RARE 2030

D5.2 RARE 2030 Scenarios: a stakeholders view

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EXECUTIVE SUMMARY

RARE 2030 applies foresight methodologies and tools to explore the future policy framework for Rare Diseases (RD). The foresight approach is designed to devise alternative future scenarios and set out roadmaps for their implementation through changes in policies and strategies, so as to better shape our tomorrow. More specifically, 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;
- 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 promptly adjust regulations to social and technological changes;
- set priorities for investments in order to anticipate/adapt regulatory infrastructures and services supply to future needs.

The RARE 2030 Scenarios are developed according to the 'intuitive logics foresight school' and 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 of, integrated into, and reflect national legislation and policies. The RARE 2030 Foresight study includes 4 major steps:


① Establish a knowledge base by critically review existing knowledge and emerging issues through a literature review.
AUGUST 2019

② Identify the major **TRENDS and DRIVERS** that may shape the future of rare disease policy.
NOVEMBER 2019

③ Build a number of **FUTURE SCENARIOS** in which certain trends are more or less prioritized
MAY 2020

④ Translate the preferred scenarios into **POLICY RECOMMENDATIONS** that will lead to a better future for people living with a rare disease.
DECEMBER 2020

This report presents the findings of the third step of this process: the so called "Building Scenarios" phase – which is consequential and builds upon (i) the in-depth analysis of the state of art of RD policies (D.4.1), (ii) the horizon scanning phase investigating the trends related to Rare Diseases cure, treatment and care (D4.2) and (iii) the scenarios space phase (D5.1).

In the latter, two axes were proposed to create RARE 2030 Scenarios space:

- **Societal attitude toward solidarity** (horizontal axis) featuring a predominant role of public

intervention in pursuance of the goal of equity and socio-economic convergence ("collective accountability") on the right side, and increasing self-regulation on the left side.

- **The Innovation** axis (vertical axis), featuring population needs-led innovation on the top and market-led innovation on the bottom
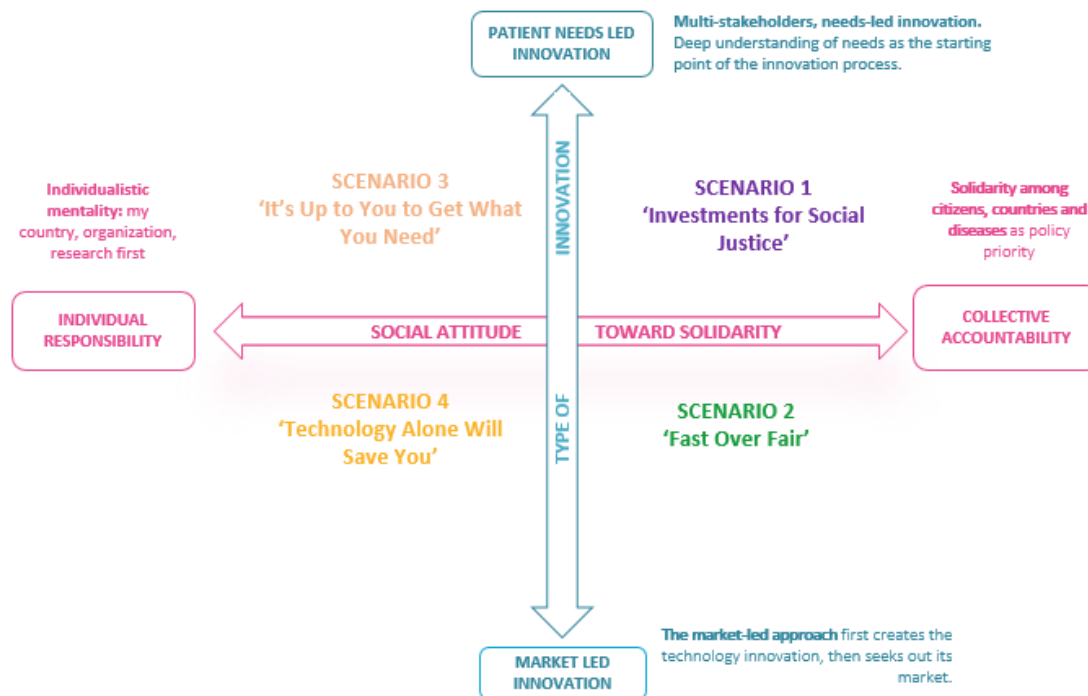
At the time of refining RARE 2030 Scenarios, Europe has become the epicentre of the Coronavirus pandemic with dramatic death rates in Italy, France Spain, and the UK. The Coronavirus has changed the way we all live, work and interact and generates considerable uncertainty – political, economic, social and technical – on what the world and the European society might look like in the next decade. The first section of this report summarizes a review of the current foresight thinking and articles on the Coronavirus pandemic in order to help appraise how the foreseen global landscape shifts might interact with RARE 2030 Scenarios and provide a better understanding on the risks and opportunities the rare disease community might face.

Taking these insights into account, the second section sketches radically different visions of how Rare Diseases cure, care and treatment could have evolved in Europe at 2040. To do so, we have systematically reviewed all the inputs received during the different consultations in order to confer coherence and plausibility to the storylines. The RARE 2030 scenarios are now available also as videos at: https://www.Rare 2030.eu/scenarios/

The third and final section presents selected findings of the conference European Conference on Rare Diseases and Orphan Products (ECRD), held online on May 15th-16th, 2020. Far from providing an exhaustive account of all the conference discussions, this section aims to highlight – for each of the conference topics – the forward-looking ideas, contributions and examples that emerged. The ECRD 2020 Conference also offered the opportunity to present and test Rare 2030 storylines and to initiate the fourth and last step of the foresight process "the back-casting phase" in which stakeholders are invited to

devise policy options, strategies and targets to reach their preferred scenario. In line with this, contributions from each session discussion (Annex I) have been captured and organized according to the following three areas:

- • Vision – statements on the future
- • Challenges – today
- • Opportunities and pathways
- • Inspiring projects, best practices and niche innovation

The next report will review, analyse and cluster the inputs received in order to formulate policy recommendations. The final aim of this work is to generate ideas that could promote sustainable and real changes in this time of crisis. "*There is enormous inertia—a tyranny of the status quo—in private and especially governmental arrangements. Only a crisis—actual or perceived— produces real change. When that crisis occurs, the actions that are taken depend on the ideas that are lying around. That, I believe, is our basic function: to develop alternatives to existing policies, to keep them alive and available until the politically impossible becomes politically inevitable*"[1].

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[1] M.Friedman (1962) "Capitalism and Freedom" quoted by Naomi Klein in the video "Coronavirus Capitalism: Naomi Klein's Case for Transformative Change Amid Coronavirus Pandemic". by The Intercept reported by Democracy Now Show. Available at: https://www.youtube.com/watch?v=IFqNAEx1lm4

1. COVID 19: ON THE EDGE OF A "NEW NORMAL"?

In foresight jargon, wild cards or black swans are defined as disruptive events with low probability of occurrence but with high expected impact. What happens if they actually occur? The events classified as such are able to provoke drastic changes and modify the foreseeable trends development in unexpected ways: accelerating some, slowing-down others and creating new ones.

In October 2019, the RARE 2030 Panel of Experts was asked to identify possible wild cards for the future of RD diagnosis, treatment and care. Not all changes proposed could be considered as wild cards or 'unexpected events' since they are strictly dependent on policy choices, strategies and programming and rather represent deliberative changes – though still potentially disruptive – than unexpected surprises.

The figure below maps the negative changes proposed along two dimensions: the speed of change (gradual vs rapid) and the policy influence over the event (reactive vs proactive). The processes classified as "transformation" and "transitions" - listed in the bottom part of these graphs - are systematic shifts that will be taken into account in the writing of the scenarios storylines. Conversely, those changes considered as "disruptive transformation" or "policy shocks" – presented in the top quadrants of the figure – will be included in the scenarios as wild cards. The bubble size reflects the number of times that the event occurrence was mentioned by the survey respondents.

Epidemic illness and economic crisis were mentioned by respondents as possible wild cards and should accordingly be considered in the RARE 2030 Scenarios – imagining the impact they might produce on healthcare trends and their implications on RARE 2030 narratives.
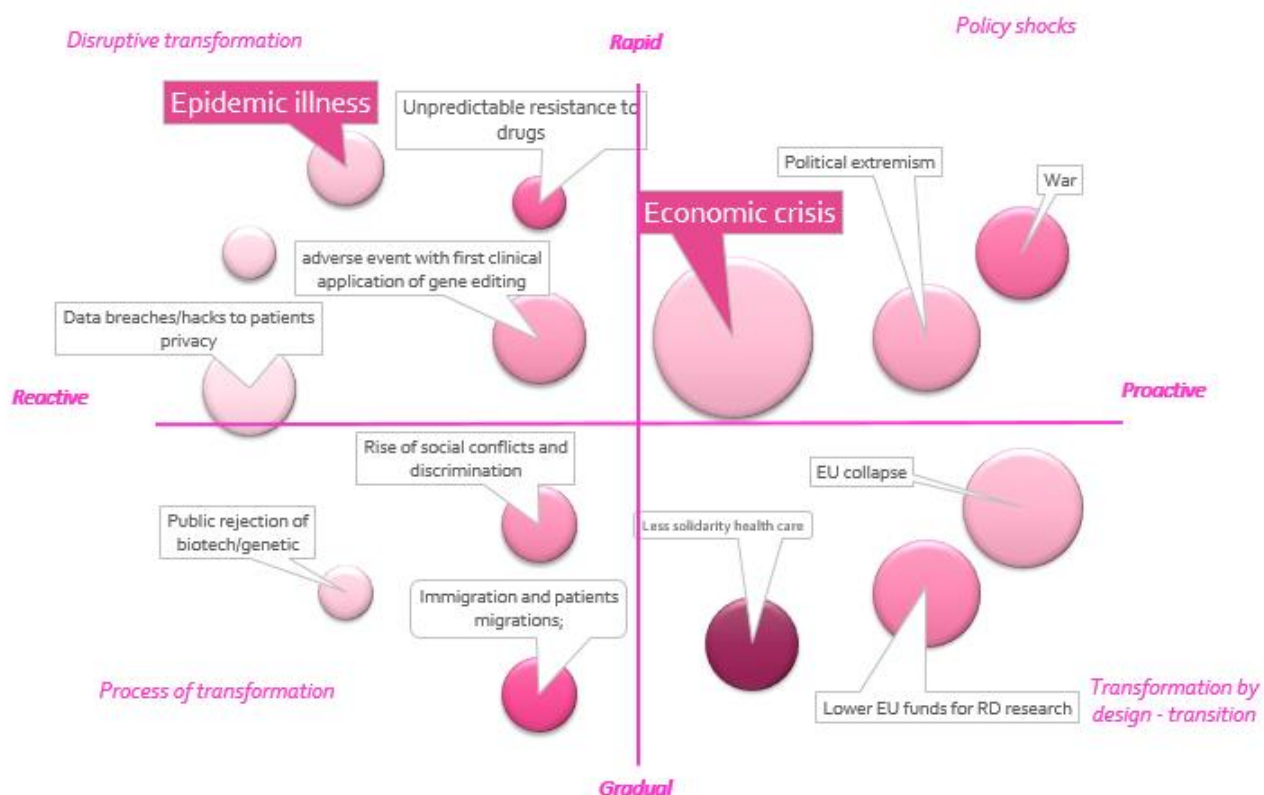

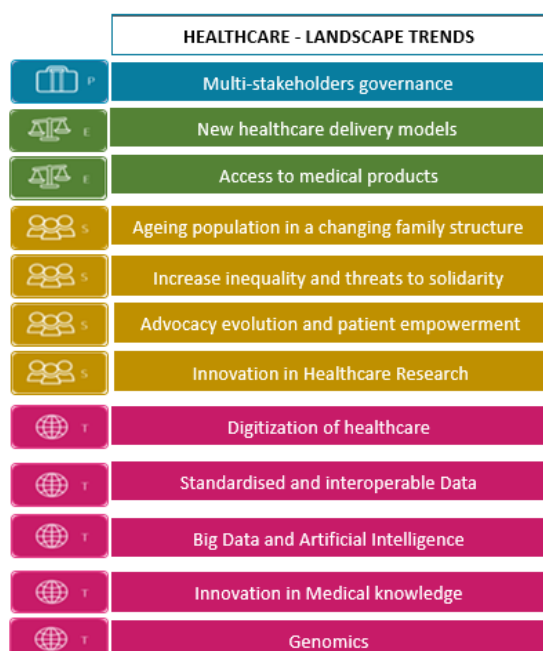*Figure 1 Negative wild card emerged in RARE 2030 survey*

HEALTHCARE - LANDSCAPE TRENDS
Multi-stakeholders governance
New healthcare delivery models
Access to medical products
Ageing population in a changing family structure
Increase inequality and threats to solidarity
Advocacy evolution and patient empowerment
Innovation in Healthcare Research
Digitization of healthcare
Standardised and interoperable Data
Big Data and Artificial Intelligence
Innovation in Medical knowledge
Genomics

Figure 2 Healthcare – Landscape trends

Throughout history, pandemics represented turning points catalysing change and shaping societies. The question arising today is to what extent and in which ways the Coronavirus pandemic will create long-term structural change in the way we live, work, interact and care. How will the 12 RARE 2030 'landscape trends' (see Figure 2) change and to what extent will the new reality represent a challenge or an opportunity for rare diseases diagnosis, care, treatment?

The prognosis is unclear because much is unknown on the COVID-19 dynamics and lasting consequences: incubation period and length of the infectious period, possible effective drugs and limited immunity after recovery – with possible virus recurrence later in 2020 and into 2021.

What we know now is that the Coronavirus pandemic has affected 15 millions of people and caused 623.000 deaths[2] worldwide. It has required governments to strike a balance between health protection and economic development. On one hand, healthcare systems are facing pressures never previously encountered in recent times, experiencing a shortage of healthcare workforce and devices, boosting intensive care and postponing elective care. The 30 million people living with a rare disease in Europe are one of the most vulnerable populations during this crisis. The EURORDIS COVID-19 survey shows that the pandemic heavily impacted the rare disease population – for example disrupting planned care, social support and exacerbating mobility issues[3].

On the other hand, many economies, currently suffering from the freezing of industrial production and trade, are at risk of recession in the near future with devastating consequences in terms of employment and welfare resources[4]. In addition, psychological and social consequences of quarantine and isolation are deeply feared, especially in view of a rise of the unemployment rate. We look at the consequences of the COVID 19 pandemic in four different areas highlighting the opportunities and risks that they might bring.

A changing geopolitical landscape. The Atlantic Council[5] has proposed three scenarios on how the Coronavirus pandemic could change the global political and economic balance of the future.

- *Great accelerator downwards* scenario: sketches a worldwide, long lasting health and economic crisis;
- *China first* scenario: features a new dominant role of China in the global political and economic landscape and the approval of "wall building policies";

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[2] ECDC. Situation update worldwide, as at 23 July 2020. Available at: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases

[3] EURORDIS RARE BAROMETER VOICES COVID 19 SURVEY.
https://download2.eurordis.org/documents/pdf/PressRelease_COVID19surveyresults.pdf

[4]   BBC News. Coronavirus: a visual guide to the economic impact. 30 April 2020. Available at: https://www.bbc.com/news/business-51706225

[5]   Atlantic   Council.   What   world   post   COVID-19?   Three   scenarios.   April   2020.   Available   at: https://atlanticcouncil.org/wp-content/uploads/2020/04/What-World-Post-COVID-19.pdf

- *New Renaissance* scenario, characterized by a better cooperation between States and a greater cross-border collective responsibility and solidarity feeling.

As for the European Union, in line with European Commission President Ursula von der Leyen statement "the EU as a whole needs to be determined, coordinated and united[6]", the need to be unite to cope and not succumb to Coronavirus emergency and its consequences could be the opportunity to concretely strengthen the EU achieving the 'United States of Europe'. In the current emergency phase, populist waves are witnessing a decrease in their consent. However, the risk of a surge of nationalist movements in response to the economic crisis cannot be underestimated.

Acceleration of scientific collaboration. A positive repercussion of the Coronavirus pandemic is the acceleration of the worldwide multi-stakeholder scientific collaboration in R&D[7]. All countries are now committed to collaborate to speed up research in vaccine and in new drugs in public private partnerships (PPP). The urgency to quickly develop and validate diagnostic tests could:

- foster genomic technologies and extensive AI use in healthcare,
- incentivize pharmaceutical innovation in areas with "high public health value but relatively lower market value[8]",
- promote the de-bureaucratization of the authorization process of devices, drugs and tests in healthcare[9].

ICT Technologies on the rise. One of the foreseeable consequences of the COVID-19 pandemic is the rise of ICT (information and communication technologies) applications in all sectors of society: work, leisure, care, security.

Lockdown has taught us that we can be distant but connected and has opened the door to a new remote-everything era that "has become completely acceptable as well as technically feasible for almost everyone"[10]. Similarly, the 2003 SARS epidemics in China boosted the e-commerce activities changing the global market dramatically[7]. However, the extent to which ICT applications and opportunities will be accessible to all is still to be understood, as 'digital divide' phenomena could generate new inequalities in accessing fundamental services such as education and care.

For healthcare, the pandemic has led to the widespread use of telehealth (+ 50% in US) whose use boosted notably to avoid intra-hospital infections[11]. People living with a rare disease made increased use of telemedicine (mostly in the form of teleconsultations) which is essential to maintain the necessary care (9 in 10 report that this experience was helpful). Some countries even made reimbursement possible when previously it was not foreseen. Flexibility has been shown when it comes to the renewal of prescriptions which EURORDIS has called for in the past. EURORDIS encourages policy-makers to see telemedicine and online consultations not only as a way to deal with a crisis, but to consider

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[6] EC. Press corner. Von der Leyen on Coronavirus response: EU to be determined and united. Available at: https://ec.europa.eu/commission/presscorner/detail/en/AC_20_466

[7] Science Mag. A completely new culture of doing research.' Coronavirus outbreak changes how scientists communicate. 26 February 2020 . Available at: https://www.sciencemag.org/news/2020/02/completely-new-culture-doing-research-Coronavirus-outbreak-changes-how-scientists

[8] Vox. How the Covid-19 pandemic will leave its mark on US health care. 22 April 2020. Available at: https://www.vox.com/the-highlight/2020/4/15/21211905/Coronavirus-covid-19-pandemic-medical-health-care-hospitals

[9] Harvard Business Review. We Need a Cheap way to diagnose Coronavirus. 26 February 2020. Available at: https://hbr.org/2020/02/we-need-a-cheap-way-to-diagnose-Coronavirus

[10] Gerd. Welcome to The Great Transformation: How Covid-19 changed our world: Futurist Gerd Leonhard looks back from the near Future. 24 March 2020. Available at:https://www.futuristgerd.com/2020/03/a-crisis-is-a-terrible-thing-to-waste-how-covid-19-changed-our-world-futurist-gerd-leonhard-looks-back-from-the-near-future/

[11] National Organisation for Rare Disorders. Update on NORD's Recent Advocacy Work on COVID-19 for the Rare Community. Available at: https://rarediseases.org/update-on-nords-recent-advocacy-work-on-covid-19-for-the-rare-community/

incorporating them as a component of routine care within their health systems with clear clinical governance standards, respecting patients' preferences and under adequate data protection safeguards.[12]

Despite the support that AI and advanced technology are bringing to the epidemic control, the current crisis has unmasked a global unpreparedness in the standardization, interoperability and cross-country sharing of data[13]. Cooperation on ICT infrastructures across the EU and beyond could greatly increase the contribution of AI and digital health in the coming future.

