define how you would measure the success? Also, what you have expressed now, like the risk, because especially for the cultural and social change is very hard to understand how much is a perception and how much is a trend. We are struggling to identify indicators that could somehow measure, for example, level of individualism. I also had the same impression on what was mentioned by different experts, but then when it comes out to research on it and try to link it with an indicator, we struggled. So, if you could also express, what indicator you will use to somehow measure these risks that you have expressed and, on the other hand, how you will see an optimistic view. What is your vision?*

I had been studying a long time ago in America, at Johns Hopkins University, and there I first heard a great quote, "hope for the best, but plan for the worst". Essentially, this implies that one should prudently start with planning for the worst because this is what you really should take care of in the first place in order to assure overall success. I guess I tried to cover all these risks in the previous "clairvoyant section" of this interview. Regarding the positive point of view, I would say that there are is great research going on with its description beyond the scope of this interview, we also have truly remarkable European projects such as Solve-RD, or many national undiagnosed rare disease programs, we have functioning and developing European Reference Networks. We currently increasingly apply novel technologies, such as artificial intelligence or rather machine learning to the automated in vitro screening for new orphan medicinal products. Artificial intelligence-powered genome variant prioritisation has recently enabled great progress in rare disease diagnostics; although 98% of our genome still generally eludes our deeper understanding. This creates an optimistic scenario – whereby drug development and genomics are now finally coming of age. We also witness great progress in terms of rapid genomic diagnostics in critical neonates, utilisation of "omics" strategies improves systems medicine approaches in rare diseases. All of this is very rapidly changing the diagnostics and treatment. In this regard, I'm very optimistic.

I have to honestly say that given the complex nature of the risks mentioned there will likely not be a single indicator for improved care, but we already have improved survival, improved quality of life indicators, there is standardised health technology assessment, and so on. EU HTA initiatives are struggling in this regard as well, since not only rare disease patients themselves, but also other social and/or economic indicators are put into the final equasion. Another indicator could be the number of health care personnel trained, number of seminars, workshops, simply let us jointly propose appropriate "deliverables" which are part of many EU-funded research projects and which proved to be very useful for project monitoring.

Orphan medicinal products often represent a breakthrough in medicine, in terms of their general innovative potential, spanning beyond rare diseases themselves. The vast research behind their development has important implications also for common diseases. In this regard, it has been famously said "treasure your exceptions" by our predecessors in genetics. Hence rare diseases represent very useful models for their more common "counterparts", as we had already discussed. Essentially, the more targeted therapies we have in place, the more potential medicines we might also have in the future for common diseases; again this is a very positive development, and again a valuable indicatory for policy makers supporting further developments in our field.

3. *The vision that you propose with this double aspect of having more preconception… How healthcare should change? What do you think a rare disease community organization should do to proceed towards your best view on the future?*

Indeed, I consider increasing, yet responsible, implementation of voluntary preconception screening, not only as traditionally applied in assisted reproduction in association with preimplantation genetic testing, but now beyond it, as being relevant for our field. Prospective couples are now increasingly aware of the genetic risks and approach planned pregnancies more responsibly. At least as European populations are concerned. In addition, internet information, social networking and "Dr. Google" helped a lot to promote better awareness of rare, genetic, diseases. This applies both to the public at large, and to various religious or migrant communities. When preconception screening is linked to preimplantation genetic testing, then you may overcome the previously applied elective termination of pregnancy, and truly offer genuine and ethically acceptable reproductive choice to prospective parents, both at risk due to their positive family history or even in low risk couples who get tested in the pre-conception phase. Don't get me wrong, this is not the only reproductive choice available, since at risk parents have multiple other choices at their disposal. They can opt for gamete donation, they can ask for adoption etc. However, all these genetic public health programs are primarily aiming at serious genetic diseases, and of course there is a potential slippery slope, when other less severe or even late onset diseases would have been included. This is beyond the scope of this interview. In other words, let us offer best available care for people with rare diseases, yet let us also offer effective reproductive choices to prospective parents! In my opinion this is on of the potential ways forward, which could assure long-term sustainability and improve access to innovative therapies. This approach could also facilitate general population-wide acceptance that rare diseases represent a joint responsibility of all of us, i.e. potential parents, caring parents, their grandparents – all us have our share of responsibility for creating a dynamic, solidarity-based and equitable society which cares for our compatriots with rare diseases, but also offers efficient reproductive choice.

Here we need to find an optimal way how realistically present rare diseases to the public at large and how to promote well-informed reproductive choice. For instance, publicly available patient testimonies received two years ago a special award from the Czech government for sensible, culturally sensitive, and realistic promotion of the rare diseases to the public at large. As we learned in history courses, *"Verba movent, exempla trahunt"*. Our colleagues from Rare Diseases Czech national alliance demonstrate how patients and their families cope, what are the health / social care system deficiencies they might encounter, what are challenges, which together give the "full picture" to all interested audiences. We should provide this balanced information broadly, since social media tend to over-represent "outliers", both on the positive and negative sides of a given disease, so to speak. We also work with media, press and try to inform the public, not only on the occasion of the Rare Disease Day. However, these communication activities need to be carried out sensibly… you know how media thrive on controversial content. Hence, we try to steer public presentation in a positive manner and detach ourselves from any "stories", which could backfire.

We also try to educate social workers because, since they have ample expertise in terms of e.g. impaired mobility. But most of them don't understand that beyond injuries there is another group of citizens with clear social needs, which are mainly due to rare, genetic, causes. Based on collaboration with respected polling agencies (in 2014-2016) we learned that the general population considers under rare diseases weird or "bizarre" conditions, such as those which had been shown previously at circuses or at unethical vaudevilles, that is excessive elephantiasis or hydrocephalus, etc. They don't realize that many kids with rare diseases don't have intellectual disability, they can go to school and live almost normal lives. These are children like anybody else, but they have special needs. So, essentially, we must promote the

special needs concept in the context of rare diseases. We, I mean professionals, really ought to work with patient organizations. Here, the Czech overarching patient association really does a great job, and recent polls already detected an improved awareness of rare diseases amongst the public at large!

Thus, in the future the commonly applied "one size fits all" approach is not sustainable anymore. Rather we should customise our awareness, diagnostics and therapeutic strategies to better target different societal groups, to different ethnicities and to different cultural backgrounds, including the offer of customised information for their reproductive choice. Therefore, for instance, due to consanguinity, you might expect presence of several different recessive rare diseases in a single individual of Middle Eastern and North African origin. In addition, we might encounter a much larger population which necessitates a specific type of care that had previously not been administered in Northern Europeans, e.g. in the case of hemoglobinopathies. Thus, if we tackle all these emerging challenges within a well-balanced "cocktail" of preconpcetion-, preimplantation-, prenatal-, perinatal- and postnatal diagnostics, neonatal screening, together with efficient prenatal / postnatal multidisciplinary medical care we will be "driving on the proper bus line" into the future.

4. *One question on this priority and also about the actor's involvement: which role do you think Europe could play, especially on these shifts that needed to focus not just on treatment, but also on care and on the involving?*

A highly topical report came from the European Court of Auditors last year when assessing various European National plans and European Reference Networks from the financial point of view. We also have the 2017 Maltese EU Council Presidency position statement which should be followed upon by policy makers, in terms of structured health care, research and improved access to therapy in the field. Both important documents clearly state that in general European rare diseases initiatives are, grossly, underfunded and this aspect represents among others the major treat for their sustainable development. It is not that the European Commission should provide all funding, also Member States should invest their fair share into European Reference Networks. In the absence of meaningful funding these could break apart or in the better case not fulfil all of their key objectives. In addition, excessive bureaucracy could hinder progress, as we witness in the European Board of Member States on rare diseases. Now is the time for the European Commission, EU Council, Member States and other stakeholders to invest into the "structure" we have in place. That is to put the proverbial water into the pipes! We have a clearly stipulated deadline of year 2023, and we need to work on this with upcoming EU Council presidencies. As with all deadlines, the last year 2022 will be crucial and the responsibility lies on French and Czech presidencies in successive order.

5. *I want to ask you two questions that are interrelated. One is about looking back, what do you think are the lesson, success and failure, that we can learn from, on what you said, that change of generation. If you could speak with someone from a newer generation, who gets involved in rare diseases, what do you think would be the lesson, that you learnt from your experience that you would give to them? And the other question is about looking forward; so, the other way around. I think we touch upon different trends that you have mentioned before, this is just a recap, if you see.*

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 thought 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 mind set" in our field. In fact, this international collaborative mind set 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 is 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.