The emergence of a new sense of responsibility? Lacking a vaccine and an effective drug, Coronavirus has underlined that collective responsibility is the only preventive action we can rely upon to stop the infection spreading. All citizens have been called to take action – stay at home – for a collective good. The lockdown could provoke long lasting changes in citizens' empowerment and stakeholders' collaboration on healthcare policies. For example, the Spanish flu has led to embrace the concept of a "free at the point of delivery" healthcare and increased cross-country health collaboration with the foundation of international health agencies[14]. The Coronavirus pandemic could also strengthen movements that advocate universal health coverage for vulnerable populations, and advance request to increase and make healthcare investments more transparent[15].

The need to imagine a new world. The Coronavirus emergency has strongly underlined the benefits of the foresight process that, short of predicting the future, helps in preparing to face with it. The shock of the Coronavirus pandemic can thus be seen as an opportunity to speed up/promote the social and technological advances matured over the past years. As the German futurist Matthias Horx summed up "There are historical moments when the future changes direction. We call them bifurcations. Or deep crises. These times are now. The world as we know it is dissolving. But behind it comes a new world, the formation of which we can at least imagine" [7].

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[12] EURORDIS RARE BAROMETER VOICES COVID 19 SURVEY.
https://download2.eurordis.org/documents/pdf/PressRelease_COVID19surveyresults.pdf
[13] Financial Times. Can Data save us from Coronavirus. 3 April 2020.Available at: https://www.ft.com/content/1f7f748f-3077-401d-afd6-742d9006ef43
[14] TIME. The World Changed Its Approach to Health After the 1918 Flu. Will It After The COVID-19 Outbreak? . 7 March 2020. Available at: https://time.com/5797629/health-1918-flu-epidemic
[15] Devex. After the pandemic: How will COVID-19 transform global health and development. 13 April 2020. Available at: https://www.devex.com/news/after-the-pandemic-how-will-covid-19-transform-global-health-and-development-96936

2. RARE 2030 SCENARIOS

The table below provides a snapshot of how trends could evolve under the four different Scenarios whereas the following four sections describe in greater detail the four different possible futures.

	1 Investments for social justice	2 Fast over Fair	3 It's up to you to get what you need	4 Technology alone will save you
SOCIAL ATTITUDE	EU increased cooperation on health policies	EU increased cooperation on health policies	Health is a national issue, less cooperation and solidarity between countries	Health is a national issue, less cooperation and solidarity between countries, citizens and patient organisations
INNOVATION	Population needs led innovation	Technology led innovation	Population needs led innovation	Technology led innovation
Rise of multi-stakeholders governance	ERNs are thriving – they are the centerpiece of RD and specialised healthcare scene in Europe	ERNs active but more as European administrative – structures, used more by pharmaceutical companies than by patients	Strongest power for ERNs of diseases/groups of diseases with more political engaged patients and/or industries connections	ERNs no longer exist - Cooperation collapses under financial strain
Rise of innovation-oriented research	Multi stakeholders, cross countries research led by government	Multi-stakeholders, cross-countries research led by industries	Powerful groups and empowered individuals lead research	Few powerful private companies lead the research
Medical Innovation and genomics	Technologies cover unmet needs, including also the needs of those diseases that are typically underserved	Innovation try to achieve maximum results with minimum efforts. Companies and regulators strike a balance between what is needed and what is profitable with redundancy of treatments for the most known diseases.	Focus on local needs and on those diseases of the most empowered groups.	No coordination between stakeholders, the market decides focusing on profit rather than needs.
Healthcare systems and new care delivery models	Needs-led, outcomes-driven system, Specialised and primary care fully integrated ensuring continuity of care. Holistic care is the pivotal principle of healthcare	Increased cost-saving policies led to top-up payments for breakthrough innovations. High quality specialized services (i.e RD Centre of expertise) exist but there is lack of knowledge in primary care.	Wide differences on healthcare services provision and quality among EU regions. Holistic care pathways often established thanks to patient organisations.	Private, insurance based healthcare systems. Healthcare professionals have no time to investigate the complexity of PLWRD. Centers of Expertise reduce paramedical and holistic care services.

Digitalisation of healthcare	Digital revolution of the healthcare system accomplished with equal role of all stakeholders (government, patients, private companies)	NHS rely on private companies for digital skills. National infrastructures are often too old for the new digital innovation that not always meet patients' needs	Companies and patients are allies to develop and improve digital solutions useful to patients	Technologies depersonalise healthcare without real outcomes improvement
Standard and interoperable data and the rise of AI	EU sets rules and builds common infrastructures for data sharing and the implementation of AI in MS	Soft government ensure some common rules to regulate the market which offers services and infrastructures	Bottom-up approaches – empowered communities set rules and infrastructures to best meet their needs	Few private global companies manage the structures and infrastructures
Access to treatment and care	Harmonisation of HTA at EU level and cooperation and transparency in pricing and reimbursement lead to equal access to treatment across Europe	Cooperation and transparency is a principle that does not translate in effective policies. The cost of OMPs and RD devices remain a barrier for many to access treatments and care. Innovative drugs take long time to reach patients	Treatment and care availability depends on country/ individuals/groups willingness to pay or reach agreements	Treatment and care availability depends on individuals willingness to pay or charity foundation support
Equity and solidarity	"Leaving no one behind" is a must for health policies at all territorial levels	EU collaboration focus on technological development – little attention payed to social inclusion, psychological and educational measures	Increased solidarity only for those of the same community/coalition (disease, territorial, category)	Increased competition between citizens and groups. Worsening of equity, exclusion in society, discrimination in the labour market for vulnerable population
Ageing of population	Harmonisation of NBS among EU countries and services set to guide the age transition	Establishment of rules for NBS market and exchange of best practices for guiding age transition	Wide difference across countries and regions on the availability of NBS and services offered for elderly	Only the better off across EU countries access to NBS and specialised services for the elderly. that are often out of pocket.
Advocacy evolution	Trained and empowered patients collaborate in a systematic way with multi-stakeholders team	Trained, empowered patients work with and received different forms of incentives (money, share)	High professionalism of the most empowered patients groups, increased competition and divisions among RD community	More trust on technologies than on human groups/knowledge.

RARE 2030 SCENARIO 1: INVESTMENTS FOR SOCIAL JUSTICE

Highlights *If we prioritize societal responsibility, equity, and the regulatory frameworks to achieve them, we will end up in the* **'Investments for Social Justice'** *world where major investments have been made by governments and are equally shared across Europe to ensure the health and well-being of all European citizens – including those living with a rare disease. The European Union's increased legislative power in areas of health and social welfare reduces the risk that people living rare diseases in some European countries are left behind.*

Not only the curative, but also the preventative, rehabilitative and palliative needs of people living with rare diseases are better understood. As such, healthcare systems are led by these holistic patient needs and are driven by better outcomes based on a growing evidence base achieved through comprehensive health data collection that goes beyond consumer and profit-driven companies. Data is seamlessly shared across borders through systems that are interoperable and infrastructures that are connected.

Multi-stakeholder initiatives prioritize investments in rare disease research that respond to patient needs thus focusing on as many diseases as possible and not only on low hanging fruits. The resulting innovations are evaluated at the European level and with greater transparency, accountability, cost-effectiveness and considering the patient experience. Given the limitation in government funding and regulations, cutting edge innovations may develop less rapidly but despite a lowered competition, needs-led innovation continues in the long run. Existing medicines, non-pharmaceutical treatments and assistive technologies are affordable and equally available no matter where you live in Europe.

The healthcare model for rare diseases has become a model for other health services and health threats where the system is resilient enough to tackle both acute and long-term patient needs. Centres of expertise dedicated to care for rare diseases are well-identified, well connected to local primary care as well as to networks within and outside the country. To ensure sufficient funds for these networks, health care decisions are not merely driven by cost savings and governments are able to increase the budget proportion spent on healthcare.

Rise of multi-stakeholders governance. European Reference Networks (ERNs) and the centers of expertise that make them up are well-known to patients and health care professionals across Europe and fully integrated in the national healthcare systems. They have indeed become an inspiring organizational model for many countries around the globe which are now building structured networks. PLWRD can easily find and access specialized centers of care that consider their health and social needs comprehensively and in an integrated way. All specialized centers are connected across Europe and doctors can now quickly and easily ask for the opinion of other experts through virtual consultations. The integration of ERNs together with the improved implementation of the cross-border healthcare directive ensure equity to access to care for patients living in different Member States and countries across Europe. Support services needed for school and labour and insurance are provided by society. Cross-programme and cross-budget initiatives are set to guarantee the best quality of care to all PLWRD. Centres of expertise contribute to foster research by adequately documenting their often experimental care and knowledge and by adopting a multidisciplinary and transnational approach.

Rise of innovation-oriented research: *Research is mission- oriented and needs-led.* Research is increasingly mission-oriented and innovation is directed to meet public health needs (Mazzucato, 2018)[16]. Governments use financial incentives and legislation to goad and reward effective innovation. Multi-stakeholder partnerships are encouraged: citizens and patients are considered equal partners in research

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[16] M. Mazzucato et al. UCL. The people's prescription. Re-imagining health innovation to deliver public value. UCL, 2018

with scientists and healthcare professionals, public funders, private enterprises. Patients' early involvement in setting priorities and design research improves patients trust, recruitment and retention in research and development projects. Patient-relevant outcomes and experiences are systematically evaluated and are essential part of research, clinical trials and of newly developed models of healthcare. Increasingly organizations learn to collaborate across countries and diseases. In some cases, the cross-countries, multi-stakeholder projects slow down innovation due to the lack of multi and inter-disciplinary skills among project participants. The research paradigm rewards clinical research whether successful or not and not just publication.

Medical Innovation and genomics. Teams are trained to collaborate in complex processes – sharing and building upon discoveries and knowledge with e.g. many organizations sharing 'common incubators'. The new culture paradigm accelerates organizational and technological innovation and eases its transfer. The results achieved in the RD field are increasingly transferred to tackle more common diseases (model of solutions). This has been achieved thanks to a profound transformation undergone by the medical education which now requires greater attention to the development of soft skills and promotes the creation of a collaborative, inter-disciplinary, international culture. The Whole Genome Sequencing is used for drug development as for oncologic diseases, and RD foster the development of precision medicine. The advances made in next-generation sequencing (NGS) technology allow to approach rare and ultra-rare genetic disorders with a more accurate diagnosis in rare diseases[17]. Driven by North America and Asia, the global 2,600 registered clinical trials using gene sequence data reported till September 2019 and the 50 population genomics initiatives[18] established in the last 10 years, increase. The national share of these gene sequencing initiatives (77%[27] in 2019) decreases in favour of international collaboration. Thanks to the setting of more transparent and accountable process and the development of effective public–private partnership, EU ATMP market flourishes[19].

New care delivery models. EU Healthcare systems (Super-max Model) are needs-led, outcomes-driven systems thanks to the strengthening of capacities and the best use of available innovation to align health services to meet population needs. This change has allowed to achieve the best outcomes and improvements for patients, reduce health inequalities and promote healthier lives. Healthcare systems management is effective, budgets are transparent, interventions evidence-based and data protected. A case manager facilitates the communication of the specialised centres with the local centres and social services guarantee continuity of care improving the daily-life of PLWRD and carers. Optimal outcomes are based on a growing evidence base achieved through greater collaboration. Regulations set market incentives able to drive down the costs of services and supporting innovation system responsiveness/flexibility. Patient-centered services generate value for RD patients and society.

Digitalisation of healthcare. Digital Health Market - which includes health IT, wearables, health sensors - now exceeds USD 639.4 billion[20]. Digital health solutions are commonly used to foster research, increase patient empowerment and coordinate healthcare services provision. In particular, these technologies allow to monitor treatment and health status remotely at patients' home providing patients with better care and reducing hospital expenditures. The e-prescribing market exceeds the projection of $4,152.7 million

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[17] Liu et al. Diagnostic and clinical utility of whole genome sequencing in a cohort of undiagnosed Chinese families with rare diseases. Nature. Scientific Report 9 (2019). Available at: https://www.nature.com/articles/s41598-019-55832-1

[18] Bloomberg Business. The next generation sequencing market is projected to be worth USD 19 billion, growing at a CAGR of more than. 15% till 2030. 19 february 2020. Available at: https://www.bloomberg.com/press-releases/2020-02-19/the-next-generation-sequencing-market-is-projected-to-be-worth-usd-19-billion-growing-at-a-cagr-of-more-than-15-till-2030

[19] Meij et al. Advanced Therapy Medicinal Products. Leru Briefing Paper n.2. September 2019. Available at: https://www.leru.org/files/LR-BP-ATMP.pdf

[20] Global Market Insights. Digital Health Market size to cross $639.4 Bn by 2026.10 June 2020. Available at: https://www.gminsights.com/pressrelease/digital-health-market

improving patient safety and optimizing healthcare services processing[21]. Wearable devices, co-designed with patients, also allow to determine new endpoints for research studies and to automatically collect comprehensive data with reduced burden for patients[22].

Standard and interoperable data and the rise of AI. National healthcare systems are the main actor and there is strong societal responsibility to collect quality data and ensure their protection. European policies foster investments in data infrastructures to allow for seamless data sharing across borders. Public-private partnerships are established to enhance public IT management skills and create high-performance infrastructures and AI applications. Registries are filled by both patients and clinicians helping the recruitment of participants in clinical trials, the understanding of the natural progression of diseases and the monitoring of clinical outcomes. In addition, these data provide support for the establishment of disease-specific standards and care[23]. FAIR data principles are widely adopted to improve the findability, accessibility, interoperability, and reuse of digital assets enhancing the potential of AI leading to quicker knowledge discovery and innovation[24]. The adoption of a minimum set of Common Data Elements (CDE) in registries helps standardize data collection, thus enabling the interoperability of data [25]. Patient registries and data collections are also adaptable to serve regulatory purposes as post-marketing drugs surveillance[26].

Access to treatment and care. Major investments have been made by governments to ensure people's health and well-being. EU, national and regional governments collaborate together to gather the necessary information and tools to understand and provide the best care for PLWRD in Europe. The EU has increased legislative power in health issues and RD is a priority on the EU Agenda. Early and transparent dialogue on pricing between industries and reimbursement authorities - taking into account clinical value assessment - is now a standard procedure. A greater collaboration across borders is also established thanks to EU Regulation on HTA – especially targeting OMPs and devices for RD.

Equity and solidarity. "Leaving no one behind" is a must for health policies at all territorial levels. This has led to an increased recognition of RD, including very rare diseases. Communities and networks of rare diseases are active at different territorial levels and especially at global level. These networks play a key role in informing policies and strategies in an increasing complex and rapidly changing world. Paramedical, social, rehabilitation, palliative needs are adequately met[27]. National government agencies of health and welfare talk to each other in order to plan integrated pathways and co-funded programmes. Patients enjoy full recognition (legal, economic and social) of their ability/disability and can access RD-sensitive professional, educational, mobility services. Altogether, patients and caregivers experience better quality of life as the proper conditions for them to work and be active part in society life are met.

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[21] Allied Market Research. E-prescribing Market by Component, Deployment and End User: Global Opportunity analysis and industry forecast, 2019-2026. Available at: https://www.alliedmarketresearch.com/e-prescribing-market

[22] Global Genes Allies in Rare Disease. Next: Imagining the future of Rare Disease. 2019.

[23] Boulanger et al. Establishing Patient Registries for Rare Diseases: Rationale and Challenges. Pharmaceutical Medicine volume 34, pages185–190(2020). Available at: https://link.springer.com/article/10.1007/s40290-020-00332-1

[24] Wilkinson et al. The FAIR Guiding Principles for scientific data management and stewardship. Nature Scientific Data volume 3, Article number: 160018 (2016) Available at: https://www.nature.com/articles/sdata201618

[25] EURORDIS. Rare disease Patient Registries Policy Factsheet.2013. Available at: https://www.eurordis.org/sites/default/files/publications/Factsheet_registries.pdf

[26] EUCERD. Eucerd core recommendations on rare disease patient registration and data collection. 2013. Available at: http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf

[27] EUCERD. Eucerd Recommendations. Quality Criteria for Centres of Expertise for Rare Diseases. In Member States. 2011. Available at: http://www.eucerd.eu/?post_type=document&p=1224

Ageing of population: support for PLWRD to guarantee a smooth age transition and EU-wide alignment of preconception care. New technologies and advanced therapeutics increase the average lifetime of RD patients. Patient registries have properly collected RD patients' data over time enhancing the knowledge on the history of RD and on the effects of comorbidities known to result from aging. Both the centres of expertise and local health services are adequately prepared to support RD patients in the transition from adolescence and adulthood. Assisted technology and supporting devices allow RD-affected adults to live a better, independent life, facilitating their integration in the society and their quality of life. On the other hand, public healthcare systems strengthen preconception care, ensuring awareness in reproductive choices, while genetic counselling is available and equally accessible in and between countries. Newborn screening programmes have also been harmonised and updated across Europe. Pre-implantation testing, pre-natal screening and assisted reproductive technologies are publicly available, helping RD patients and carriers to make more informed reproductive decisions.

Advocacy evolution. Patients and patients' organisations have developed a long-standing experience in working with multi-stakeholder teams at different territorial levels. This has been possible thanks to awareness-raising campaigns and trainings which have empowered patients and patients' representatives to actively participate in policy formulation, clinical trials and drugs development. People (including but beyond only those living with a rare disease) are more conscious of the ecosystem in which they live and are willing to contribute to system sustainability by offering their time, knowledge, experience and their data for the public good.

RARE 2030 SCENARIO 2: FAST OVER FAIR

Highlights *Should current trends proceed unabated, we'll end up in the **Fast Over Fair** world where public and private stakeholders collaborate but only when they share the same interests.*

Due to significant private investment in research and development for rare diseases, many breakthrough technologies are available for diseases that are well understood, but patients with very rare and complex diseases are left behind. The innovations that are proposed are not sustainable as they focus more on developing economically rewarding products than addressing long term patient needs. Patient organizations and health care professionals operate across multiple countries and rare diseases, helping identify and appropriately address gaps and disparities in healthcare, treatments and research in RD by collecting and exploiting patient reported experience.

New IT solutions that allow to gather and process large amounts of health-related data offer a great potential to advance care and treatment. However, major bottlenecks exist due to a lack of clear and simple rules and incentives to share information, especially between publicly funded structures and the private healthcare industry.

Health remains the responsibility of each country in Europe but certain disease areas and some healthcare related services benefit from coordinated public efforts at the European level. Driven by budget constraints, services are prioritized and access to new technologies is slow and limited even though it remains free of charge at the point of access. However, "top-up" payments are ever more common for those who can afford to pay for breakthrough innovations.

The process for assessing new innovations is centralized at EU level but lacks transparency and true patient needs are only partially considered. As a result, developers ask high prices for innovative products with small impact on the patients while payers claim process complexity to block or slow-down the market entry of new products. The challenges in driving fast but fair innovation are likely to create frustration as well as an increased distrust in science, health care, and the systems that govern them.

Rise of multi-stakeholder governance. ERNs active but more as an administrative European structure that is unable to achieve its full potential. These networks are used more by pharmaceutical companies than by patients.

Rise of innovation-oriented research. Innovation aims at developing individualized and tailor-made treatments. However, these are not always produced for those who need them most. Innovation targets knowledge base, trying to achieve maximum results with minimum efforts and companies and regulators strike a balance between what is needed and what is profitable, often along unclear processes. The lack of a proper discussion on inclusion and the detachment from society's values reinforce the risk of leaving patients with more complex and rare diseases behind. Incentives are set at intermediate steps to support the successful market launch of products based on existing knowledge in order to shorten the cycle of Research and Development (R&D). The combination of these governance factors leads to concentrate research in certain diseases areas (e.g. metabolic diseases) while others disease areas and the development of more advanced technologies stagnate. Generally, innovation aims to "faster commoditization" and is focused on efficiency rather than on piloting breakthroughs. Companies' profits are used to repurchase their own shares and reward shareholders[9]. Government funding provides insufficient incentives to shape research and innovation priorities. Mission-oriented research and patients' involvement is officially advocated but their actual realisation often fails. Without a cultural shift, patients' partnership is often enacted merely to comply with formal requirements, without no real endorsement of consultation findings. Academic researchers concentrate on topics that can enhance their "H-index" and their individual career.

Medical Innovation and genomics. Technologies have developed at a fast pace, which has allowed more PLWRD to benefit from treatments specifically developed for them. Rare diseases are researched and OMPs are rewarded as long as their orphan status is recognized as profitable. Direct to Consumer genetic testing companies continue to proliferate in the private sector. The availability of tests increases people knowledge of their genetic predisposition (with possible positive impacts in prevention and in the early detection of diseases). Nevertheless - since health systems struggle to "manage and rule" this phenomenon – patients run the risk of privacy breaches and unclear/incorrect information about their effective risk for diseases development. Due to the significant private investments in research, many breakthrough technologies are available but developers ask for high prices from governments, which in turn struggle to obtain fair pricing or alternative and sustainable payment methods. RD centres of expertise are established in some countries but not in others. Save for a limited number of outstanding experiences, the healthcare and social workforce is in general not adequately prepared to make the best use of innovation technologies or to work in integrated ways with trans-disciplinary teams towards offering holistic care. Welfare and healthcare systems work in silos and the "health pathways" implementation process is often unclear and can hardly be taken up by patients.

New care delivery models. Health management by the public system relies on the teaming-up of many different actors who work together to the extent that they have common goals. Advanced technologies for improved diagnosis and treatment are available and lead to collaboration between multiple private and public stakeholders, but only when they share the same interests. Treatment and innovation focus on the most profitable products and services which will leave many PLWRD behind. However, those who have access have a better care/treatment and even potential cures. Healthcare systems are payment-led and characterized by largely interoperable systems and streamlined, mature regulations. Greater collaboration between different stakeholders along with more interoperable systems, enriched with data, lead to better informed health decisions. Driven by budget constraints, services are prioritized and cut down but remain free at the point of access. However, 'top-up payments' are increasing when it comes to innovative therapies, for those that can afford to pay.

Digitalisation of healthcare. Assistive technologies improve PLWRD lives especially thanks to the solutions offered by the rising private market. EU collaboration strives to create common digital health infrastructures but governments' limited resources and capacities slow down the process while private companies keep up with the speed of innovation. Health systems are still hospital-based, as only few healthcare systems have been able to shift from hospital to home those 30-50% of post-acute phase patients that could be safely cured at home with digital solutions[28]. However, tech-services and telemedicine are available in all countries for those who can pay. Leading private companies in digital health are the best allies for governments – however digital tools and solutions provided do not always guarantee real improvements in the quality of care.

Standard and interoperable data and the rise of AI. EU has established minimum common infrastructure to collect and share data such as the European Platform on Rare Disease Registration. However, the implementation has proven harder than expected and the take-off is slow and partial. This is partially due to the AI and Big Data knowledge gap between the private and the public sectors. Industries have the proper skills and resources to collect and integrate real world data, store big data and foster AI use, but while the private sector collects data from mobile app, devices and the newest digital health tools, the

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[28] KPGM. Healthcare 2030. The consumer at the center. 2019. Available at: https://institutes.kpmg.us/content/dam/institutes/en/healthcare-life-sciences/pdfs/2019/kpmg-healthcare-2030.pdf

healthcare system is still anchored to a hospital based-model in which data are collected only by healthcare professionals. Public EU policies grant some data protection and establish some ethics rules; however, citizens are often unaware of their digital rights. In many cases, companies are the reference points for information and training on digital skills and rights. As a result, only the most educated or well-off citizens are able to manage and protect their data.

Access to treatment and care. Diagnosis and care are facilitated by technologies and multi-stakeholder mechanisms are in place to assess, select and develop innovation assets. Cost effectiveness of innovation is a priority and much attention is dedicate to contain services costs. Those who have access have better health outcomes, but only services that are profitable are likely to be available, as skills and knowledge are exploited only if they are considered 'productive'. The cost of OMPs is often viewed as a barrier to access and European innovative drugs struggle to reach patients quickly: the average length of time from market authorization to reimbursement in Europe continues to exceed the 318 days reported between 2014 and 2016[29].

Equity and solidarity. Innovation in drugs and technologies is prioritized compare with social inclusion, psychological and educational measures which are integrated in national programmes. The unstructured social and financial support makes it difficult for PLWRD and their families to live an independent life and contribute to society. As in the past, 7 out of 10 PLWRD and their carers had to reduce or stop their professional activity[30] with ensuing economic and psychological distress. 1 out of 5 PLWRD does not receive any sort of disability assessment and adequate information on suitable employment opportunities[2].

Ageing of population. Most EU governments have not adopted targeted policies to manage the ageing of population and are now unprepared to answer to elderly's rising needs. Social structures and workforce are not able to adequately support RD age transition to adulthood and old age. There are wide differences in the offer of newborn screening and preconception care within EU countries – markedly in Eastern and Northern countries[31]. While some basic pre-conception analyses are publicly available, the newest and less invasive ones require a co-payment from patients and are provided only in few private specialized centres. Over time, the failure to early detect RD diseases leads to delays in diagnosis as well as increased costs for healthcare systems.

Advocacy evolution. The new delivery model and the personalized medicine development offered by healthcare systems are not fully able to respond to patients' needs. This is partly due to the limited involvement and engagement of patients and patients' organizations in setting priorities. Conversely, there are examples of ground-breaking innovation brought about by private companies in partnership with patients – in these cases patients organizations are offered training and some form of reward for their timing and participation. In these cases, patients are co-owners of the results achieved and are granted priority access to the therapies, devices and apps produced. Patient organizations work together across countries and diseases to empower citizens and attract companies' interests on the unmet needs of PLWRD.

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[29] Deloitte Centre for Health Solutions. Patient Access to innovative medicines in Europe. A collaborative and value based approach. January 2019. Available at: https://www2.deloitte.com/content/dam/Deloitte/uk/Documents/life-sciences-health-care/deloitte-uk-patient-access-to-innovative-medicine-in-europe.pdf

[30] EURORDIS. Achieving Holistic Person-Centred Care to leave no one behind. May 2019. Available at: http://download2.eurordis.org/positionpapers/Position%20Paper%20Holistic%20Care%20for%20Rare%20Diseases_Final.pdf

[31] Loeber (ISNS). Current Status of Newborn Screening in Europe. 2018. https://www.isns-neoscreening.org/wp-content/uploads/2019/04/NBS-in-Europe-2018.pdf

RARE 2030 SCENARIO 3: IT'S UP TO YOU TO GET WHAT YOU NEED

Highlights *If distrust in supranational efforts to manage health and other societal needs continues, we may find ourselves in the **It's Up To You To Get What You Need** world with distinct national two-tiered health care systems in which basic care is provided by the government and a second tier of care exists for those who can rely on powerful networks or pay for additional, better quality or faster access.*

In this scenario, patients may get the holistic care they need but it will highly depend on the country in which they live.

Given that no country has sufficient numbers of patients to conduct adequate research for rare diseases, great advancements in innovation are hampered due to a lack of investments in multinational research efforts, data collection platforms and data sharing infrastructures.

The innovation that does reach the market for rare diseases is extremely expensive, only accessible for the richest of countries and patients. Ultimately, interest in investment in developing new technologies decreases due to a diminishing market.

Most people would agree that everyone has a right to healthcare and a right to the highest attainable standard of health. But there may be disagreement about who should be responsible for achieving and paying for it.

Rise of multi-stakeholder governance. The limited cooperation at European level makes the ERNs a primarily bureaucratic network that failed in most cases to be integrated into national healthcare systems – with some exceptions in the most virtuous countries. Multi-stakeholder European governance also fails to effectively regulate key questions such as data governance and protection.

Rise of innovation-oriented research. Cross-country, multilevel research initiatives are considered ineffective in producing real innovation. Patients' organisations and individuals thrive and become exceptional innovators, game-changers. These game changers are able to "create, contest and shape the mission and purpose of innovation"[9] towards a medicine that meets their specific needs and is able to achieve fast and satisfying results. Patients organizations are required to change their skin and acquire solid business skills to manage business partnership without betraying patients trust. However, research is characterized by "silos" reflecting the interests of the more represented and powerful groups. Great advancements are hampered by the lack of sharing and cooperation between researchers. On the other hand, the public innovation is much focused on process and systems, rather than on drugs or technologies.

Medical Innovation and genomics. There is a flourishing of highly specialized, biotech industries and digital health companies. These companies work with specific patients in a co-creation process, shaped by their needs. Whole genome sequencing developments and advanced therapeutics revolutionize the diagnosis and the care of a wide range of diseases including RD but investments are not equally distributed across the EU. Access to treatment strongly depends on country and on the kind of disease. With limited public funding and weak European collaboration, it's up to the patient groups to promote and establish collaboration with industries by promoting the opportunities to develop advanced therapeutics for specific groups as test/pioneers for diseases with higher prevalence.

New care delivery models. Healthcare systems (Two-tier model) are price-led, demand driven. Their main characteristics are a reduction in available free services, the increasing of health inequalities and a worsening of the health outcomes of the general population. Healthcare systems and budgets are stretched, leading to limited capability of adopting innovation except for those new models of care and service improvements that drive cost-containment/savings. Top-up payments for innovative therapies are frequent for those who can afford to pay or can rely on philanthropic support. Better opportunities to

access integrated care are available in some countries and regions which show the strongest welfare culture and have established specialized RD expertise and resource centres.

Digitalisation of healthcare. The governments' digital health strategies are limited in scope and uncoordinated, which leads individuals to launch their own digital health initiatives and solutions. Patient organizations or empowered individuals set up fruitful partnerships with private companies such Backpack Health[32] for the establishment of a patient registry. Digital health companies emerge as powerful allies for patients to collect, manage and share their healthcare records and data. As a result, there is a multiplication of collaborative forms and business models at all territorial levels, yielding an overall improvement in the quality of data. However, the increased creativity and freedom come with a cost: since a lack of coordination is seen even in patient communities, patient organizations duplicate efforts in experimenting digital solutions already available for other conditions and most solutions are geared to the specific context in which they have been originally developed, with limited replicability potential.

Standard and interoperable data and the rise of AI. Notwithstanding the General Data Protection Regulation (GDPR), countries have adopted different legal requirements for the protection and safeguard of health data. As competition and mistrust among countries is on the rise, the most powerful patients groups promote and manage data collection themselves or in partnership with private companies. The latter offer their infrastructures to foster research but there are high risks of data breaches and there is no provision of "standard information" regarding the secondary use of the data provided. Patients are empowered to use data for self-management and to directly populate data platforms but it's up to their level of empowerment and skills to supervise the good governance and protection of their data. AI algorithms are on the rise, easing diagnosis and care, but they are only available for selected diseases, under the pressure of patient organizations.

Access to treatment and care. The lack of EU strong political commitment leads to an unequal access to treatment and care between EU countries and regions. Access to most advanced treatment and care is guaranteed only to the most powerful groups. Much depends on the power of the single disease groups and on their ability to create coalitions with others groups and stakeholders. The heterogeneous picture of OMP access across Europe generates a 'geographical lottery' of sorts leading to inequalities for patients. Holistic care provision is entrusted to private healthcare and patients and family have to face substantial out of pocket costs especially to access informal care.

Equity and solidarity. This scenario is characterized by two major shifts. One the one hand, the implementation of personalized medicine has delivered the potentials of more patients' needs-led holistic healthcare. However, it's only a half revolution. The limited resources and the lack of coordination among MS have created wide disparities between patients depending on their country, type of diseases, knowledge, social networks and economic resources. Due to the weakening of the collective vision and strategy, competition is growing between diseases and intra-rare diseases groups. Financial constraints and the lack of organized networks make national healthcare systems unable to offer holistic care suitable to PLWRD. While healthcare workforce often lacks the knowledge of RD diseases[33], local RD patients' organisations build strong networks at regional level and collaborate with public and private institutions to raise awareness, develop innovative business models and provide specialised

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[32] Global Genes Allies in Rare Disease. Next: Imagining the future of Rare Disease. 2019.

[33] Von der Lippe et al. Living with a rare disorder: a systematic review of the qualitative literature. Mol Genet Genomic Med. 2017 Nov; 5(6): 758–773. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5702559/

psychological, social and educational services. In this context, ultra-rare diseases struggle to find proper social attention and support network.

Ageing of population. As governments fail to provide information and support to PLWRD age transition, patients' organizations take up this role and successfully self-organize. Structured RD patients' networks are able to establish preferential clinical pathways for the reproductive and the "elder age" needs of RD patients. Through "cross-country corridors" and international networks, patients' organizations orientate patients to receive the proper pre-conception care even outside their home country. They are also able to personally bargain the affordability of pre-conception care with private providers ensuring the right to an aware family planning for RD patients. Thanks to new technologies and private funding, organizations are increasingly empowered and are able to offer job placement, adequate accommodation solutions and a wide range of social activities.

Advocacy evolution. Only those patients empowered and engaged in advocating for their health and voicing their needs manage to be listened to and to be included in the healthcare systems. It's left to patients' individual responsibility to acquire those skills which allow them to be involved in the research process and in the testing of new models of care. Patient organizations play an important role in advocating for the needs of PLWRD but they do not necessarily work together in a systematic way. This is partly due to the rise in competition for government and private companies' attention. Best empowered and organized groups are able to use public healthcare and private companies in a co-creation process of innovation in drugs, devices and healthcare delivery model shaped by their needs. Patient organizations acquire substantial and advanced resources (i.e. data collection initiatives) along with the expertise to create infrastructure and personalized healthcare models suitable for patients. They also directly promote training for patients and healthcare professionals.

RARE 2030 SCENARIO 4 TECHNOLOGY ALONE CAN SAVE YOU

Highlights *We may find ourselves in such a scenario, **Technology Alone Will Save You**, where private companies have the prevailing role in managing the health of people living with rare diseases. Many innovations such as health applications are available for people living with rare diseases to manage their own health. These innovations can help them in their everyday life but leave them largely responsible for their health and for making sure that their right to health is respected.*

Health care systems are private, insurance-based, market-led and profit driven. Voluntary intergovernmental coordination exists but not enough to regulate health, health related data and research.

Several private companies have created fast and accurate diagnostic options but only for those who can pay out of their own pocket. Thanks to the investments of health data companies, artificial intelligence and other cutting-edge science have led to breakthroughs for some of the most complicated and rarest diseases but most diseases remain without treatment options. Again, only the richest of patients can have access to these innovations and often rely on themselves or on the generosity of others through crowdfunding to access treatment for their diseases. Genomics has also developed dramatically and is regularly used by doctors and individuals. When commercially exploitable, information is gathered through collective channels to help sort out what is helpful to patients. Patient organizations support has largely been replaced by technologies that allow patients to manage their own needs and those that have access are reasonably empowered, and sometimes even devise breakthrough technologies themselves. Others believe it is the duty of governments to achieve equity in health and to alleviate social inequalities through innovation and systems of care.

Rise of multi-stakeholders governance. Without a strong MS and EU political will, ERNs no longer exist or are heavily /underfunded. Cooperation collapses under financial strain which leads to a "free for all" situation.

Rise of innovation-oriented research. EU Research is fragmented and priorities are set primarily by interests of specific countries or private groups. Investment and efforts are often duplicated, which leads to inefficiencies and delays. Private companies establish unbalanced partnerships with healthcare practitioners and patients without taking their needs into real consideration. Innovation usually results in "me-too devices" and "me-too drugs" which are modified versions of existing medicines. These products – covering more than 51% of newly approved medicines[9] - do not offer any additional health benefits but are sufficiently different from existing drugs to warrant patent protection. Conversely, many potential medical research avenues are not being explored simply because they are non-patentable, for example those based on drugs that are already known[9]. Private companies performing low-effectiveness multiple clinical trials compete to enrol RD patients which are continuously "solicited by competing pharmaceutical firms"[34]. It's important to be the "first to clinical trial" - even though the product may not represent the best therapeutic option and does not reflect patients' needs[10] and, to do so, companies attract patients as well as researchers with economic incentives. On the other hand, the unclear communication makes it difficult for patients to take an "informed decision" on their clinical trials involvement and a feeling of being exploited is common among patients and their families.

Medical Innovation and genomics. The development of AI and health data collection shortens the research and development process with a wide range of different technologies and advanced

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[34] Berry et al. Developing interactions with industry in rare diseases: lessons learned and continuing challenges. *Nature Genet Med* 22, 219–226 (2020).Available at: https://www.nature.com/articles/s41436-019-0616-9

therapeutics available. Without a regulation on the cost-effectiveness of new therapeutics and technologies, drugs and technologies proliferate offering false hopes to patients, especially to PLWRD. Breakthrough innovation in diagnosis and treatment exist for some diseases but the access is limited to those who can pay. The low health literacy and digital health literacy of most people open the door to unauthorized treatments pushed by reckless companies' advertisements. Genomics express its full potential thanks to the continuous decrease in the cost of whole genome sequencing – now available for USD 100[35] compared to USD 1,000 in 2020. Outside the healthcare systems, Direct to Consumer genetic testing proliferates outside the public systems raising ever increasing privacy issues.

New care delivery models. Most EU Systems have followed the US private model becoming insurance-based, market-led, profit-driven. Healthcare is characterized by a greater deregulation with increased healthcare costs and a decrease in demand due to the lack of affordability. There is a drastic prioritization of services against population needs, health inequalities increase but those who can pay can access healthcare and innovation and have significantly improved outcomes. They even run the opposite risk respect to people who cannot access care, i.e. to be over-treated. People who cannot afford the services costs turn to voluntary, charity-led basic care.

Digitalisation of healthcare. There is a high competition between companies to acquire a share of the digital health market but the limited engagement of practitioners and patients in the design process results in products of hardly any use. The data collected don't improve patients' outcomes nor health professional practices or governments policies. On the contrary, the new technologies somehow have often depersonalized the relationship between healthcare practitioners and patients inducing citizens to rely ever more on their own free web search. Similarly, companies continue to release new technologies on the market such as assistive technologies and devices to support functional impairments (mobility, language) that claim to be game-changers in PLWRD lives. Most of these innovations are, however, far away from the "everyday" of RD patients as they do not meet their daily life needs.

Standard and interoperable data and the rise of AI. Patient medical data has become a "multibillion-dollar worldwide trade industry" between drug companies, data companies and health-care providers[36]. Personal Data including health data are commercialized in a free-market and market purposes drive the development of new types of businesses in data mining and in AI applications. To share their personal health data, compensations and services are offered by companies to citizens who have very little knowledge of their digital rights and possible data secondary use. By mining data, companies sidestep privacy and antidiscrimination laws to obtain information most people would rather not disclose[37] and sell them to insurance companies, banks, employers[38].