6. *Thank you. That was very inspiring. This conversation is very interesting, you mentioned very different trends. So I would like to go through them with you very quickly, just what come in your mind. I will mention one field and if you can recap a trend that you believe we should include in our horizon scanning, please do it. So, for example, if I think for economic field, you have mentioned different times this shrinking of resource, on how this could threaten the health care system and directly also rare diseases. But if I mention to you cultural and societal change, what trends do you think should be included in our horizon scanning?*

I would say that, mainly focus e.g. changing epidemiology of rare diseases, increasing percentage of rare diseases patients reaching adulthood, impact of intra- and the extra European immigration on rare disease prevalence together with the impact of preconception and neonatal screening programs, and most importantly on placing access to orphan medicinal products into a broader societal context of solidarity and equity. Easy said, right? However, I am optimistic that together national associations and Eurordis we may mitigate stagnant and/or even shrinking health care resources and leverage structuring / policy initiatives together with European Reference Networks and European / Member State policy-makers.

And for the technological field, what trends do you think should be there?

In terms of technology, and I may be biased as a medical geneticist, it is genomic medicine, since from all of the other "-omics technologies", so far only genomics plus advanced artificial intelligence-based bioinformatics tangibly improve rare disease diagnostics. But, you know, genomics and all these technologies *per se* are useless if you don't engage patients in the diagnostic process. For instance, when working with our Spanish colleagues within "Foundation 29". Here we learned that we don't have the capacity to study the natural history or all presenting symptoms of rare diseases. What I mean, is that patients reporting their age-specific symptoms together with improved technology and close collaboration might substantially improve diagnostic rate within undiagnosed rare disease programs. In this regard, international match making should not be underestimated.

Gene editing could bring breakthroughs, in particular the recently introduced "prime editing" offers a new promise, providing that safety issues, in particular in terms of our germline are fully accounted for. We also need to apply gene therapy as early as possible in order to avoid irreversible damage early enough. However, even if successful, the "the elephant in the room", are its potential off target effects which are really difficult to control and to detect. Notably, in my opinion it will remain difficult to tackle development of intellectual disability due to the very complex interplay of genes and environment, and which may start already prenatally as some studies carried out in the Down syndrome seem to suggest.

Finally, in terms of novel technology, a trend that should clearly be taken into account is that via embedding patient information into blockchain patterns, patient networks could then efficiently work with doctors and make use of machine learning for complex diagnostic and therapeutic algorithms, and maybe even improve clinical trials which suffer in our field from inherent problems, such as insufficient numbers of available rare diseases cases. It is not "artificial intelligence" *per se*, but rather "augmented – specific intelligence" utilizing high quality international rare disease -related "training sets". Here the responsibility is" collective", the technology will utilise models prepared by us and utilize data that we will render. Lets us involve patients not only in pre-market access-, but also post-market access research and thus tap into the wealth of underutilised shared data for the benefit of all of us.

And at political level, do you see any major trends that should be corrected?

Well, these will be difficult to influence by the rare disease field itself... However, with gradually increasing economic and demographic uncertainty, increasing disparities in income, differences between multicultural European cities versus countryside that is losing its younger populations. Also and there are unfortunate trends in terms of rising intolerance and decreasing societal solidarity. Moreover, with the demographic transition and ageing populations health care funding will come likely under increased strain. Remember, care for marginalised populations within given health care system is together with the quality of the social system represents one of the major indicators of a developed society. Thus, politically speaking, it is tolerance, openness and the international collaboration which need to be maintained. Finally, I very much hope that our UK colleagues and friends will be able to continue working with us following Brexit.

And for ethical or legal? Do you see the trends that we should look at or do you think this technology *or* a social change should be posed as a new ethical question?

Ethical issues are very important, for instance in the fields of preconception-, preimplantation and prenatal diagnostics. This is a very broad question with very complex answers, some of them also being ambiguous. In fact, ethical issues have been recently thoroughly discussed at the 20 Anniversary of the Oviedo convention meeting under the auspices of the Czech Council of Europe Presidency, held in the autumn of 2017 in Strasbourg. Discrimination, stigmatization applied within the context of economic or political expedience are potentially serious issues. Moreover, genetic testing could identify risks for late onset diseases, which creates a potential problems with increased insurance premiums in these cases, etc. In addition, we will need to decide which embryos should be prioritised for implantation within preimplantation genetic diagnostics when there will be several with more of them bearing different risks or even different rare diseases, in particular with rapidly improving diagnostic technologies. We all have several severe and many less severe variants… and many of severe variants do not manifest at all, as we see in the elderly, so there are many unanswered questions, thus far. However, we do not have the space within this interview to cover all of these difficult ethical and in fact also practical aspects, such as how far could we go in preconception prevention, which diseases should be included, what to do with unclear clinical significance of many variants, or do we have the realistic capacity to provide genetic counselling to all tested individuals? Importantly, the "Additional protocol on genetic testing for health care purposes" to the Oviedo convention that was ratified last year, in part through our Czech initiatives, and thus came into force for all Council of Europe Member States, and that renders "protective provisions" in this regard.

Postnatal ethics are related to access to orphan medicinal products, intergenerational solidarity and to the difficult field of palliative care. It is important to realise that the more you personalise care in rare diseases the more you need to tackle disease group-specific versus personal utility of access to care. So, for instance, I see that some patients may get treatment because they have certain variants for which a targeted "mutation -specific" treatment is available, but others, often majority, don´t. Then a small subset may require much for resources for their treatment compared to the "rest", due to e.g. a finite budget allocated for a certain disease category by payers; moreover based on previous budget forecasts that did not obviously take "historically" into account utilizaiton of orphan medicinal products. Frankly, there is a small group of rare diseases which are now ahead of the peloton, compared to other disease groups. Thus we all need to find a "cure for all "and not be complacent with apparent successes, applicable to a sub-group of rare diseases patients. Ironically, these are previously unexpected ethical aspects of personalised care we all are

aiming for in our field.

In terms of legal aspects, and here I do not want to speculate, some provisions of the orphan drug regulation could be amended, e.g. in my opinion long market exclusivity should not be "carte blanche", hence introduction of some conditional treatment efficacy indicators might be helpful for all stakeholders. These might even improve post-marketing research, foster access, yet not endanger economic incentives aimed at the industry. In addition, as e.g. in Czechia, where were we were able to introduce the term "rare disease" into our national health care legislature in 2014 (Act 28/1997 Coll. Therefore, other European Union member states ought to consider implementing the rare disease "legal concept" into their national legal systems as well. Such legal initiatives help us better negotiate with policy makers, facilitate access to diagnostics and high quality care. This way rare diseases get on the same level as common diseases, and cannot be wilfully disregarded. Finally, together with the European Society of Human Genetics we were able to assure EU-wide recognition of medical / clinical genetics in the EU Professional Qualifications Directive in 2011, since this medical specialty traditionally has been at the first line of contact for most rare disease patients and their families, essentially at the start of the patient pathway through the health care system.

So, for the economic area, you have mentioned the shrinking of resources as a possible threat and risk for rare diseases, but do you see any other trends in the economic fields that that could have an impact on rare disease field?

We had discussed these aspects already. Here, I only would like to say that when have been negotiating with other medical specialties we realised that they unfortunately view us as their "competitors". Informally their representatives tell something along the following lines: "we are dealing with common diseases which have substantial socioeconomic impact and so on, while you guys, it's fine what you do, we understand, but you are dealing with substantially smaller population which, in the end, may have a comparable budget impact on health insurance funds as "our" patient cohorts ". Conversely, we argue with an analogy of a maritime rescue operations –" when a large or small boat capsizes the rescue crews use the same resources, they do not differentiate based on the size of the boat, i.e. in this case the respective patient cohort". This is obviously a difficult discussion involving also difficult social priorities etc. So, when they put on the weight the potential budget impact of small cohorts of patients with rare diseases versus some other serious unsolved issues in our health care, then we are in a challenging negotiating position. Our negotiating position is sometimes even worsened when some pharmaceutical companies adopt a tough business stance, do not offer sharing, concessions or appropriate "discounts" in particular when negotiating access to smaller European "markets". There is publicly available information on this controversial subject and a lot of discussion by various rare disease patient support groups in the social media.

Alternatively, some manufacturers even do not bother registering their novel drugs in smaller countries, since their potential market there is insignificant in global business terms and thus is not worth their effort, investment and/or potential regulatory hassle. Another problem is related to so-called re-export of specific drugs from Central and Eastern European markets to more "profitable" Western European drug markers. Here, for instance a drug undergoes pricing negotiations and its price is substantially decreased to in accordance with the lower purchasing power of the Czech health care system; but within the EU common market distributors use the opportunity to freely re-export this particular drug which they bought at the Czech "regulated price", back to Western European countries thereby gaining unfair and substantially higher profit margins. This results in long procurement delays or even long-term absence of a given drug on our market(s), since the production capacity for some medicines has already been maxed out. Therefore, I keep reiterating that we need international collaboration, international approaches and as much transparency as much as possible at the European level. Providing that we would remain within our "national silos" we might continue struggling against a much steeper hill, so to speak.