Access to treatment and care. The European Union still exists but only as a formal union of states, with no concrete power to influence national health decisions and drugs pricing. The costs of OMP rise and since governments are less inclined to pay for expensive RD treatments,, therapy availability depends on individuals/families' willingness to pay. Only 5% of rare diseases still have a dedicated therapy and a

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[35] Bloomberg. A $100 Genome Within Reach, Illumina CEO Asks If World Is Ready. 27 February
2019. Available at: https://www.bloomberg.com/news/articles/2019-02-27/a-100-genome-within-reach-illumina-ceo-asks-if-world-is-ready

[36]Adam Tanner's book "Our Bodies, Our Data: How Companies Make Billions Selling Our Medical Records",
https://www.penguinrandomhouse.com/books/539847/our-bodies-our-data-by-adam-tanner/9780807059029/

[37] STAT. Tech companies' dangerous practice: using artificial intelligence to mine hidden health data. 17 September 2019. Available at:
https://www.statnews.com/2019/09/17/digital-traces-tech-companies-artificial-intelligence/

[38] OECD. Health Policy Studies. Health Data Governance: Privacy, Monitoring and Research. 2015. https://www.oecd.org/publications/health-data-governance-9789264244566-en.htm

heterogeneous picture of OMP access across Europe generates a 'geographical lottery' of sorts, leading to increased inequalities for patients. In addition, the high OMP costs compels the few existing centers of expertise to reduce the paramedical and holistic care services. Overloaded with work, healthcare professionals have no time to investigate the complexity of RD patients. The limited coordination between centres of expertise and local health services create a situation where more than 70% of RD patients are requested to repeatedly move and visit different health and social services[39]. Deprived also of a therapeutic alliance with healthcare professionals, most patients develop a feeling of being trapped, as they continuously need to "start all over again"[32].

Equity and solidarity. Patients experience the lack of RD knowledge outside the medical ward with denials or ineffective offers of specialised social services. RD patients and their families feel socially isolated, desperately lonely and suffer a moral and economic damage provoked by the exclusion in society and the discrimination in the labour market[32]. Patients have full access to internet information and new technologies but tele-health innovation merely ends up by depersonalizing the therapeutic alliances. New technologies can hardly meet the patients' real needs and are often economically unaffordable.

Ageing of population. Social networks and online platforms are the main information source for RD patients, including for such fundamental healthcare issues as reproductive health. Genetic counsellors are replaced by low-cost tests at home, online self-test and peer-to-peer advices. Pre-conception analyses and pre-implantation testing advertising inundate the web often inducing PLWRD to undertake long and expensive journeys in foreign countries to see their reproductive needs met. RD people are left alone to surf the web and search the right information and the most suitable services. Web frauds are common – with unclear display of costs, risks and use of patient data. In addition, elderly RD patients face the uncertainty of the future of their health and social condition since there is very limited economic and social support and a lack of research on multi-morbidity and treatment in the elder age.

Advocacy evolution. Companies and health systems usually involve patients' organizations in a late phase of the process, generating frustration and disappointment in patients who hardly see any substantial improvements in convenience, costs or outcomes. There is a considerable information and power asymmetry between patients organizations and companies. Without a collective supervision, companies feel free to set the rules (i.e. to change the policy on ER data sharing without patient consent)[40] generating patients' distrust and undermining their engagement in research and in the co-production of health solutions.

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[39] EURORDIS. Rare Barometer Survey. Juggling care and daily life. The balancing act of the rare disease community. May 2017. Available at: http://download2.eurordis.org.s3.amazonaws.com/rbv/2017_05_09_Social%20survey%20leaflet%20final.pdf

[40] Fast Company. You can now make money selling your own health data, but should you?.
 27 September 19. Available at: https://www.fastcompany.com/90409942/would-you-sell-your-own-health-data-theres-a-market-for-it-but-ethical-concerns-remain

3. RARE 2030 SCENARIOS AND THE EUROPEAN CONFERENCE ON RARE DISEASES

European Conference on Rare Diseases on-line seminar

EURORDIS organized a pre-conference seminar before the ECRD on April 23rd, 2020 with the aim of presenting RARE 2030 Scenarios as framework to be used for the conference policy discussion. The on-line seminar is now available on-line at: https://www.Rare 2030.eu/our-work/

The Panel of the webinar was composed by representatives of the RARE 2030 Consortium (EURORDIS and ISINNOVA), the Panel of Expert (PoE) and the Research Advisory Board (RAB). In details:

- Anna Kole: Project Leader, Rare 2030, EURORDIS-Rare Diseases Europe
- Yann Le Cam: Chief Executive Officer, EURORDIS-Rare Diseases Europe
- Andrea Ricci: Director ISINNOVA
- Maria Montefusco: President of Rare Diseases Sweden , Rare 2030Panel of Experts and Co-Chair ECRD 2020 Programme Committee
- Milan Macek: Professor and Head of the Dept of Biology and Medical Genetics Motol University Hospital, Charles University Prague, RARE 2030 RAB and Co-Chair ECRD 2020 Programme Committee

The presentations were supported by two International sign language interpreters: Tina Vrbanić and Oliver Pouliot.

T1 THE FUTURE OF DIAGNOSIS: NEW HOPES, PROMISES AND CHALLENGES

T2 OUR VALUES, OUR RIGHTS, OUR FUTURE: SHIFTING PARADIGMS TOWARDS INCLUSION

T3 SHARE, CARE, CURE: TRANSFORMING CARE FOR RARE DISEASES BY 2030

T4 WHEN THERAPIES MEET THE NEEDS: ENABLING A PATIENT-CENTRIC APPROACH TO THERAPEUTIC DEVELOPMENT

T5 ACHIEVING THE TRIPLE A'S BY 2030: ACCESSIBLE, AVAILABLE AND AFFORDABLE TREATMENTS FOR PEOPLE LIVING WITH A RARE DISEASE

T6 THE DIGITAL HEALTH REVOLUTION: HYPE VS. REALITY

Figure 3 ECRD main themes

Anna Kole welcomed the webinar presenting the panel and underlining as ECRD represents an unique opportunity to support RARE 2030 project in the elaboration of RD policy recommendations.

Then, Yann Le Cam presented the programme of the 10th edition of the ECRD, the largest patients led policy event (Annex II). The conference aims to lead, inspire and engage a wide number stakeholders to shape future rare policies. The online organization, due to COVID crisis, allow reaching participants that could not normally afford the meeting in terms of costs and time. By quoting B. Franklin "*by failing to prepare we prepare to fail*", Yann highlighted that conference themes should take advantage of RARE 2030 scenarios in order to identify the most desirable future for PLWRD and propose policy options on "how to get there". The proposed recommendations will be refined in six national workshops, discussed in a Young Citizen Conference and tested with a Rare Barometer Survey. The final set of policies will be presented during the RARE 2030 final conference (February 2021) at the European Parliament. Taking as basis the findings of the current EURORDIS Rare Barometer voice survey, the ECRD will inevitably also look at the short and long term impact of COVID-19.

Andrea Ricci offered participants an overview of the main phases and outputs of RARE 2030 project stressing the strong participatory dimension of the foresight process. Andrea showed the 12 trends, selected by RARE 2030 and categorized according to a PEST[41] analysis, mentioned the wild cards emerged and reviewed the two axis adopted as RARE 2030 scenarios in order to sketch the main characteristics of

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[41] PEST analysis: political, economic social, technological.

the 4 RARE 2030 Scenarios. Andrea reminded participants that foresight, differently from forecast, aims to produce different, plausible and conflicting scenarios which should be used to as framework to identify "where we would like to be in the next decade". As final step, the back-casting phase will look at the most desirable scenario to identify which policies are needed to go there and which might be the trade-offs to be taken into account. Andrea concluded inviting all stakeholders to work together and "be the future we want".

Maria Montefusco, as representative of PLWRD, expressed her own views for two Scenarios: "Investment for social Justice" and "Fast over fair". According to her, the "Investment for social Justice" scenario is characterized by a smart distribution of resources and full social inclusion of people with disability that feel equal to other people and able to "*aspire to live and not only survive*". In this scenario, society adopts a holistic view and is able to meet PLWRD needs. In turn, patients increase their trust and don't have any more the feeling to be "*a burden for society*". To better support national care, patients and clinicians rely on international networks and cross-border healthcare opportunities. To reach this scenario, are needed political will, the creation of adequate infrastructures and greater cooperation among national and regional governments. National strategic plans need to be implemented and barriers removed to make the cross border healthcare effective and real. In "Fast over fair" scenario the system is characterized by silos and PLWRD have to be "heroes" with good skills to coordinate and manage all clinical and bureaucratic aspects of their condition. Access to treatment and care is easy for some RD and difficult for others due to persistent strong inequities. Patients and patient organisations struggle to obtain access even in those more advanced economies/countries. People do not fully know what occurs abroad in EU and also in different part of the same country where the opportunities to access to care offered by multi-professional teams varies a lot. As Maria Montefusco said, all different RARE 2030 scenarios have positive and negative aspects, ECRD will be the opportunity to agree on which scenario is most desirable and discuss how to reach it.

Milan Macek stressed the achievements accomplished by EU RD policy in the past decade: the 2009 "EU Council recommendation on an action the field of RD", the 2011 adoption of the Directive on Cross-border healthcare - that claims for a structured cross-border cooperation between countries on research and access to specific OMP and care - and the creation of IRDiRC- International Rare Diseases Research Consortium. Against these progresses, it was recognized that there is much to be still done in terms of access to care. To conclude, Milan Macek reminded the RARE 2030 next consultation events: not just the ECRD (May 2020), but also the Young Citizens Conference (July 2020) which will see the participation of 32 young people from 18 EU member states, the regional workshops (September – October 2020) and the European back casting Workshop (October 2020). All these participatory events have the final aim to build a structure dialogue and draft solid recommendations and guidelines to shape future RD EU policies.

European Conference on Rare Diseases

ECRD Opening

The section below describes in full details the conference opening where high level speakers offered an insightful overview of the current RD policy framework – highlighting future opportunities as well as emerging threats.

Conference opening	
Moderator : Lise Murphy, Patient Advocate, Marfanföreningen (Swedish Marfan Association)	
Opening	HRH Crown Princess Victoria of Sweden
Welcome and opening remarks	Terkel Andersen, President, EURORDIS-Rare Diseases Europe
	Ana Rath, Director, Orphanet
	Maria Montefusco, President, Rare Diseases Sweden
Keynote Addresses	Lena Hallengren, Swedish Minister of Health & Social Affairs, Sweden
	Lena Hallengren, Swedish Minister of Health & Social Affairs, Sweden
	Stella Kyriakides, European Commissioner for Health and Food Safety
	Helena Dalli, European Commissioner for Equality
	Irene Norstedt, Director in DG Research & Innovation of the European Commission (Statement by Mariya Gabriel, Commissioner for Innovation, Research, Culture, Education & Youth, Bulgaria)
Inspirational Speakers	David Lega, Member of the European Parliament, Sweden

Crown Princess Victoria of Sweden, patron of Rare Diseases Sweden, welcome the participants to the Conference in a pre-recorded video recognising the challenges that PLWRD face in their daily life like navigating through the healthcare system, finding the right doctors and treatments, struggling with emotional and sometimes even financial stress that takes energy, strength, and resilience. She also underlined the key role and importance of patient organisations and Conference like ECRD "*to give voice to those who need to be heard, to share knowledge and experiences and to remind us that even when the world gives you plenty of reasons to feel that way, you are not alone*".

Terkel Andersen, President of EURORDIS – Rare Disease Europe gave an overview on the state of art for RDs. The pandemic has forced us to hold the conference as an exclusively online event bringing us into the "new normal" of these strange and freighting times. The epidemic has brought anxiety and distancing into the life of all individual but at the same time it creates the need to come together, share our skills and curb the impact of this disease. The RD community suffers the consequences of the epidemic as much as any other vulnerable groups. Thanks to EURORDIS, the preliminary results of the RARE 2030 Barometer Voices survey, based on the analysis of 5.000 responses, now revealed that nine out of ten RD patients have experienced the disruption of their care due to the impact of Covid-19 and that six out of ten perceive it as potentially detrimental to their health. Concerns have been expressed that complex care requirements of many RD patients could not be met in a scenarios of threatening breakdown of health care and social services systems. It has been reported the spreading of the infection into some homes for the disabled people and it is known as the deplorable isolation and psychological impact of confinement is greater for people that strongly depend more than anyone on social contact for their quality of life. The economic cost of Covid-19 could also weight on health care systems and social care and, in this period, even clinical trials and therapeutic development have been slow down or put on hold which inevitably leads to postponement for their availability to patients. The economic cost of COVID19 could be so significant to threat the already struggling healthcare systems.

Nevertheless, there maybe be lessons learnt and positive development from this epidemic. Most agree that the crisis showed the need for more Europe and international cooperation in health threats, not less. The pandemic has shown that "if we fail to prepare, we prepare for failure" highlighting the importance of coordinating cross border healthcare. Countries need to create more robust and resilient healthcare systems and organise surveillance and monitoring systems enabling an uninterrupted flow of information and standardized data. The crisis revealed the need of establishing mechanisms for seamless coordination, trans-national actions and sharing of resources. It has stimulated new interest in science, gene technology and innovation as preconditions for faster development of diagnostic tools and a cure. Even the general public is now more engaged in medical regulatory affairs and clinical trials, calling for ways to ease and speed up the development a accelerate access to such new therapies.

At political level, it getting clearer that healthy society and healthy economy rely in healthy citizens – that it is a matter of community added value. In essence, it is about moving from an approach of just responding to new challenges to one that is able of being prepared to what the future will or may bring. From diseases as a cost to health as an investment, from design by accident to design for success. The EU Rare disease policy is a showcase of the benefits of European structured cooperation: from the European Joint Programme on Rare Diseases - bringing together 130 research institutions from all over the EU and beyond- to the creation and consolidation of ERNs, from the approval of EU pharmaceutical regulatory framework, the establishment of European Medicine Agency, and in future prospects of increased HTA collaboration on RD at EU level. Other virtuous examples are the network of RD resource centres providing holistic care, the Orphanet focal contribution to knowledge and the international cooperation at UN level – with the recent approval of the political declaration on universal health coverage.

With 20 years of experience, EURORDIS is in the unique position not only to explore the impact of COVID19 on PLWRD but to provide assistance. For its experience, activities and governances structure, EURORDIS has been entrusted by EU Parliament and Commission with the RARE 2030 foresight project which is embedded in many sessions of this conference. ECRD2020 aims to explore how we can go further in a number of issues: from improving diagnosis and link out challenges with opportunities offered by informational technology and artificial intelligence so as to prepare therapies which are available, accessible and affordable to all and to *"move towards longer and healthier lives for RD patients wherever they live"*. Participants to the six different ECRD themes are invited to engage with RARE 2030 and provide ideas, reflections and insights to shape the EU policy framework for Rare diseases in Europe.

Anna Rath, Director of Orphanet stressed a strong parallel between COVID-19 and RDs defining COVID-19 as some kind of *"concentrated, accelerated and magnified picture of the situation of the rare disease community"*.

A disease has just been discovered and information is emerging, fragmented and even controversial. It is a potentially fatal disease that affect people all over and needs international collaboration between doctors and a multidisciplinary approach to be managed. There is no cure, no evidence, no guidelines. It brings disruption from one day to another into the life of the affected person but it also affects the life of the relatives. A disease for which open science, international research and coordination in data sharing are game changers and can rapidly make a difference. A disease for which it is critical to apply innovative methodology for clinical research to generate evidence quickly and a disease for which it is propose new, timely and affordable treatment. It's not about COVI19, it's about any Rare Disease. In the world we can expect it would be after COVID19. It is, of course, counterproductive to create competition between diseases, to pick one struggle against another. However, the similarities are numerous COVID-19 is in a sense *"concentrated, accelerated and magnified picture of the situation of the rare disease community"*. The rare community has shown notable experience in all the mentioned themes: coping with uncertainty

is something that rare disease patients and doctors know very well, organizing expertise, multi-stakeholders and trans-national networking enabling the working together of all kinds of expertise, data scientists, medicine, biology, social studies and patients. And in looking for new ways for organising science and care for the 300 ML of people living with RD. Despite its intrinsic diversity, the RD field is a fantastic land of innovation and solidarity. RD community is well prepare for the world post COVID. However, as the times will bring profound changes – also RD community will need to adapt.

The aim of ECRD2020 is to anticipate the future, to look to the horizon of 2030 and 2040 and to think about the various possible scenarios: what the future can look like? What rare disease patients will look like? Rare 2030is an instrument to imagine the future and this conference is a milestone for shaping its recommendations. As this conference as shown, we need to adapt and make an opportunity out the difficulty but if we can project us in the future world - we go a step further and try to shape it.

COVID-19 seems to be ten times more frequent than the most frequent rare diseases but RD together are 100 times more frequent and share the same characteristics of vulnerability, uncertainty, social disruption and need for adaptive healthcare and social care. COVID19 is speeding us along towards a scenarios of needs-oriented innovation and collective accountability concerning everyone health and let's work to produce rare disease policy which are strong enough to fit within this new frame.

Maria Montefusco, Director of RD Sweden welcome participants and highlighted that now more than ever is crucial to ensure health and inclusion for all. What the world is facing with COVID-19 - the struggle to access to information and treatment, the issue of prioritization, not only in triage and medical trials, by having someone else evaluating your quality of life and make decisions of the value of your life according to mainstream protocols, these situations are not news for PLWRD.

In these times, RD community could be an example of how to cooperate and organize across sectors and countries. "*No country is big enough to solve these rare and complex health issues. We focus on and we find solutions in ways to share knowledge and resources. We walk on unknown grounds together and we solve medical mysteries and we are an extremely resilient movement because we have to. This is where we also find our strengths*". The journey of PLWRD in 2030 gives a holistic view because the RD affect health, social, private and economic aspect of PLWRD. ECRD six themes will be the opportunity to dig into subjects on the future of diagnostic, on how to ensure access to care, how to put value of equality on real politics, how to use technology as a tool for inclusion, how to reach the desired situation in which PLWRD and their families enjoy life on equal terms as people who are not living with a rare disease. In this mission- the strength, the cooperation and the competence of international networks and structures as ERNs are fundamental for the entire RD community.

Lena Hallengren, Swedish Minister of Health & Social Affairs in a pre-recorded video reinforced the need to work together across national borders and sectors to ensuring an effective, equal and accessible healthcare systems. Even though having a rare disease is not rare, each disease might be very rare due to the rarity of some of the diseases, so it's crucial working together. The Minister acknowledged the key work of family and relatives of PLWRD. On the other hand, she highlighted 2030 Agenda, and especially Sustainable Development Goal 3 strictly linked to health. The Swedish government has taken a series actions to ensure the quality, equality and availability of PLWRD. Among other actions, the government has approved a long term strategic plan which includes the financial support to medical centres for RD, a stronger patient perspective in healthcare and a national coordination among regional health care structures. Another example, is the life-science initiative that aims to create a national infrastructure for molecular diagnosis and the implementation of

precision medicine in healthcare structures. This new approach will lead to early diagnosis and more efficient treatment for patients with RDs.

The plenary went on with some inspirational thoughts by Lise Murphy focusing on the need of joint efforts to build a society where PLWRD can reach their full potential "*I'm a patient at times when I go to hospital, when I am in recovery after a period of ill health but I am not a patient all the time, I am a person, I'm just Lisa with dreams, needs and with a potential of to be of use in society just like all of us*".

Then the session moved to the European perspective and the EU efforts and commitment for PLWRD with Stella Kyriakides, European Commissioner for Health and Food Safety, Helena Dalli, European Commissioner for Equality and Irene Norstedt, Director in DG Research & Innovation of the European Commission with a Statement by Mariya Gabriel, Commissioner for Innovation, Research, Culture, Education & Youth, Bulgaria.

Stella Kyriakides, European Commissioner for Health and Food Safety, stressed as the crisis has impacted us all at an individual level, it has severely affected our economy, our livelihoods, our travel, our supply chain but it has also highlighted just how interconnected all our lives and all our communities really are. The pandemic has reinforced the importance of a true health policy and holistic approach to RDs focusing on equality and research and innovation. RDs policy remains a priority for EC – it has promoted important initiatives in the last decades and it time to consolidate these achievements. RD remains a priority for EU policy. This is reflected in the development ERNs – the implementation of Orphan Drug directive and the RD registries. *In the upcoming years, the EC intends to carry out take stock-taking exercise reflecting on the lesson learnt from RD drugs substitutes, and the results of Rare 2030coordinated by EURORDIS will be taken into account.* The EC has developed this plan before the COVID crisis, what is needed now is to take lessons on what we have learn from this crisis. And in this process, Mrs Kyriakides underlined as patients will always be the driving force, the centre of the development of the European RDs policy. "*They need to have a voice at the table where decisions are made*". In this respect, it is important to stress the role of ERN which are new structures but already providing care to more than 1,5 million patients around Europe, developing guidelines, collecting patients data and promoting research with more than 2.000 scientific publications and 3.000 research project proposed. As regard treatment, under the EC new mandate the Commission has the goal to ensure that Europe has a supply of affordable medicine to meet its needs, and it is important that this will include also for RD patients in this goal and the evaluation of the Paediatric legislation that will be published in 2020 will be a way to address many of the challenges of RD community face every day. .

Helena Dalli, European Commissioner for equality, in a pre-recorded video underlined as all people should be able to participate fully and equally in society and in the economy. Rare diseases and disability are strongly connected. RDs are often associated with a wide range of impairments and a high risk of discrimination for PLWRD and their families. These impairments and the interaction with barriers and environment can lead to disability. In this regard, the EURORDIS Rare Barometer Voices program- supported by the EC DG Employment and social innovation - highlights the impact of RD in daily life. The RARE 2030 project aims to identify emerging challenges such as the PLWRD' reproductive choices and the transition into adult care. The Coronavirus pandemic has underscored the need for specific measures for vulnerable groups as the need for equality for all. Equality for all requires having dedicated legislation and policies in place but it also implies spreading the equality perspective into all those EU policies that have an impact on people's lives. In the field of employment and

occupation, the EU has adopted a legislation ensuring extensive protection against discrimination on various grounds, including disability but a "horizon equality directive" able of protecting those who are particularly vulnerable in all aspects of daily-life is now needed.

Irene Nordstedt, Director in DG Research & Innovation of the European Commission read a Statement by Mariya Gabriel, Commissioner for Innovation, Research, Culture, Education & Youth.

As the previous speakers, she also underlines that pooling resources is the only way to progress and help patients, especially in the RD field. From 6 to 8% of the EU population suffer from a RD. New effective therapies are needed for more than 90% of the RDs patients. Over the last 13 years, the EU framework programme for research and innovation funded more than 200 collaborative RD projects with more than 1.4 billion euro of investment that strongly impacted the RD diagnosis and healthcare. The European Joint Programme on RDs launched in 2019 is a multi-stakeholder integrated programme of research and innovation. It pulls together resources at national and European level (including ERNs), representing a crucial milestone and an example of effective partnership between actors. This partnership offers a unique opportunity to connect healthcare and research - accelerating research impact. The access to knowledge and the quality of data is necessary for the translation of research into clinical practice and, in 2018, the EC adopted a communication on the digital transformation of healthcare that has identified RDs as a pilot area to test the practical implementation of cross border healthcare for research and health policies. The EU joint Programme of RDs is contributing to the implementation of digitalisation in healthcare by establishing a virtual platform to connect and access research data and resources across Europe, overcoming the fragmentation of information. Access to health data is the corner stone for gaining full benefit of the digital technology. This is also why the EC developed the European platform on rare diseases registration to promote the interoperability of the existing registries and to help creating new ones to also facilitate recruitment of the critical number of RD patients needed for an effective research.

The next EU programme for research and innovation (Horizon Europe) that will start in 2021 aims to increase the impact of research in society creating seamless solution between research and policy bringing results rapidly to the people needing them, including PLWRD. In this line, conferences such ECRD provide an important forum to build a connection between researchers, innovators, clinicians and PLWRD across Europe and the world.

"I saw the help and support I needed, I went from being someone that only needed help to someone that is able to help others and I want to give back and bring the same possibilities and opportunities for other people as I had to fulfil their own dreams and their own goals".

David Lega, member of the EP and also a Paralympic winner affected by RD stressed the advances made in the last 10 years in the RD field, as the national disability strategies and the EU funded projects, but there is much more still to do. He strongly believes in a society built from the bottom up and the civil society, organisations like EURORDIS and conferences such ECRD play an extremely vital role in this regard. There is the need of a new Eu disability strategy post- 2020 because there are areas that need improvement such as inclusion, shared expertise, patient diagnosis, information and care. *"There is a big difference between what the Eu can do and what we want the EU to do".*

Respect to the support system for disabled people, Dr. Lega highlighted as putting a EU benchmark based on the average level counted in MS could somehow lead to disastrous cut in those governments with high

welfare standards. Each MS is different, solutions have to be tailored in the national contexts but "*We need to raise the bar for everyone, not argue out of a comparison with other countries*".

He also pointed out as in many countries people with disability have been often forgotten during the COVID-19 pandemic and as they suffered more than others the social distancing and the restrictions needed to reduce the spread of the virus. He also reported some discrimination episodes towards disabled people that Covid-19 epidemics have brought to light with disabled people isolated without proper access to care or to online education or made less of a clinical priority in hospital triage regardless of whether or not the disability actually affects their chances of survival. The EU has a responsibility not only to support and include people with disabilities in the policy and decision-making but also to act against MS not willing to respect the human rights. The EU role is to make sure that each country makes all the efforts possible to establish and maintain a society based on inclusion, independence and support for those who needed the most. And when a MS is unwilling to guarantee the freedoms and rights, there must be consequences such as withdrawing of financial support, limited power and right to vote and, most of all, EU condemnation. *"There is no excuse or place for such prejudice in our Europe. The biggest threat for us today is the ignorance and lack of knowledge that exists within the borders of our own countries*", EU should keep raising awareness and bringing issues on accessibility, discrimination and human rights to the agenda to make sure no one gets left behind and an important step in the light of a more equal and including society was represented by the ratification of the UN CRPD by all European Countries and by EU.

"It's not about my disability, it's about all my abilities, about all parts of my own personality". "All the support received from civil society, family, government, friends …made me more than a person with a rare disease or disability …"

ECRD RARE 2030 foresight scenarios session

In the plenary session **RARE 2030 foresight scenarios, Milan Macek, Chairman of the Department of Biology and Medical Genetics at the Charles University in Prague,** member of the RARE 2030 Research Advisory Board with a long and huge experience in RD and **Rebecca Tvedt Skarberg,** member of the RARE 2030 PoE and e-PAG representative in ERN Bond stressed the role of the RARE 2030 foresight project for PLWRD declining the four alternatives future scenarios developed in the RARE 2030 project.

"The COVID 19 has clearly shown as we cannot predict the future but we can prepare for it"

Milan Macek provided an overview of the RARE 2030 project structure, aim and process toward the building of a new policy framework for PLWRD. The RARE 2030 foresight study is working to give evidence to policy-makers to be more resilient in the future and to address PLWRD challenges in the best way. The trio EU presidency in 2022/3 will provide a roadmap for this framework. Dr. Macek underlined the strong participatory approach of RARE 2030 reporting the numerous previous and future opportunities of consultation, then he entered into details of the four RARE 2030 proposed scenarios based on the two main domains (axes) identified in the project: **values and innovation**. He declined the four scenarios in terms of the four extremes highlighting as the Fast over Fair scenario is the one we live in the current years and the Social for Justice scenario, characterized by high collective responsibility and patient need led innovation, can be summarized by interconnectedness, interdependence and jointly responsibility keywords. Milan Macek gives to the video realized within the RARE 2030 Consortium and available at https://www.Rare 2030.eu/scenarios/, the task to better describe the main relevant aspects of the four different scenarios.
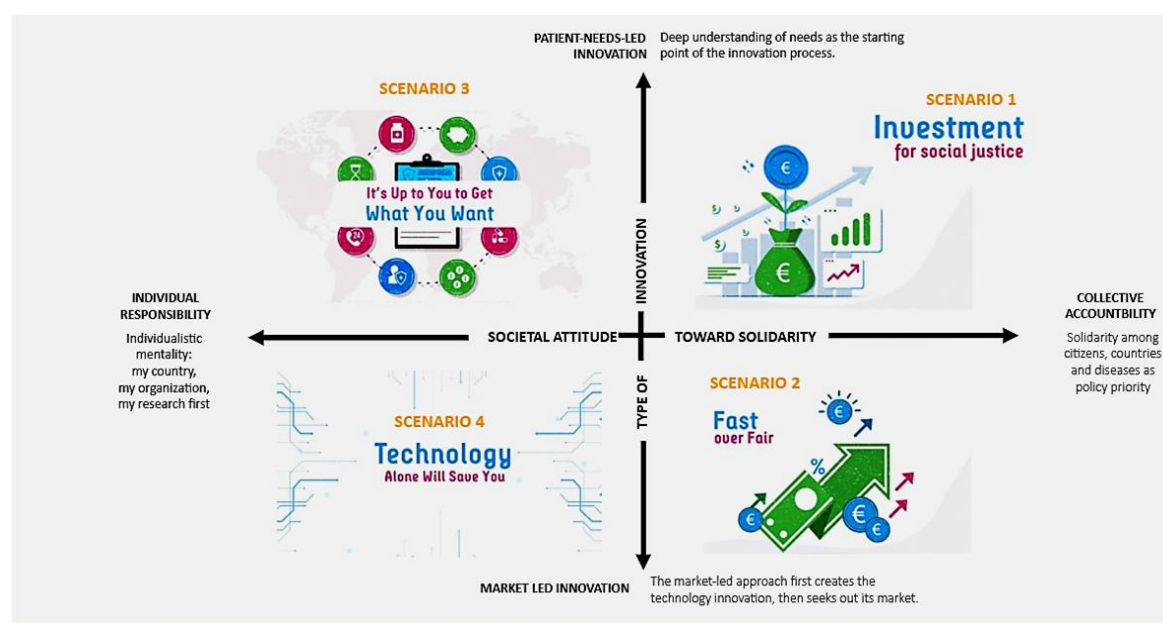

Figure 4 RARE 2030 Scenarios

"*RD cannot be controlled and prevented…It can happen to anyone, anytime and anywhere, we cannot controlled health and we will be very careful to define quality of life by health alone. The quality of life has far more variables than bodily or intellectual functions. For me rarity of course gave me challenges but also many great assets*".

Rebecca Tvedt Skarberg spoke about her experience as a PLW *osteogenesis imperfecta* disease and about how life for a PLWRD could be in the 4 different RARE 2030 scenarios.

She stressed as "*with every crisis also comes possibilities for change*". In fact, the online ECRD gave the opportunity to reach out more PLWRD who in fact live large part of their lives in lockdown or social distance even in no pandemic times.

What unites RD is not a specific range of disability o medical challenges, it is the low prevalence, RDs affect few people when comes to the specific conditions, but many people on a whole worldwide. RD patients are an heterogeneous group that share in common the experience of not finding adequate information and of lacking treatment or coordinated care, as she herself and her family experienced when she was diagnosed with *osteogenesis imperfecta* "*There was no road map and very few people to ask*". In ECRD she feels as "*one of many*" but **"in society, in my everyday life, I'm one of the few, I'm rare"**.

Many steps have been made in the last years in the RD field: the voice of RD community is stronger, some treatments have increased life choices and opportunities, technologies are helping in providing a faster and more accurate diagnosis, more RD people are empowered and actively participate in the society "*instead of being left out in the forest to fight for themselves*". But some RD treatments are being increasingly overpriced and often "*in the hands of few instead of the many*". Government and politicians often put price on RD life trying to strictly calculate the most value for money but the life of PLWRD does not "*really fit into a spreadsheet…We are talking about life and human right to be able to live these lives*". Another threat is the vulnerability PLWRD expose themselves by sharing personal data. Data are crucial for ensuring better treatment and care for PLWRD but who owns these data? How do we ensure safety of these data in the future? Can data fall into the hands of people who would force PLWRD life into financial spreadsheet?

RD can happen to anyone, anytime and anywhere, we cannot control health and we have to be very careful to define quality of life by health alone. The quality of life has far more variables that bodily or intellectual functions and she underlines as rarity gives her challenges but also many great assets in her life.

The four RARE 2030 Scenarios provide gleams into the future but it's up to us to decide what future we want. The scenarios are theoretical models with strength and weakness aspects, we can identify different scenarios and steer to work towards what we want avoiding what we don't want. While Coronavirus is government' wildcard, the wildcard of PLWRD is the rarity of their condition.

Focusing on the four RARE 2030 scenarios, she stressed as she herself has seen some of these scenarios play out in her life or that of people she cares about. In "**It's up to you to get what you need**" scenario lots of people will be left behind. In this scenario, how we do ensure that people who actually need the help get it? Here it's up to you to know your rights and to have the resources as the adequate knowledge to exercise these rights as for the off label use of drugs for RD patients, an use that in some countries can be recognized and accessible and in others not. In "**Technology alone will save you**" there are strong and exaggerated believes in technologies. Private companies could offer false hopes and dreams, "*the worst*

prognosis, the easiest is to offer false hopes and dreams at top prices" as RD community has already experienced sometimes. Regarding data sharing who will make sure that data are not sold off? If data collection is not trustworthy, few will be willing to contribute and this will not foster innovation.

The "**Fast over fair**" scenario is maybe that one we live in Europe today. RD groups with strongest voice advocated for them for years. Some researches has led to new treatments or care and this, with a domino effect, has led to more trust, resources and breakthroughs but access is still a game between private stakeholders and public funding structures. The prioritization and the "*putting prices on lives and medicines*" pose risks in the access to care "*if there is medicines out there, are there someone say that our life is not worth the price of it? Is my life less worth than yours*?" This business divides patient organisations and weakens the RD joint mission *"We all are in together, whether our condition is better understood or not, whether is interesting for research or not"*.

In the "**Innovation for social justice**" scenario the joint collective responsibility pursues that no one is left behind in line with the UN SDGs and the UN convention on the rights of person with disabilities (CRPD). *"Priorities are made together because we understand that we actually do depend on each other"*. This scenario does not rely on charity and generosity, is a scenario that understands that all of us are connected, that RD can happen to anyone and that their impact can only be managed together. In this scenario it is clear that the life of PLWRD "*cannot be measured and forced into spreadsheets*", that the quality of life of PLWRD depends also on labour, independence, community and on the fulfilling of their potential to live their best life.

For each scenarios there will be trade-offs, each scenario has positive and negative aspects but we have to bear in mind that "*We are all dependent on each other. Development is dependent on all of us, doctors, researchers, social workers, policy makers, teachers, parents, loves one, everyone. It's about our society and what we wanna see*". The time to stir towards a better world for RDs is now.

The session ended with a pool on the RARE 2030 preferred scenario and on the one considered the most likely to happen. **Innovation for social justice** resulted to be the most preferred by the session' participants, the **Fast over Fair** the most likely to happen. Audience were also asked to write down the single policy interventions they considered relevant to reach the scenario they want. Among the actions proposed:

- Less commercial interest and more community driven initiatives
- Co-creation between patients, health care professionals, innovative companies
- Uniform data sharing and patient view integration in IT systems and ontologies
- Patient empowerment and involvement on all levels, research, treatment development, clinical treatment, innovation on all levels
- Patient centred approach
- Patient rights
- Patients organisations seating at the medicine price table
- States agreeing to a patient led European Rare Disease Patient Charter
- National and pan national investment in research and therapy development. Reduce company owned IP
- A strong European health strategy, state-led (EU as main policy driver)
- Obligation for pharmaceutical companies to share freely their data
- Connecting treating physicians with experts to optimize care plans.

The most part of the session participants were represented by patient representatives, followed by academia and private stakeholders.

ECRD Thematic Sessions: highlights

The sections below report the conclusions and the "take home messages" of the ECRD six thematic sessions presented by the panelists in the plenary session of the 15th of May 2020. More insights on theme discussion and insights are contained in Annex I.

Theme 1 The future of Diagnosis: new hopes, promises and challenges

The theme closely examines the current landscape and also debates future trends and scenarios. It also explores how new technologies can be applied to accelerate and improve access to diagnosis. The conclusions were presented by Christine Patch in the plenary.

This theme highlighted the diagnosis as a crucial phase in the PLWRD journey. Diagnosis means positive and negative implications and patients and families have to receive all the social and psychological support to face these implications.

In detail, session 1 stressed the need for better triage so that people get into the first stage of diagnostic pathway more easily and as soon as possible. The triage starts at primary care and that is about raising awareness, education and healthcare workers training in triage in primary care. Currently many screening tools are being developed but many are not helpful and mature enough. Furthermore, the classification of RD is changing also thanks to the spread of the genome sequencing, whose cost-effectiveness at first line testing has to be considered.

Session 2 focused on new-born screening and on the big problem of the variability across Europe (what is not offered in some countries and over-offered in others) with missed opportunities to save or improve the lives of PLWRD. The potential of genome sequencing for new-born screening would probably expand the number of conditions as appropriate for new-born screening but the expansion of any screening panel should be based on scientific advancement and health technology assessment. Screening is not just a test, it is a process and also needs adequate information and communication with families and public and adequate training for healthcare professionals.

Session 3 and 4 mainly focused on the effect of having a RD diagnosis and the concept of the patient journey came up very strongly when talking about what it meant to be undiagnosed.

While the diagnosis brings lots of positives, there are also negatives as it is just the start of the next phase of the patient journey. We heard some very powerful testimonies of PLWRD and families with the conclusion of the need for more support and psychological support after the diagnosis. We also heard about interventions to help improving clinical management system - as promoted by ERNs - and about initiatives to hopefully work towards identifying which treatments might be worth developing. A big thing which came out in these sessions is the need for continuing collaboration internationally and across Europe. We are in a difficult situation in the UK at the moment and there was some concern over what is going to happen to the European initiatives after the end of this year but whatever happens, the need to collaborate both on the developmental science and the care pathways is absolutely essential.

Theme 2 Our values, our rights, our future: shifting paradigms towards inclusion

The theme looks at the ongoing advances in international advocacy and discusses the significance they have for different stakeholders of the rare disease community. A key goal of the theme is to discuss how the rare disease community can translate those global commitments and aspirations into concrete regulatory practices and policies in the national context. The conclusions were presented by Maria Montefusco in the plenary.