7. **Thank you. That was a very clear picture of possibility and also risks. Now the last question is very open. It is about the Epitaph. If all constrains were removed and you could direct what is done, what would you do? What would be your really first priority?**

In the ideal world, my priority would be to assure a sustainable centre-based multidisciplinary care for all rare diseases, irrespective of the availability of targeted – innovative therapy, together with respective patient associations. That is we should primary aim for a comprehensive structure within European healthcare systems, optimally diagnosing and managing all rare diseases, in particular the ultra-rare cases. In terms of advanced therapies, as already discussed, find an appropriate and sustainable business model for access to orphan medicinal products, involving all stakeholders, and based on broad based international data-sharing.

Thank you. I really liked this interview. It was very inspiring. This interview is called sometimes a strategic conversation, but it is not always managing this question. We are really helping to support the kind of having an outlook to threats and the opportunities and you really give us such a broad, comprehensive and very strong views of vision and very clear identification of risk. And, I must say, I'm very happy and surprised because reading your CV, I have imagined something on treatment, while it's very good to have such a different view that there is the risk of overdoing and your attention towards the importance of a good health system, comprehensive and multidisciplinary.

Well, this is more of the above. Hereby, I can tell you, the main thing we have learned from the former health care system in our country is that, sometimes, a very good functioning system which is integrated, optimised and well-functioning, comprises well designed preventive schemes, can have equally good overall results compared to a poorly organised system where you have all the imaginable high tech available, but available only to few citizens. Of course this statement represents an oversimplification, but I hope that you understand the main notion I am trying here to convey. Essentially, if you want to assure equitable and solidarity-based health care, proper organisation of health care and setting optimal health care pathways linked to appropripate funding, is what is it all about right? It is not primarily about novel medical technologies; these will work even better if responsibly applied within a functioning health care system, and within the frame of multidisciplinary care. As I said in the beginning, we have a very good system now in place for rare diseases, we have European Reference Networks to which we should give maximum support! Thus, as in the case of our deteriorating environment, in rare diseases you also need to “think globally, act locally”. Most importantly we should approach all rare disease-related issues with a genuine conviction and let our hearts speak!

I really agree. Thank you. We really thank for this inspiring interview.

Robert Madelin

Bios

Robert Madelin is the International Chairman of FIPRA (Foresight International Regulatory and Policy Advisers). From 2004---2016, Mr. Madelin held a series of senior leadership positions at the European Commission: as Senior Adviser for Innovation, as Director General for Communications Networks, Content and Technology (DG CONNECT) and as Director General for Health and Consumer Policy (DG SANTE). Prior to that, Mr. Madelin was for 20 years a negotiator in international trade and investment, first for the UK, and then for the EU. Robert served notably in the Cabinet of European Commission Vice---President Leon Brittan. He studied at Magdalen College, Oxford and at the French Civil Service College (ENA). His other current major engagement is as Visiting Research Fellow at the University of Oxford's Department of Politics and International Relations. He is also an Honorary Doctor of the University of Edinburgh, an alumnus Policy Fellow of Cambridge University's Centre for Science and Policy and an Honorary Fellow of the Royal College of Physicians of London. Robert is the author of 'Opportunity Now: Europe's mission to innovate' (2016)

Interview transcript 8 October 2019

1. Meet a clairvoyant. If you could speak someone from the 2040 who could tell you anything about Rare Diseases governance and treatment, what would you like to ask?

I think I would like to ask, firstly, how far the potential of genomic medicine has been developed by then. And secondly, how far diagnosis has been a major breakthrough and how far treatment.

2. Optimistic but realistic outcome. If things went well, how would you expect the Rare Disease Governance and treatment to develop in the next 20 years and what would be the signs of success? what is your vision?

If we start with screening and diagnosis, I think that you can imagine a fairly comprehensive benchmark set raise to find out whether at conception or birth people are susceptible to a range of rare diseases. And I think that sort of upstream identification, both enabling treatment to begin and avoiding the current sort of months and months of uncertainty that typically goes with rare diseases, would be one improvement in the management of rare diseases.
Then the question about Whether you could use personalized medicine and again genomic interventions to treat the cases, that's a more delicate question and maybe in some cases yes, in some no. But I think the signs of success therefore would be both the patient population would be 90% known and the known population would be, let's say 75% treatable. And then the treatment means a significant improvement in life expectancy and life quality, which may vary from disease to disease. So that would be my view.