The sessions underlined the need to turn away the strict medical view paradigm on PLWRD and disability in the human rights perspective that even if a person has a complex health condition, "*person is not a diagnosis*".

Fighting for human rights for PLWRD is what we do all day long in the rare disease community. However, our focus has often been or care, development, provision and access from a resource perspective but we need to consider universal health coverage (UHC) wide in scope, covering all human rights and integrated in the local, national, European and international legal framework and agreements.

In this regard as Todd Howland, Chief of development and the economic and social issues branch at the UN office has underlined, "*human right should be goal but also the tool to reach the goal*".

The first live session was about the theme of universal health coverage from political commitment to reality for all. This concept is huge and complex in a way but also quite simple, is about work in order for all people on the planet with whichever health condition they may have, shall be able to experience health basically. In this regard, we have many challenges but also tools which can be used to obtain equality and health on all levels. One of those examples was presented by Matt Bolz-Johnson (ERN and Healthcare Advisor- EURORDIS) on increasing access to knowledge and expertise by globalisation of the ERNs with hubs at university hospitals in bigger cities. That was a very concrete example of what we can do with already existing elements.

Ms. Nata Menabde who is the Executive Director of the WHO office in the UN has underlying special attention to vulnerable groups in the declaration to universal health coverage. Her take home message was about how the scarcity of knowledge is a strong reason to collaborate on a global level in research and development of diagnostics and treatment but also in data sharing and collection from many different places and areas. Another point was about the integrations of ERNs in specialised care and the necessities of work in a multi-stakeholder approach.

In the sessions we also talking about what holistic care is and how it is financed in different contexts. The person centred approach goes on at a micro level between professionals as well as at the meso and macrolevel in which the people, who are the target group, should be involved. There should always be a contact with patient organisations representing people with disabilities when designing, evaluating and implementing holistic care services. Several good practices in holistic care services do exist, but adapting them to different local needs and circumstances it is not always easy. Patient organisations could help in making sure that we are on the right track.

As about ensuring non-discrimination on the basis of disability, we got better acquainted with some of the legal and strategic tools that are available and under construction as the European disability strategy, the WHO global disability action plan, the UN's conventional rights of people with disabilities and the European declaration of fundamental rights among others. But we need to have a clear and well-structured plans for inclusion and implementation of the rights and needs of people with disabilities on local, national and international levels.

What is disability from a human rights perspective? A person with a rare disease has serious health conditions, often functional impairments, but he/she is also in contact with the barriers of the environment where the disability appears. Societies systems and people often have quite low expectations of what a person with rare disease and disability can be and do in her life. These low expectations and treating a person accordingly to their limitations need to stop. Breaking barriers of the environment including bad attitudes of low expectations is a human rights way of working strategically for inclusion.

In this regard the disability assessment - which is fundamental in order to get service and support measures including economic support - has to be needs-based and not diagnosis-based and has to take into account the environmental barriers that must be removed.

To reach the desired Investments for Social Justice RARE 2030 scenario we must face barriers as the lack of coordination in the systems, the working in silos and the conventional medical model focused on disease. On the contrary we need flexibility of the systems, person centred approach, linking the complex medical needs with the needs of being included in society and creating real relationships between patients and professionals sharing knowledge. We have to work together to counteract the system in which we live *"where risks are distributed in society whereas profit is gained individually"*.

Theme 3 Share, care, cure: transforming care for RD by 2030

This theme explores the rare disease population's needs in 2030-40, as well as the opportunities and the challenges of care provision of the future. The sessions within this theme put a spotlight on emerging trends in best-practice, promising technologies, and cutting-edge thinking, showcase forward-looking services and their potential to be scaled-up and to transform the delivery of healthcare. The conclusions were presented by Birute Tumiene.

Tremendous innovation have concerned the healthcare provision for RD in the last ten years but we are expecting it will exchange even more in the upcoming years. However, to get to that bright future we have to overcome numerous challenges today.

In the first session, "*Live longer healthier lives RD population needs in 2030 and beyond*" we shortly reviewed policies including soft EU acts - excluding EU cross border directive which is a hard law – and also national plans and strategies at country level and we tried to investigate emerging policies trends. Indeed, today we have the obligation to build policies which take into consideration patients' needs and that means not only creating patients center healthcare but also citizens and community driven policy and decision making. And patients and RD community to thrive for more European solidarity, for great competencies in health ad for more equity.

We talked about policies to meet these needs, and in particular about ERNs and national plans. As conclusion for ERNs – it was recognized that we put very high expectations on them and their value and breakthrough potential is unquestionable. However, what is also unquestionable is that Member states which are the main beneficiaries of these structures may lose their potential if they do not take the necessary political, organizational and financial measures to ensure the ERNs integration into national systems.

Regarding RD national plans (NPs), 27 MS have adopted them out of 30 EU and EEA countries. However, we have to acknowledge that some NPs simply expired, others are not more up to date while some were of low quality or simply not implemented. Therefore, MS will benefit a lot if they revise NPs taking into consideration lessons learnt to make them effective, up to date, based on EU common values and

supported by tools for their real and concrete implementation. The need to revise EU policies is not just acknowledged by RD community but also by external evaluators such as the Court of Auditors.

One of the global trend – which now include also RD patients – is the ageing of population, but it is completely new for RD community.

In this context, there is very high and largely unsolved need not only for guidance for making the most of the complex pathway across healthcare and social assistance but also for clear guidance and awareness on the different life stages (childhood, adolescence, adulthood and ageing) and how to ensure a smooth transition.

Another relevant trend is technology and how to create the proper conditions for their deployment and not only during pandemic but on a constant base. In a digital era, it is key the question of data collection, sharing and management - safeguarding the data security and the data ownership of PLWRD is also a trend that needs to be managed.

The second session "*ERN & CoE Accreditation as Quality Improvement Framework*" addressed very sensitive and complex issues of quality insurance on one hand and inclusivity on the other hand. A vision of mature ERNs that are able to realize the full potentials of these structure was presented. As conclusion, the process of establishment of ERNs was and still is a very risky – it is *"learning by doing"* - process, there is no precedent – "*we are pioneers*". After three years, we had great outcomes and the great news is that ERNs coordinators are still full of energy and motivation to act despite the administrative and bureaucratic burden, and the frequent lack of national support. They already see the fruits of sharing and caring like generation of knowledge, the sharing of guidelines and generation of registries and research. And they find their own solution when political decisions are not speeded enough. As example, the establishment of national coordinators in countries with multiple ERNs members and the creation of ways to monitor and benchmark through registries.

To have the full potential of ERNs deployed, it is crucial the integration at national systems and this is a constant cry for help and MS should find sufficient motivation to move forward – and should hold the promise and commitment expressed also in the statement of integration adopted by the Board of MS. In the context of this session, integration means striking a balance between rigid quality insurance and inclusivity. Quality insurance is absolutely indispensable if we are uphold our promise that ERNs are the best care available to offer to our patients. At the same time, we have to ensure possibilities for every patients across Europe to find his/her way to the ERNs.

Finally, it was discuss the question of accreditation and quality insurance in healthcare provision and identified a highly diversified quality insurance landscape across Europe as the current European legislation and principle of subsidiarity allow a number of soft and hard approaches. However, ERNs as well as patients have developed tools for monitoring and benchmarking. Patients provide a voice through e-PAGs and help to find the ways on what is the best. On both these processes, we have a request of open, transparent information on performances that would hopefully finally lead to improvement of transparency and accountability also at national level and could possibly shape the composition of ERNs in the future.

In the third session, "*Clinic of the Future & Digital Care Pathways*" a large part was dedicated to artificial intelligence and its possible future potentials in support of clinical decision. Among the potentials highlighted: reducing the workload of professionals, to establish digital care pathways, care coordination, and risks management, to foster patients empowerment and to improve cost-effectiveness of care as well through diminishing hospitalisations and workload. It is the time to use AI and, on lesson learnt to do so, it is time to also strength the role of public private partnership (PPP).

Clinic of the future is somehow already here, during the pandemic - virtual care and telemedicine become the norm. On the other hand, we will never use only virtual in RD care but it can support facing challenges such as the shortage of medical doctors, the increased migrations, the ageing of workforce, the demand of lifelong training and the need to strike a balance between general and hyper-specialization.

A challenge specific for RD is the role of GP which is still not well-defined. Also a lot of discussion was around expert patient and patient empowerment, especially taking into account the new technologies. In addition, it emerged the need for more soft skills of RD physicians because indeed the interrelation between patients-doctor is recognised of crucial importance for the final success of the care process.

Final points were made in session "*Addressing Health Workforce Challenges and training: the New Generation of Rare Disease Experts*" on medical education and the need to develop capacities to work in teams. It has to remember that workforce is not just about numbers "*Workforce is made by people for people*". We need to create an attractive environment for healthcare professionals to retain and motivate them. This work has to start now in order to see a difference in 2030.

ECRD Theme 4 when therapies meet the needs: enabling a patient centric approach to therapeutic development

The objectives of this theme is to take stock of the experience gained so far in the development of medicines for people living with rare diseases, and to examine the evolution of the field. The session looks at recent scientific innovations and clinical research, regulatory solutions, roadblocks and challenges in developing therapies that match the needs of the patients, as well as ways of embedding real life evidence into the therapeutic development processes. The conclusion were presented in the plenary by Diego Ardigo'.

This theme has discussed a "present of exclusion and a future of inclusion" in therapeutic development starting from the current state of exclusion of disease, exclusion of patients and information still lost in drugs development.

A disease could be neglected or disregarded if there is no public research, no diagnosis, no therapeutic development. And this is, unfortunately, the situation of the majority of RDs. We have a problem of equity in Research and Development in RD with few diseases getting all the attention and many diseases completely disregarded. What makes a disease to be disregarded? When it is too rare to attract investments, when there is too limited organized information (available, usable, published) and/or when the disease is particularly complex. Conversely, patients are excluded when they cannot be enrolled in clinical trials and cannot access early access programs or marketed treatments. They are excluded when they do not fit with the eligibility criteria of clinical trials – which are of course established for a good reason – but this means that some patients -sometime even from the same family- are excluded from accessing new treatment while it is under development which means that sometimes they might be excluded from the label and then also from reimbursement rules.

In addition, the country in which patients live in could still make a major difference in access and this starts already at the level of clinical trials. This is due to the fact that technological complex treatments need standards and procedures that are not always accessible in all EU countries. This inequality continues at the level of early access and compassionate care and even exacerbates after the formal regulatory approval at the time of the reimbursement.

Finally, there is the issue of all precious data that can be excluded, forgotten, lost. This is the case of all the knowledge and information coming from the personal daily experiences of patients and their families

but it is also the case of their personal data and health records which are "buried" in some hospital database and will not be proper analyzed and shared.

Borrowing from RARE 2030, we have to embrace a "*different vision of the future*" working towards a future of inclusion, balancing the push of science, technology and business and the pull of patient needs at the top.

In this future, all inequalities in RD R&D are overcome by a new integrated and coordinated research agenda, generating the knowledge ground for any diseases – which is needed to support any development efforts. This is realized by incentivizing and driving the focus of R&D efforts especially in neglected diseases.

In this future, patients are trained to collect their own data, are fully owner of their use and participate in R&D networks from design to the execution. This is based on the idea that patients are fully trained but are also adequately aware of the uncertainty and the risks of R&D – providing a solid foundation to make informed decisions at individual level but also at collective level of society for all other patients.

A future in which the information from Real world evidence is integrated together with well design randomized clinical trials to fulfill all the regulatory and standard requirements while at the same time covering all the gaps in the knowledge and establishing the true value of each product.

In this future, real world data are collected and managed by network of stakeholders who cooperate applying FAIR principles – in ways that are respectful of data ownership, informed consent principles and public interest in general- but also fulfill data quality requirements as well intellectual property rights.

A future in which the whole spectrum of therapies is available ensuring a technical and financial sustainability. It is therefore a future of collaboration among stakeholders and among countries - sharing the risk and decision for the individual and collective benefit.

The good news is that we are not envisioning a fantastic future, the 4 sessions discussions have clearly shown that there are solutions already out now that go in this direction, starting from patients and their needs, their experiences of the past and their picture of the present, their vision of the future and their view on the collection and the use of their data, building solid pillars for patients involvement in research and development.

We recognize how much patients can be "eyes openers" in understanding their conditions, the clinical relevance of data and the real value of drugs.

We also talked about advancements in clinical trials design and execution, innovative clinical trials design and how to use them in order to respond to the rightful research way. We talked about Real world evidence efforts and how to integrate these efforts together with traditional clinical trials with references to clear cut examples and on-going experiences in the field. We explored the role of ERNs and what they can play into this – with examples of core data collection including patients reported Quality of Life and clinical outcomes data. We looked at how patients can keep the ownership of their data while participating at Research and Development network at the same time. We discussed the case of oncology, and what RD can learn from this field which moved from a disease defined based on organ to a disease defined based on the underlined mechanism stressing how this could allow us to be more effective, precise and safe in treating each sub-population of patients.

We also prepared for the audience a recorded webinar of the International Rare Diseases Research Consortium (IRDiRC), the "Orphan drug development guidebook", which enlists how to use tools incentives, designation, resources and best practices that are already out there to support developers in rare diseases.

During the sessions, we heard specific initiatives and guidance by EMA on how to keep a fruitful dialogue with regulatory agencies at different levels. We also examined the case of the advanced therapy development which is a great example of collaboration between patient push, the publically funded research (i.e academia) and the industrial development putting together all those complementary competences for a successful case. In general, the theme has reported a number of examples in which the silos thinking has been overcome by a greater level of collaboration.

"We are talking about a mutual effort for a mutual benefit. It's time to understand how independent we are and that we are independent only if we support each other so we also recognize not only our independence but also our inter-dependence".

ECRD THEME 5 When therapies meet the needs: enabling a patient-centric approach to therapeutic development

There are more life-changing therapies in development for people living with rare diseases than ever before, yet at our current pace it will still take decades to cover all our unmet needs. The rare disease community still faces a number of challenges in accessing authorised therapies, which indicates that the system in its current design is not functioning to the benefit of all, particularly those people living with a rare disease. How can we improve the functioning of the system by 2030? What are the solutions to ensure the sustainable development of therapies that are truly available to all? This theme examines the different aspects of the system which need significant change to make it 'fit-for-purpose' now and for our future needs. The conclusions were presented by Ana Palma in the plenary.

Session 1 was about rare diseases in numbers and what do they mean. Avril Daly, our chair, made clear that access to therapies are significantly delayed in many countries and that the approved treatments are only on some countries and not in others. This poses the question of equal rights under the EU law, given the absence of equality amongst citizens in the EU in terms of access to therapies. It was also remarked that there is a need for structured evidence generation and that currently more studies get going in this direction also in order to further empower patient-led advocacy.

It was presented the recent Orphanet study which provided an evidence based clarification around the prevalence of rare diseases. The work underpins how important it is for all stakeholders to have uniformity of numbers, data, definitions and generally a common language. So we learn that today there are 6.172 rare diseases, 86% are prevalent – meaning that they are chronic- while 14% are incident diseases. And these diseases affect between 3.5 to 5.9 of the world population which is equivalent to 263 to 446 million people. We have also learnt that 390 diseases do capture 98% of all rare diseases patients. The conclusion was that data needs to be generated globally, across sectors and coded in the same way.

Then, the social science related study and data from EURORDIS Barometer voice were presented. The survey, gathering more than 7,500 responses across the world, investigated the burden of RD in daily lives. Although it is reported a slight improvement in term of access to treatments, still more than 31% of the respondents have never experimented treatments because it is either not available, accessible or affordable. The survey has clearly shown a great variation in access to treatments depending on the diseases areas. Many patients reported to have adopted treatments which are not approved such as off label and medication used for compassionate use. This clearly highlighted how the need to access is so huge that justify them running the risk of trying not approved drugs. This also highlights how huge must the need of rare disease patients be in order to justify them to take higher risks in trying non-approved drugs.

The next study was conducted for 10 inherited retinal diseases and explored – for the first time- the cost of wellbeing in such rare conditions. Wellbeing costs were seen to be the highest costs in the country where the study took place, they in fact accounted for 1/3 of the total costs. These were mostly related with aspects like anxiety, depression, social isolation and even financial stress but most importantly this was the case not only amongst patients but also their families and carers. This pointed out to the need to broader the evidence based beyond the traditional costs in order to demonstrate the full spectrum of the real RD impact for patients and their family and provide adequate information for HTA and payers' decision- making.

The next session highlighted the lesson learnt in 20 years of drugs development in EU and how OMP regulation has so successfully incentive investments in the development of drugs for RD – even if the current treatment only covered 5% of the known RD diseases. It was stressed that a strong set of incentives continues to be needed in EU to find treatment for the remaining 95% RDs which still don't have one. This is also what the COVID crisis pointed out: the need not to lose sight of innovation while facing the economic crisis that we will all face after this period. The OMP should be read in the context of developing innovation ecosystem in the EU and should take more into account the patients' perspective. It was stressed the importance of the number to describe the lives the RD patients live and the impact they suffer and the difficulties encountered in accessing affordable therapies

The second session related to new disruptive technologies like gene therapies and how to prepare the healthcare systems. The findings of the RARE IMPACT project were shared. The project aimed at optimizing patient access to effective gene and cells therapies in the EU. The study has already provided recommendations for 10 countries on several dimensions. In relation with assessment dimension, the study highlights the need for more collaboration between HTA bodies and regulatory agencies, a consistent approach for RD registries and the requirement for the use of Real World Evidence. The latter need is even more acute in relation with Advanced Therapy Medicinal Product. With regard to affordability, there is the need to consider long term benefits of these products that are often one time treatment and the outcome based agreements were mentioned as one of the possible solutions. It was noted that ATMPs will not be affordable if they are not societally acceptable and so the solution it is really to increase education on these new mechanisms to come. With regard availability, the challenges are more pertinent to the cross-border collaboration and more guidance and collaboration from EC is needed. In terms of accessibility, several practical factors were discussed that exist today that still impede patients to access their treatments. In 2025, it is estimated that FDA will approve between 10 and 20 gene therapies per year[42]. However, there are still a number of barriers notably regarding the identification of patients. There are also new-born screening that needs to be expanded and sometimes even a genetic diagnosis is required. To finalise that session we concluded that there is still clear gaps between regulators and HTA bodies in the evidence requirements and that there should be more flexibility on the use of pre-existing data for HTA, and that patients and doctors could work on core outcomes for the conditions to facilitate assessment and for the use of registers

In the session from research to access, a number of key barriers were identified such as the lack of trust between stakeholders, the limited focus on public-private partnership (PPP) development, and the fact that regulations are in some cases impeding data sharing. And lastly there is still a fragmentation of approaches and processes that do not lead neither to better treatment nor to greater availability.

Conversely, key enablers were considered the greater implementation of multi-stakeholder and community approaches, the increased use of PPP for research and the improvement governance

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[42] https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics

processes. From the projects, it was highlighted the need for stronger regulatory science and more blunt strategies choices. In addition, synergies between OMP and paediatric legislation should be improved and investments should be done for the setting of long term infrastructures and the improvement of stakeholders interaction (academic, industries and patients). Among the projects of successful partnership proposed: EJP-RD, European paediatric transnational research infrastructures.