1. **A pessimistic outcome. What are the dangers of not achieving your vision? How could the environment change to threaten RD governance and treatment?**

I think that an obsession with privacy and individual rights and a paranoid fear of how governments and corporations could misuse knowledge around genetics could combine to diminish available research and discourage potential starts from entering these fields and, it could be it very hard for the broad diagnosis and treatment vision to come to pass.

2. The internal situation. From your knowledge of the Rare Diseases system organization and resources, which are the priority changes to make your vision a reality?

One of the challenges I see is whether the rare disease framing is the right framing anymore. In a way, the rare disease framing goes to the idea that rare diseases suffer a market failure because the volume of potential treatable needs is too low. And a lot of the logic around intellectual property reform and funding for research has been devoted to that. I think we're now in a situation where you need a new way of framing. And I think we need to look at diseases where we think that a deep investment in the potential of genomic databases and personalized medicine can provide the breakthrough. Then maybe other diseases, where that's not the answer, we still need to look for other answers.

So, I think that one priority changes is to keep the framing of the set of problems called rare diseases open to improve the framing as knowledge improves. Secondly, I think most people can't really relate to the endless list of bad things happening to small groups of people. And so, there's a real tension in the rare disease movement between a desire for those who relatives or patients or survivors of a specific rare disease to focus on their specific rare disease and the need to create rather coalitions for paths to treatment. Clearly when you then say, I need human faces to sell this need, you go back to people who are suffering from specific diseases. But I think that, just as we may need to reframe rare diseases to segment the body of rare diseases on the basis of their treatability and in the light of current knowledge, we also need somehow to be more willing to join together and to look at the rare disease problems without getting too obsessed with whether the solution is for my disease or somebody else's.

And then I think the third point is that in some areas, it will be important to ally with those who are seeking funding for common diseases, especially if I'm right that the genetics piece is the crucial way forward, then there will be some rare diseases and some less rare diseases who could together benefit from certain genomic breakthroughs. And I think we have to be open to collaboration so that rare disease doesn't get caught in a silo of its own.

3. Looking Back. Looking back at the past 10/20 years, are there particular lessons – successes, failures – we can learn from?

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.

4. Looking forward. What major decisions with long term implications are faced at the moment? What needs to be done now to ensure that your vision becomes a reality? Please take into account the following PESTLE categories: Political; Economic; Societal; cultural; Technological; Legal ; Environmental

I think in the political framework, we're currently in Europe discussing new concepts such as the economy of wellbeing, such as an economy that works for everybody, such as all policies for a healthy Europe. All of these means invite to think about the relative priority we give to promoting health, preventing disease and treating it. I think that's the right strategic framework. The tragedy is that people want concrete, verge, vertical initiatives. So for wellbeing, you do Alzheimer's and instead of doing health in all policies, you do cancer. And I think politically there is a challenge for the incoming institutions to keep the picture broad enough.
If I then move to the economic, I think in economics the key challenge is how to have all of the potential health benefits of innovation while maintaining a sustainable health system. And the question, is the market functioning, in which case we need more money or is it misfunctioning, in which case we must ration or manage the prices. I think this is huge and it will be a central issue during the five years ahead. A period of relative austerity and at the same time of health innovation. If I then look at social -cultural, I think the tension, I mean, whether it's there or legal, ethical, I don't know, but it's the tension between wanting to, exploit all the potential advantages of technology and on the other hand not wanting to play God. I mean, I think that there is a real issue, I do see this as a social cultural thing. Innovation is not favored as a good thing. And therefore, there is a degree of fatalism still underlying our social -cultural stance and people who are born victims of very serious diseases. I think, you know, the question is, do we screen them out through therapeutic abortion? or do we accept the costs and the challenges in our society of trying to cure sick people? I think that's a really tricky one and I think it will get worse. In the technology area I see the main challenge as moving from technology push to responsible innovation where questions of the sort, I'm just exploring it are dealt with as an integral part of the innovation pathway and not ignored. Which would mean a redesign of who is an innovator, who do we put on innovation teams? Do we have enough disciplines around the table?
And I think therefore the issue about technology is not, if we want more or less of it, but can we make responsible technology in the same way that we want to make an economy of wellbeing and the sustainable food system and so on. So, the reinsertion of a value proposition in technology. The legal ethical space, I have partly spoken to it. I think if we get the ethics and rights too heavy, we'll stop curing stuff. I think a good focal, a good case study remains data protection and how it's varied. That just an anecdote, it's very clear when you bring something like the Finnish health systems decision to make primary legislation in Finland called the fin data act or something like, that to enable the pooling and secondary use of health data. And you describe this to the audience in the Brussels bubble, a lots of privacy lawyers say, but surely this is not possible or isn't right. But it is possible. So, there's a sort of a risk that both on the legal front through instruments such as GDPR and on the ethical front through prioritization, disproportionate prioritization of goals such as privacy. We may undershoot the available health-giving benefits of this decades. And then environmental, in the rare disease space I think the environmental considerations are minor, though not insignificant, but is that the same as pharmaceutical production and pollution in the whole of the medical field, I would say.

5. The Epitaph If all constraints were removed and you could direct what is done, what would you do?

Firstly, I would be much more directive about the creation of a multimillion genome database making genomic pooling opt-out rather than opt in, for example. But at the same time, strengthening prohibitions on the discrimination against people who have contributed their genome to such databases. So, protecting them against insurance premium increases, refuse it, refusals to employ. So, that will be the first thing. The second would be to increase the funding for the diagnostic step and to make it acceptable that a much higher battery of preventative screening takes place early on. Thirdly I think, I would want to increase the proportion of overall funding in fields. I mean, such as rare diseases, but as I said, halfway through not being too rigid about what is a rare disease and what is not.

Didier Schmitt

Bios

Didier Schmitt currently works on space policy at the European External Action Service, the diplomatic service and foreign and defence ministry of the European Union. At the European Commission his first focus was on space policy, having worked in the Space Policy Unit at the European Commission from 2009–12. From 2012---2014 he was scientific adviser and foresight coordinator in the Bureau of European Policy Advisers to the President of the European Commission. He co---authored the first inter---institutional report of the European Union on future trends: "Global trends to 2030: Can the EU meet the challenges ahead." Prior to that, at the European Space Agency he managed human and robotic exploration preparation programmes, including the use of the International Space Station (1997–2009). In his academic career, he was associate professor at the Toulouse medical school and the International Space University (1992–1997). His educational background is a PhD in biosciences in addition to being a certified medical doctor. Currently working in the European Union diplomatic service, he is a regular opinion writer in mainstream French newspapers on future issues in science, technology and policy.

Interview transcript - 8 October 2019

1. **Meet a clairvoyant. If you could speak someone from the 2040 who could tell you anything about Rare Diseases governance and treatment, what would you like to ask?**

It would be about cost. This is the central point. Take as example the human genome. It started in the 90s it took more than 10 years. But by now you can do your sequence from 200 euros. So, I would like to know about the cost of genetic modification. My question would be “How far will they go down in the future?”.

2. **Optimistic but realistic outcome. If things went well, how would you expect the Rare Disease Governance and treatment to develop in the next 20 years and what would be the signs of success? what is your vision?**

For me it’s a societal view. I think RD is now not ‘fashionable”, it’s rare. We put it in a corner because its rare. Therefore, I think we have an effort has to be done to make people, general public, understanding that everybody is different genetically and RD is one of the multiple variabilities of humankind. I think this is important and affects how we view and how we talk about the subject.

We have now to make programs in the areas of genetics and Rare Disease would benefit from this. It’s not that we are investing billions for treatments that help just few people, we have to invest in order understand genetics and, in doing so, we will also help RDs patients too. When we set programs, we need to think more globally and in larger scale. And , it may not be easy to convince people to do so, even the scientific community.

How would you measure this change? This progress? I don’t know. Measuring changes in the comprehension and detection of diseases is difficult. Legal initiatives can also rapidly change the framework. It’s not acceptable that people have to decide. One way, could it be to measure impact in the media of this issue.

3. **A pessimistic outcome. What are the dangers of not achieving your vision? How could the environment change to threaten RD governance and treatment?**

This answer is very easy. The costs in every country for medical care are going up. And RD are very sensitive to this because treatments for some cases are very

expensive. However, any new treatment is expensive due to the pharma need to recover R&D costs. So, every new treatment is more expensive than the previous one. However, the national budget for health will probably not increase in the next decade and, on top of this, economy may face a new crisis in the coming years. If our economy will not growth, the health budget will not increase. So, any new, expensive treatment will not make it. Healthcare systems will ask themselves why treating one child instead of hundreds with more common diseases. In an economic crisis people become very egoistical. And that is the pessimistic outlook.