Then the aspect related to the post authorisation was analysed through the presentation of the findings of the project IMPACT HTA and the work stream focusing on orphan therapies. Among others, the project investigated to what extend RD drugs deserve a special appraisal system and from the responses from 32 countries 13 have already adopted special processes and 12 out of the remaining 19 have already adopted some sort of adjustments. The project does not state what an ideal process should look like but identifies features to better deal with RD treatment specificities in a structure and consistent manner. Then, there was the presentation of two tools both developed in a multi-stakeholders way and aiming at reducing uncertainty. The first tool was developed in the framework of the TRUSTFUL RD project thanks use Real World Data and it is leading to the Initiative Real World Evidence to Decision. The initiative aims to reduce the lack of trust between actors who are not speaking to each other's by developing a common framework to reduce uncertainty. The second tool – developed in the framework of the Hercules Project- aims at providing better data to appraisals so that they could get better understanding and develop improved responses to the patients' key needs. Out of this session there was a clear message on the need to streamline HTA at EU level.

Then we moved on to our last session 'from research to access'. Is a European collaborative approach possible? We had a presentation of the Rare 2030 scenarios and then we asked the audience to vote for their preferred one as well as the panellist's perspectives on the 4 scenarios. The participants in the poll have chosen scenario 1 which is "Investment for social justice" as the most preferable Scenario. Surprisingly, when we asked the audience to vote which of the scenarios would be most realistic in the context of their countries healthcare systems, scenario 2 "Fast over Fair" which was the chosen one. The different panellists gave their perspectives on scenario 1 and it was acknowledged that this was the scenario which offered the greatest equity between patients to achieve better access to healthcare, hence this is why the whole community and stakeholders should be giving priority to achieve this. It is a scenario which highlights the holistic approach to healthcare needs. It is also a scenario where the patient's needs are the main drivers for innovation. We also discussed in that context the PPPs again which should be one of the priorities. The panellists also went over the other three scenarios. It was mentioned that scenario 2 was a very worrisome scenario for rare disease and one which is - to a large extent - already experienced today. In this scenarios, one of the main concern is that for PLWRD was that their number are also small and so they would never find enough of a voice to strive for their rights. It was clearly stated that patient organisations need to advocate more because access to treatment will not be assured in such a scenario. There were similar thoughts expressed around the scenario 3. It was acknowledged that this scenario would increase inequality in the access to healthcare within Europe. In other words the wealthier will get treatment while the poorer would not. Another weakness of this scenario would be that innovation would be quite local and as such, it would not be available to all patients. Finally, the last scenario 4 was explained to be a very extreme scenario, one which foresees total privatisation of healthcare in many ways and because of that, it is extremely alarming. Privatised care is already in existence in many countries and again, it is already a concern today.
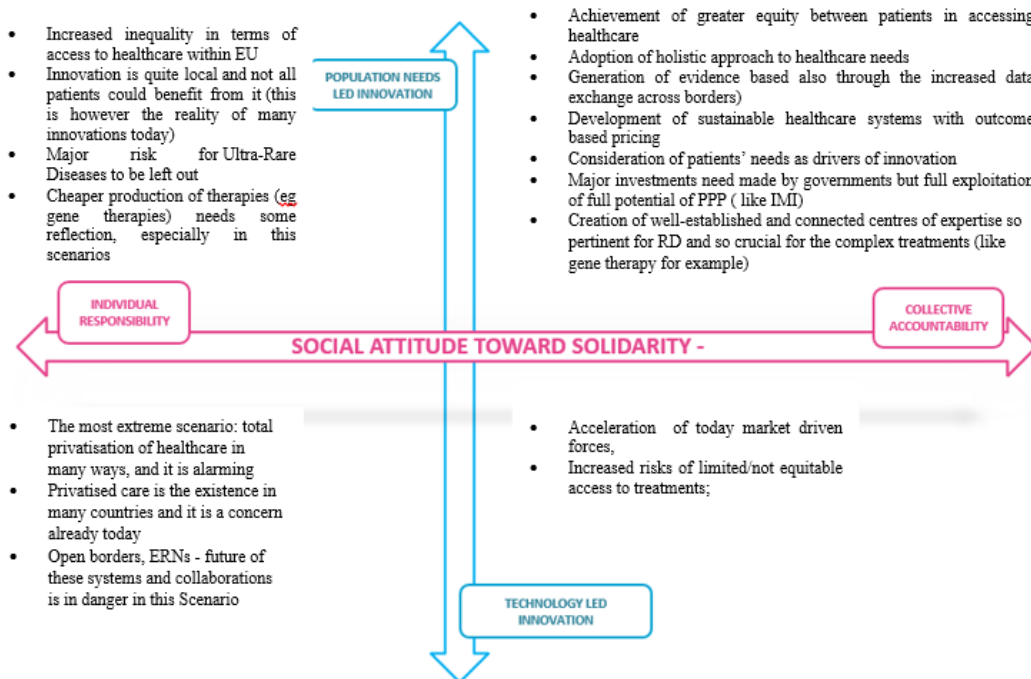
Increased inequality in terms of access to healthcare within EU
- Innovation is quite local and not all patients could benefit from it (this is however the reality of many innovations today)
- Major risk for Ultra-Rare Diseases to be left out
- Cheaper production of therapies (eg gene therapies) needs some reflection, especially in this scenarios

POPULATION NEEDS LED INNOVATION

- Achievement of greater equity between patients in accessing healthcare
- Adoption of holistic approach to healthcare needs
- Generation of evidence based also through the increased data exchange across borders)
- Development of sustainable healthcare systems with outcome based pricing
- Consideration of patients' needs as drivers of innovation
- Major investments need made by governments but full exploitation of full potential of PPP (like IMI)
- Creation of well-established and connected centres of expertise so pertinent for RD and so crucial for the complex treatments (like gene therapy for example)

INDIVIDUAL RESPONSIBILITY ← **SOCIAL ATTITUDE TOWARD SOLIDARITY -** → **COLLECTIVE ACCOUNTABILITY**

- The most extreme scenario: total privatisation of healthcare in many ways, and it is alarming
- Privatised care is the existence in many countries and it is a concern already today
- Open borders, ERNs - future of these systems and collaborations is in danger in this Scenario

TECHNOLOGY LED INNOVATION

- Acceleration of today market driven forces,
- Increased risks of limited/not equitable access to treatments;

Figure 4 Summary Scenarios discussion

To summarized, the RARE2030 discussion highlighted:

- The importance to develop new reimbursement models such as outcome based payment schemes for gene therapy in order to ensure a more easy access to such kind of treatments. Payers may establish risk sharing agreements after the setting of standards processes on how to do/measure them. E.g "Luxturna"
- The pivotal role of patients and patient experiences to develop therapies and improve access to treatments through evidence based research (Bench to bedside concept).
- The key role that patient's organisations could play in closing the gaps between technologies advances and policy process and in promoting a greater alignment between research – HTA – regulators.
- The use new technologies should be more explored to ensure the 3As
- The future policy should take into consideration the relevance of trust and collaboration among countries and stakeholders to create real change and innovation.
- The COVID 19 crisis could be a lesson learnt on the risks of lack of cooperation at EU level and it raises awareness on importance of cross-countries multi-stakeholders collaboration.

ECRD THEME 6 The *digital health* revolution: hype vs. reality

This theme examines the technological innovations that are underpinning disruption in medicine and science, as well as the legal, ethical and policy foundations that can frame future outcomes in this area. The theme also looks at how technology can support the social inclusion of people living with a rare disease. Attendees should come away from this theme with a greater understanding of the role of quality data in technologies such as Artificial Intelligence and how this impacts the development of medicines and delivery of care and other services. The theme aims to question the value of such technological innovations, as well as to show the policy frameworks and ecosystems which patient representatives can

involve themselves in, in order to bring the patient's voice to the evolution of policy and ethics in this area. The conclusions were presented in the plenary by Denis Costello.

The team leaders have deliberately chosen a title that was slightly controversial: hype vs reality around digital health. The ambition was to provide a greater understanding of the role technologies such as AI and to question the value that these innovations can really bring to the space of RD. The session got a significant dose of reality with great presentations of real life case studies and some very practical examples from the community as well as the solutions providers who really gave us some tremendous hopes for the future. Rather than going chronologically for the 4 theme sessions, the report highlighted some key trends and cross cutting issues emerged. One the ideas that came out is from the entire theme that there is a significant role and opportunities now for patients organisation. Prof Crooks from Digital Care and Health Institute, Ireland, reminded us of the sheer power of the digital health data and, in the appropriate context, how that data can be put in the hand of health providers. How we can really make an impactful difference but that really is up to us, the patients organizations and patients to avail now of the technological enablers that are coming on stream to be empowered and proactive in the use of those models and those technologies. It came through that this result is on line with EURORDIS Rare Barometer survey on this topic which was conducted quite recently and investigating patients' attitude toward the use of their data.

Two models were presented over the course of this theme one by Rosa Juuti from Finland entitled Findata, a government-promoted independent model, whereby an agency would act as the kind of independent broker between the patient community and research community and take into account all of the patients' needs in terms of their desire to control and anonymise their data vs a more bottom-up community-driven model presented by Salus Coop from Spain. Joan Guanyabens represented a great about model about how a cooperative could in fact bring together under a specific standard the different stakeholders in the world enabling data donation from the patient movement. If we look at that under hospices of the RARE2030, one could imagine how these two very different kind of data sharing models might sit on the different RARE2030 scenarios. Another opportunity for the patient organisation movement to be involved was highlighted by Brian O'Connor from the European Connected Health Alliance that has really encouraged health organisations to get involved and not be afraid to co-design solutions and collaborate with other stakeholders. "If they are listening to you, it is really important that you are there so that you can articulate your needs and so that we can all act upon these together".
An important area of advocacy regards healthcare providers that should now take up the integration of digital health solutions into healthcare. This integration seems to be not happening fast enough, although COVID 19 situation has accelerated the process to some extent, but it is clear that patients and patient organisations have a role to play in the advocating for the uptake of these solutions where appropriate.

The second theme that came out of this theme was that - despite all of the innovations that are happening somehow - we are still really at the start of what is a journey. There is the need to build trust in these kind of solutions and work needs to be done not just in the area of privacy and security but also in the area of determining the real clinical value of these technologies. A wonderful presentation by Liz Ashall-Payne from ORCHA Health, working in the UK and in the Netherland, introduced a very interesting model for the standardisation of the digital solutions, namely apps and another digital solutions. ORCHA Health has developed a protocol for the validation for these technologies as well as all kinds of search engines to enable patient organisations to be able to access these solutions in a trustworthy manner. How industries are beginning to use artificial intelligence was shown by Peter Speyer from Novartis Initiative. The initiative, called Data 42, built upon the fact the company is "sitting upon two million hours of patient data" gathered over the course of company lifetime. The company has now decided to start

curating and building ontologies on top of this data to make it in fact useful for data scientists and drug developers and to be able to answer the kind of questions that they need to answer now going forward.

It came clear also that we are at the journey's start because we need standards. In fact, collaboration across industries and stakeholders in the field of digital health needs to become available and meaningful and to achieve this we need standards. In line with this, Marco Roos from University of Leiden presented the GoFair standards which aims to make data more findable and interoperable.

Then we had stories of hope. A wonderful story from Sweden from company called Tobii Dynavox presented how eye tracking technologies has really helped patients with Rett syndrome in Canada to develop a personality through being able to communicate and speak. The Ring20 community presented some devices that support patients with epilepsy detecting brain waves and alerting them and people around them on the seizure. We had a presentation of the registry of the future where patients could be monetarily rewarded with cryptocurrency and through block chain means to proactively sharing their data. Finally, we also had an example of virtual reality built to help rare disease patients in Agrenska showing how technology can really support inclusion and accessibility.

ECRD Conclusions

The closing session of the ECRD saw the contributions of Jana Popova, Adam Vojtěch and Yann Le Cam reporting their personal take-home messages of the Conference and their insights on policy options emerged from the Conference.

Jana Popova, as an expert patient advocate and a RD patient herself, expressed her perspective and her feelings on what is like to be a person with a rare condition.

"Once you become a person with a rare condition, you have to face with this hurricane of emotions and feelings that you have never experienced before. Firstly, you start to feel that your future is going to be very different from the one you have imagined for yourself, You slowly start to realize that this rare condition is going to be part of your life for a very long time. You start to ask the question why is this happening to me as a person, and why is this happening to us as a community of people. You start to feel some feelings like fear or uncertainty, vulnerability and some loss of dignity. You start to feel some boundaries; some of them are because your chronic condition has influence on your body and some of them are because of the society. You have to face different forms of discrimination and stigma very often because you realize that your condition is not going to get consequences only on your body but also on your whole life in general. The good new is that there are some people which can help patients to overcome this process and to improve the situation so that they can live their lives in the best possible way".

Jana went on highlighting as ECRD has stressed the huge amount of innovation and technologies that promise positive impact on the diagnosis and the treatment of RD patients. Numerous steps forward have been made in patient engagement and involvement in R&D and in the evaluation of healthcare in a more patient-centered approach. Patients could bring valuable contribution to all public sectors and they deserve to be treated like every other kind of expert and stakeholder without any form of discrimination.

There are crucial points for the implementation of the best scenarios of the RARE 2030 project.

The COVID-19 pandemic has shown us that government should invest more money and resources in digital health because this could be an important source of information and care bringing good contributions to the standards of care for people living with rare conditions. Therefore, digital health tools should be more included in the daily lives of PLWRD.

Regard to solidarity and equity, there are great examples of solidarity to improve the life of PLWRD but we don't have a lot of time to address all those issues that still remain.

Patients with rare diseases should have equal access to health care like everyone else without any form of discrimination. They should be empowered and supported by a comprehensive and innovative legislation on patients' rights and should be fully involved, with their caregivers, in the implementation and development of clinical research, especially for their own condition. Patients' organizations should be authorized and included in the decision making process, not only on national but also at European level to be able " *to provoke the positive change they want and to represent patients' needs in the best possible way*".

If the community of patients with rare diseases work together prioritizing social responsibility, equity and the regulatory framework, we will end up in the Investment for Social Justice scenario where "*major investments have been made by governments and are equally shared across Europe*" to ensure that people living with rare conditions realize their full potential to live in the best way.

Healthcare professionals have to fully apply the Principle V of the Alma Ata Declaration on the people's right and duty "*to participate individually and collectively in the planning and in the implementation of their healthcare*". They have to understand that interaction with patients is necessary, that patients contribution in research and development and evaluation showed to reach quality of evidence and that they need to work on a prolific communication with patients, caregivers and families. Collaboration and cooperation are the key factors for success between EU and countries, between countries, between stakeholders.

"*United we are stronger. That is why, for me, the most important message from this conference is that only if we continue to work together we will be able to provoke the positive change we want in the world and to provide brighter future for the community of people living with rare diseases*".

She also stressed the power and potential of the young PLWRD.

"*The way for the future has to be led by young PLWRD working with other stakeholders as policy-makers that could aid in helping them to create the best opportunities to live the best life they can*".

Adam Vojtěch, Minister of Health of the Czech Republic, in a prerecorded video, underlined as COVID-19 has revealed even more the RD patients vulnerability as people at more risk of suffering Coronavirus complications and at more risk to see the access to care limited. But COVID-19 has also revealed the benefit of the mutual cooperation in the international community. Many progress have been made in RD MS national plans and EU alliances, progress of which ERNs are clear examples. The commitment of all MS and EU needs to be strengthened and renewed increasing the early diagnosis through new born screening policies and primary care actors education and training.

Yann Le Cam, CEO of EURORDIS, closed the ECRD conference highlighting the wide multi-stakeholder participation of the Conference as patients, researchers, industries, members of regulatory agencies, national and EU politicians. "*As a community, we are working at the forefront to respond to the immediate challenges and impacts of COVID-19 on people living with rare diseases but also on their carers, on the healthcare professionals, on the social professionals. But, at the same time, we are preparing for the next decade and we are bringing forward innovative concepts and innovative models created at the margin of society and of healthcare and social systems but becoming mainstream particularly after this pandemic with benefits across and for all*".

He underscored as the RARE 2030 foresight study is the backbone of the ECRD and that the Conference is to moment to start to move on towards policy recommendation. The contributions and outputs received during the Conference are " *clearly a new impetus to review, update, and scale up a new legislative and*

policy framework for rare diseases" entering the robust multi-stakeholder participative policy design process of the RARE 2030 project.

ECRD insights and the outputs that will be received in the next numerous RARE 2030 consultation events (i.e. Young Citizens Conference, Rare Barometer Survey for PLWRD, Back-casting Conference, the six national workshops) will be conveyed in the RARE 2030 Policy recommendations that will be presented at the EU Parliament in February 2021 to really propose a well-defined policy framework for PLWRD.

Yann summarised the audiences reactions to the 4 RARE 2030 Scenarios.

But RARE 2030 scenarios are simply and merely instruments "*to help us think about what do we want by 2030 for the patient journey and how we get there, what are the policy options, the actions, the choices to make now to get there ten years from now...the perspective is that there are choices, we can shape, we can design this future. As Terkel Andersen called it, it's success by design*".

The collective goal of RD community is that by 2030 every person living with a rare disease in Europe lives the full potential of his or her life. That calls for a holistic approach to respond to the person's needs all along the life of that person, focusing on improving health and social outcomes with the ambition to leave no one behind in a high-level collective responsibility that reflects the SDGs of the UN Agenda 2030.

RD must be a priority in EU but also in Europe at large, we need to take much more care of what happens outside the EU. The framework and the tool to reach this goal is the legislative body of human rights as the European Convention on Human Rights and the UN Convention on the rights of persons with disabilities (CRPD), but also a new holistic approach to development from health and well-being to social, to poverty, to gender, to inequalities, to science, innovation and partnership, a framework in which we can position also RD for the next decade.

Universal Health Coverage is part of this framework and calls for valuable, accessible, affordable services that do not put financial hardship on families. That calls for the solidarity model, which we have in Europe, a model that we want to hold and share making the most of it and not a barrier to access. Within the SDGs framework the public-private partnership model is essential. If we do not succeed to bring together public and private partners - intended as companies but also as civil society - to design solutions and to implement them, we will fail. An international vision is essential because local, regional, national, international level are fully interconnected and interdependent when it comes to rarity, to knowledge, to resources, to innovation and to policies.

Another turning point of this conference is that collective responsibility takes us in the direction of population needs-led policy actions. For the first 20 years we needed to grasp on all RDs across Europe collectively to generate the critical mass to empower our community and to influence. This unity will continue to be needed for a lot of upcoming solutions. But to reduce inequalities we need to do more for those who need more. And to adjust to the realities and the new knowledge with a tailored approach. What do we mean by a population need-led approach? Instead of contemplating the 25 million people affected and the 4-5% of the population of Europe affected we need to consider the newly understood details. We know that out of 6,000 RDs 72% are genetic diseases. And out of this population 4-6 million are affected by one of 200 rare cancers. We need to be more mindful about rare infections... viral and bacterial. And rare poisonings - food poisonings, environmental poisonings, consumer product poisonings, unwanted effects of medicines. All those are part of this strategy and population needs. We also know that 70% of RDs appear in childhood. That also calls for specific strategies. But the RD population is also ageing. Because fortunately for some RDs we are living longer and with better lives.

And out of these 6,000 RDs 150 of them affect 80% of the population of people living with a rare disease. That also calls for a specific policy for the rare, the very rare but also for the extremely rare if we really want to leave no one behind. And rare diseases for which today there does not exist enough knowledge to envisage a treatment. We need to recognize that this may improve with more science in the coming years or decades but for now we need palliative and supportive services, we need to address the impairment – we need this holistic approach to really leave no one behind.