4. The internal situation. From your knowledge of the Rare Diseases system organization and resources, which are the priority changes to make your vision a reality?

You have seen it a few months ago, when one child had a genetic modification. The argument is that if you modify this gene then people will be superior. This is the first sign of human augmentation. It has been done in China [*note: The twins, called Lulu and Nana, reportedly had their genes modified before birth by a Chinese scientific team using the new editing tool CRISPR]*. This trend will increase significantly. You will take a trait that is "normal" and make it better.

If you look at the technology used for human augmentation is the one that can also be applied to RD. There might be the opportunity to use the investment made by billionaires for human augmentation for good and treat RD patients. At the end, it may be like doing a pact with the devil, but why not linking the two? On the one hand, you have money, but on the other hand, you have ethics considerations. It's a wild card but as a futurologist you can consider this.

If you look at another thing, that is a bit out of the box, it is prevention. The scientific community does not look at prevention. And we always go for better treatment which often involve technology and innovation and it is expensive. Prevention is also an area which is barely of interest for policymakers because it's a long-term investment. Who is really interested in health prevention? Thinking out of the box, the insurance companies might… This might be true especially taking into consideration the ageing trend. So a big change in health-care may come from insurance companies. There could be a opportunities to collaborate with insurance companies and see if they could interested in Rare Diseases. As example Axa has done a foresight exercise.

5. Looking Back. Looking back at the past 10/20 years, are there particular lessons – successes, failures – we can learn from?

Not answered

6. Looking forward. What major decisions with long term implications are faced at the moment? What needs to be done now to ensure that your vision becomes a reality? Please take into account the following PESTLE categories: Political; Economic; Societal – cultural; Technological; Legal; Environmental

My attitude is relatively simple. It is obvious that human augmentation is one of the major societal changes. We have to rethink the role of humans in society. There will be a huge shift. This will be one of the major topics. Who can afford to become "superior" human? It is a trend in China and in Silicon Valley. There are thousands of parents who are ready to make genetic changes in their kids to make them more competitive. Its sounds crazy today but it will be less and less so as time goes by. The phenomenon has economic and political implications and open immense ethical issues.

Human augmentation is also about genetics. It's not just physical augmentation (virtual reality etc). And, if human augmentation develops, it could also help to correct a genetic problem. You can use CRISPR either to correct something or change someone. Where does our society go in the future? If indeed the costs go down, which will probably be the case, then everyone can decide what changes they want to make. So I anticipate this is one the most important trend for RD together with costs, and it would be good to link the two. Having said that we should discuss whether it is better to augment someone who is 'normal" or to cure someone with a disease.

This is the conversation we need to have a societal level.

If we look at space policies, we have the same problem. Europe has to be a strong player in making the balance between exploration and exploitation. It's the same balance. And this is where we have to open the debate. We have to link it to the society discussion about humanity and about what is augmentation and genetic modification.

Does Europe have a role? Which one? Leader or Follower? Let me make another analogy. About AI in defence and other sectors. AI in the US is just getting wide and the main question is how can AI help the economy growth? In China, it is used more to control the population. These are two great extremes: one is capitalism and one is political control. Can Europe represent a third way? At the end, AI development is also about values. What makes more sense for society. How we can make a better society with AI.

In US, if you have the money you have the treatment. In China, it's the political system that will choose. And I do not think that RD for them is a hot topic. So, Europe could also play role in here by developing a third way which is more empathetic. And not just look at the money and/or at controlling society. So, if we want to promote RD as a priority, we should say this is the European view. And this is different or unique from the others. A third way that encompasses the values we have in our society. This is a challenge but also could also represents an opportunity. It could be a kind of "European" label seen as trying to do things a bit different. It's a "branding" for Europe. It could raise interest from citizens. And unify citizens toward a more the European perspective.

7. The Epitaph If all constraints were removed and you could direct what is done, what would you do?

The obstacle is cost of treatment. If you could divide cost by 100, which would require having a bigger market. So, if you could then generalize CRISPR technology and others to come, then you could decrease the cost.

But then anyone can have access to this treatment to enhance him or herself. And that why we have to prompt this third way based on ethics and values. We have to be careful on how we use technology. If we open the pandora box wider, we will get the bad with the good.

If my wish comes true, it brings huge risk. It's a good topic for the press, for the media, if we now say that the cost of genetic modification will go down. As was the case with genetic screening, there is a huge risk to change us as humans - if these modifications can become permanent.