These strategies per population, strategies per group of diseases, strategies of territories also need to grasp on strategies of technologies and systems and on processes and budget. Money is quite essential here and properly resourced to deliver with measurable outcomes to be accountable for.

To do that we really need to push from the top on the health care system from European level to member States but also to stimulate the bottom up dynamic and inject sufficient funding and political will to build up this experience.

Next on the patient journey we move to clinical excellence. Here we must push forward for improved quality of care where ERNs are the skeleton. But we need more than the bones. We need the flesh around the skeleton. The current vision and the policy options are good but the challenge of 2030 is to turn ERNs into a sustainable system, a policy which delivers improved health outcomes. And for that we need to balance between collaboration and inclusion of health care professionals with quality assessment.

Options here include accreditation of HCP and virtual clinics of the future, so these blurring lines between hospital community and home, between medical and social care to provide holistic care. The assessment of functions and impairments of PLWRD and case managers of PLWRD are PART OF in these options.

The digital transformation of healthcare needs to put data at the center, especially data quality. Without data quality, the data collection, sharing and interoperability are not able to speed-up the research innovation and their effective implementation. We need to invest in training in new competencies and professional skills and in new jobs about it.
Put the person at the center is what we need. We need to be driven by the population and person needs with the right incentives, rewards, funding for all actors that deliver quality and are accountable for their work. Putting the person at the center means going beyond the empowerment and the engagement of PLWRD towards a full partnership as citizen, person, as equal partners in research and in the delivery of care driven by patient reported outcomes and measures and continuing the real world evidence generation.

Regarding the Availability, Accessibility and Affordability of treatments, 20 years ago the first patient was treated for SCID (Severe Combined Immunodeficiency) with a curative
treatment. Today uptake of new technologies remains too slow and the decision making processes make the curative treatment potentially available need to be adapted. More knowledge gathering for common assessment through an HTA legislation and a greater critical mass and bargaining power of Member States into a European collaborative effort with a structured approach to evidence generation and structured negotiations are required.

Yann moved on stressing that we need to invest in ERN, we need to invest in public-private partnership, we need to progress on cross-border healthcare for access to innovative care and second opinion, we

need to invest in social-economic burden studies if we want to provide better informed data on the value of the new treatments for PLWRD.

To reach the scenario we want, we need legislation, policies and funding but first we need the full implementation of legislation and policies that already exist. We need to accelerate to deliver results. We need financial resources both top-down and bottom-up, we also need the flexibility, the agility and the openness of policies to adapt to the science change, societal change and partnership.

In RARE 2030 Project we have 6 months to co-design this new legislation and policy, even if it means to revise existing policies or create new ones, "*we have 6 months to create the society we want, to leave no one behind*".

Annex I Insights from emerging futures

"I love technology and new tools/medical/artificial intelligence but be careful not to overestimate and do not forget that everything must be read and interpreted by a specialist, especially for rare diseases. Rules are needed"

"Countries will need to adopt recommendations and standards established by the ERNs. I have a dream that in 10 years time ERNs will be integrated into our national health systems. This will make the difference and give all RD patients equal access to the care they need"

'We have to find a way to involve all MSs in all disciplines but focusing only a few centers that are the nodes on national level developing national networks'

The ECRD 2020 Conference also offered the opportunity to present and test Rare 2030 storylines and to initiate the fourth and last step of the foresight process "the back-casting phase" in which stakeholders are invited to devise policy options, strategies and targets. In line with this, contributions from each session discussion (Annex I) have been captured and organized according to the following four areas:

- Vision – statements on the future
- Challenges – today
- Opportunities and pathways
- Inspiring projects, best practices and niche innovation

Next report will review, analyse and cluster the inputs received in order to formulate policy recommendations.

Vision – statements on future

Theme 1	Diagnosis	• Ensure a diagnosis for all and shorten the diagnostic odyssey. Paying more attention and fight the diagnosis odyssey of the undiagnosed and supporting more the families of newly diagnosed/undiagnosed RD patients. • Promote equity of access in genetic testing.
	NBS	• Harmonize Newborn Screening (NBS) with equal implementation across Europe. • Expansion of NBS panel. • Ensure timely and adequate communication of results in order to access to treatment.
Theme 2	*UHC*	• Turn UHC political declaration in concrete actions in MS and make equity a daily reality. • Reach the historical commitment of all governments to make key investments in services to deliver UHC. • Reorient services in order to include the most vulnerable groups moving from "diffused focus to spotlight focus".
	Holistic care	• Adopt a patient-centered and patient citizen-driven policy. • Support a paradigm shift in current healthcare systems to promote the development of diseases specific pathways/services. • Integrate primary care provisions with network for specialised care.

	Equity and non-discrimination	• Adopt an holistic vision of RDs in a human rights perspective. • Develop greater ability to work on the ground and connect political levels. • Ensure real implementation of Principle 17 of the European Pillar of Social Rights about the inclusion of people with disabilities. • Reach equal access and accessibility and reasonable accommodation (assistive technologies assistance).
	Progress by design	• Preserve human dignity and build cooperation between countries and institutions. • Strength links between the medical needs with societal needs and combine health and social support. • Create flexible systems able to recognise and respond to the different individual needs.
Theme 3	*Ageing RD population*	• Develop a comprehensive understanding of patients' needs as the first step to respect and meet them. • Promote more European solidarity and pan-European solutions –entailing the establishment of greater EU competencies in health as a way to ensure equal access to care across all EU countries. • Ensure easy access to adequate integrated care – provided by Multidisciplinary Teams (MDTs). • Guarantee guidance for life-pathways for the ageing RD population – not only from pediatric to adulthood but also from adulthood to geriatric care.
	ERN & CoE Accreditation	• Reduce health inequalities by promoting earlier diagnosis, access to clinical trials, new guidelines on treatments and care and setting lifelong learning workforce education. • Integrate healthcare service provision within countries and between MS in EU. • Generate knowledge through improvement of networking within the RD community and with other existing networks at EU and international levels. • Unlock the true potential of networking and sharing of knowledge by linking registries. • Improve the transparency and accountability of ERNs and Centers of Expertise at a national level. • Strike a balance between the need of rigid quality assurance and the quest of inclusivity in ERNs. High standards are key for patients to access the best care at the right time. Quality assurance is difficult, but indispensable.
	Clinic of the Future & Digital Care Pathways	• Use of virtual consultation to remotely connect with other multi-disciplinary experts in other hospitals and countries. • Make the best use of our knowledge from datasets and EMR to scale up the use of AI in clinical care and guarantee access to AI benefits to patients and healthcare professionals. • Strike a balance between data sharing for clinical care and data protection – especially for the most vulnerable people. • Recognize the role that care-givers and patients could play in co-design pathways and apps as they are the ones able to capture the outcomes of treatment and are the co-owners of data.

	Health Workforce	• Increase the International collaboration in training and care. • Set investment to train and motivate workforce in RD in order to retain and enrol professional in the RD field. • Encourage training also for professional outside the ERNs structures – with the aim of reaching GPs. • Build a workforce that has more time for human connection; "leave machine work to machines".
	Therapy development	• Patients involvement is a systematic way in setting research priorities and incentives ensuring research added value. Research incentives target especially neglected and complex diseases. Multi-stakeholder networks work together in every stage without lowering scientific standard but developing more efficient and patient-friendly processes. • Registries – coordinated by ERNs – are filled by patients and clinicians and are fed by real word data that integrate data coming from clinical trials. • Patients are in charge of their own data: collect relevant data (PROMs), store their own clinical data from different data silos (EHR, registries and companies databases) and decide themselves with whom to share. • Patient preferences are taken into account before the trial starts (from bedside to bench), and outcome measures relevant to patients (including HRQoL) become the core of drug development. • Research in neglected and complex diseases treatments. • Equal access to clinical trial opportunities and to treatment (i.e. studying the use of repurposing drugs).
	Innovation in clinical research	• Data and techniques are reproducible and reliable: ensured by standardised analytics, data interoperability and accessibility and a strong research community with openness and transparency with respect to science and results. • Adaptive research methods that could overcome the limits of RCT in RD fields and close the gap between efficacy and effectiveness in real life. • Researchers work with Randomised Controlled Trials (RCT) and Real World data (RWD) and learn how data coming from one side can inform the other. • RWD support a patient centric approach. • Acceptance on the use of RWD is not just for post marketing safety purposes, but also for the pre-marketing. Regulators now consider RWE to improve RCT effectiveness.
Theme 4	*Advanced therapy medicinal products*	• Recognition of the complementary competencies between academia, industry, charity foundations and patient organisation and creation of new partnership and business model e.g. Telethon-ITALIA, San Raffaele Hospital and GSK. • Creation of methods/process to ensure a cooperation oriented to results between different partners. • Sustaining smooth transition from one partner to the other (e.g. GSK to Orchard that is now the MAH for Strimvelis) ensuring the maintenance of the production. • Establishment of knowledge transfer processes from sponsor of a CT to patient participants with constant follow-up and support and assistance in a patient centred approach. • Speed-up the MAA of ATMPs and the access to patients.

	Life into therapeutic development	• Patient voice is key and act as eye-opening when it comes to clinical relevance. Patient communities have better access and knowledge to available sources of information and have to trained to have the skills and capabilities to be partners in research process obtaining funding and support (i.e. nitisinone case study). • Consortium academia-PO-pharma provide complementary competencies. • Venture philanthropy and PO are able to build a global network to push patient-led development. • Develop Patient Reported Outcome measures that are reliable and valid and meaningful in research (including HRQoL). • Registries capture information directly from the patient in the real –life setting and act as platform for patients to be better aware of their condition and to provide feedback to Healthcare Professionals and researchers. Patients have the opportunities to access their personal data and patient involvement improves data quality.
Theme 5	*RD in numbers*	• Agree on a common clinical definition of RD and use a common language to produce evidence and tools. • Develop new structure and knowledge to classify, count and cluster the diseases. There are 6.172 rare diseases according to the epidemiological data, 70% are exclusively paediatric, 12% exclusively adult, 18% both adult and paediatric. The majority have genetic origins. There are more than 6.000 diseases -and the number on rise as new diseases are discovered. • Gather economic evidence on the costs of well-being (e.g. hereditary retinal diseases study) to support advocacy – among others for improving the process for reimbursement of therapies. • Set a strong set of incentives – linked with the promotion of an EU innovation ecosystem – to support the creation of treatments for the 95% RD that still don't have one.
	New disruptive technologies	• With regard to the assessment - there would be more collaboration between HTA bodies and regulatory agencies, a consistent approach for RD registries and requirement for the use of Real World Evidence. • With regard to the affordability: there would be more consideration of long term benefits of these products, the development of outcomes based agreements (e.g Italian experience) and an increased education and social acceptance of these treatments. • With regard availability: improved cross-border collaboration and more guidance and collaboration from EC institutions and actors to guarantee a smooth implementation process. • In term of accessibility, removal of economic, social and logistic practical factors that are still impeding patients to access their treatments.
	From Research to Access	• Greater implementation of multi-stakeholder and community approaches e.g Initiative Real World Evidence to Decision project. • More patients and doctors collaboration to facilitate the assessment of new drugs e.g. project Hercules. • Increased use of PPP for research and therapies development.

Theme 6	*Data Management Model for AI*	• Develop a new data management models to capture, process and analyze medical data generated by various sources. This question is particularly significant for RD patients as they often have to visit multiple specialists in different healthcare centres. • Rise the number of data collected in RD and integrate them with Real World Data. • Reduce drastically time for data collection (from months to seconds) • Step away from hospitals being the main "data holder" and involve more actors to collect, store and analyse data.
	Ethical and Legal Aspects of Data	• Create a more citizens' focused healthcare system in order to be able to take into account the socio-determinants of health. • Build an ICT system that is not just designed for governments or hospitals but it takes into account patients. Everyone should have all their data centrally and have the possibility to choose to share and edit them.
	Data policies	• Make it possible for technologies to be used by those patients who need them the most by increasing digital education and by making sure these devices are reimbursed.
	Technology for inclusion and empowerment	• Increase data sharing while ensuring patients control over data and access to the results of any research for which their data used.

Challenges – Today

Theme 1	*Diagnosis*	• RD classification based on symptomatology is now ineffective. • Many screening tools are being developed but few are really helpful and/or mature enough. • In most cases the phenotype is a poor predictor of the genotype. • After being assessed through specialists and services, patients and families still seek help, understanding, management, connection with others. Families often 'overloaded' with information and the time and opportunity to understand and make sense of what they are told, and come up with questions. • Pilot platforms to ease the diagnosis are emerging, however governance and funding are needed in order to start with implementation and maintenance.
	New-born Screening	• Lack of interest of politicians, due to the frequent change of governments and diversity on regulations within EU countries. • Unclear governance of NBS programs (Key stakeholders that are involved in NBS decision making). • NBS using Whole genome sequencing (WGS) fit within the system (Is it in parallel with conventional methods?). • Cost effectiveness of WGS : Right now 50% of patients with a RD remain unsolved even after Whole Exome Sequencing analysis.

Theme 2	*UHC*	• The low enforceability of UN Declaration. • The high power of MS and the difficulties in reaching common decisions. • Low interoperability of technologies among MS hamper the proper use of new technologies.
	Holistic care	• Invisibility of many rare diseases, the rarity of expertise and frequent lack of incentives. • The fragmentation of budgets and portfolio and the persistent "silos working". • Short-sighted and weak national strategies.
	Equity and non-discrimination	• Important gaps in employment are perceived by PLWRD as reported by the Rare Barometer survey: 70% of them stop/reduce work after diagnosis; 76% feel limited professional choices, 69% decrease income.
	Progress by design	• Lack a coordination and centralized funding (as for ERNs). • Limited patient representation especially at the local level. • Limited scientific evidence – and recognition - of the effectiveness of treatments that increase life quality for PLWRD e.g rehabilitation. • Difficulties on measuring independence, autonomy, happiness, personal fulfilment, social justice. How can we measure quality in life?.
Theme 3	*Ageing RD population*	• The trend of RD ageing population risks to bring greater complications and co-morbidities. The opportunity to have children requires the development of new knowledge and expertise for handling complex pregnancies. There is the quest for greater harmonization of access to care in EU, i.e in the approaches to NBS and diagnostics. • Research and Development are focused more in some conditions than others, there is the need of investing for greater understanding of diseases for all conditions. • MS should adopt a comprehensive approach to RD, and ensuring also (but not only) the integration of ERNs into national health systems. • There are still steps to be taken in order to guarantee coordination, standards and goals sharing in healthcare. • The process of making innovation available to patients in form of services is still too scattered and slow. • Greater involvement of patients in the data pooling has to be ensured in order to make them feel as the driver as well as the owner of how the data are collected and used. This would be possible only is the challenges related to data quality and security are overcome. • The use of telemedicine - learnt from the COVID-19 crisis – should be balanced making available also consultations face to face.
	ERN & CoE Accreditation	• The success of ERNs has had a downside: in some case non-expert centers try to be recognized as experts' centres with a risk of inflation of full members and a blurring expertise. • It is still not found the balance between need of quality assurance of CoE and that of guaranteed inclusivity and equal access to care (even geographically). • ERNs are still not integrated into national healthcare systems. • Cross border care is not fully implemented.

	Clinic of the Future & Digital Care Pathways	• Datasets are not still standardized and ready for statistical programmes and AI analysis (i.e AI use in medical imaging). • Data protection is robust but cannot be guaranteed 100%. • There is still room to learn how to work with technologies (using AI systems as teammates) and fully understand their potential and limitations. Virtual assistance can't always replace physical contact in care. • Attention has to be taken not to overburden patients with digital health and let them measure everything by themselves.
	Health Workfor ce	• New competencies in order to deliver on data collection, sharing and quality and new holistic functions
Theme 4	*Therapy development*	• Patient involvement not always in the first phases of the process and PROs are not fully valorized. • Registries lack standardization of data and patient access to data • Variation in access to highly innovative treatments even at the CT stage due to need for highly specialized trial settings. • Small study populations complicate the accrual of robust evidence on which to base treatment decisions and HTA evaluations (and reimbursement). • MA is based on CT; for regulators, a small RCT even if unpowered is preferred. • Reimbursement at national level hamper the effective access to treatment.
	Innovation in clinical research	• Data currently have low reproducibility and registries show limited interoperability and data privacy hurdles. • CT study designs are not enough for RD. • Persistent efficacy-effectiveness gap in the market authorisation as regulators still think Clinical Trials is gold-standard for pre-marketing. Disparities between real world and guidelines based on classical CT.
	Advanced therapy medicinal products	• ATMPs are complex therapies. Challenges at different levels: 1) manufacturing constraints (continuity of material supply, upscale of manufacturing from start to MAA, GMP requirements for production, etc., 2) availability of animal models for toxicity testing 3) clinical aspects in research : possibility of blinding, availability of comparators, feasibility of dose finding, inter- individual variability. • ATMP starts at an academic level that is unable to go on until the commercial manufacturing process. • Regulatory Incentives as the Certification of ATMPs are underused. • Reducing animal testing for ATMPs . • Long follow up for safety and efficacy.

	Life into therapeutic development	- Patients have to be more at the centre when developing registries and need access to their personal data (Limited involvement of patients from ERNs when developing registries and in access to their data). - Development of PRO is to include patient with the relevant condition – include patients speaking different languages and countries (to ensure translatability) – Challenge in RDs. - Core measures/questionnaires may not be relevant for RDs – specific modules should be developed. - No set standards on how quality of life measures can be used/analysed in clinical trials – problems for comparing them. - Lack of standardisation in QoL – questions too broad too vague. It means it will be very difficult to interpret the QoL results in a given trial.
Theme 5	*RD in numbers*	- Most (89,1%) are of RD are very rare diseases (prevalence less than 1 per 100 000). Almost all of the people with RD (more than 98%) have one of the 390 most prevalent diseases (more common than 1 per 100.000). Thus, it would be important to prepare the health systems based on the most prevalent rare diseases making sure of not leaving behind the very rare diseases (2%). - From the EURORDIS Barometer voice survey - gathering more than 7500 responses from 91 countries– emerged that more than 31% of RD patients have never experimented treatments because it is not available, accessible or affordable. Out of 69% who have already experienced a treatment only 5% had curative one, 3% a treatment to prevent the disease, 31% a treatment to slow down the disease, and 62% a symptomatic treatment. In addition, it is clearly shown a great variation in access to treatments depending on the diseases areas. Many patients adopted treatments which are not approved such as off label and for compassionate use. - Taking as example the study of 10 hereditary retinal diseases – the cost of wellbeing in PLWRD are currently beared mainly by patients and their families. E.g costs beared: individual 51%, family 16%, government 12% (Ireland), employer 4%. - OMP Regulation has successfully incentivized companies to invest in the development of OMPs – with a growth rate of 12% of the marketing authorisation for OMPs granted by EMA. However, significant financial challenges in developing OMPs were registered between 2008-2018. In addition, EU continues to lose competitiveness in Biotech compare to US and the COVID 19 crisis risk to overshadow RD research and innovation strategies.

	New disruptive technologies	• ATMPs assessment: there is a gap between regulators and HTA Bodies in evidence criteria. The registry-type of data required for post approval regulatory requirements differs from that required by payers for managed entry agreements or other innovative payment model. • ATMPs affordability: there are barriers to annuity payments and innovative funding option across MB. • ATMPs availability: Variability in the use of cross-border healthcare legal provisions across MS and uncertainty of the pathway. In addition, high variation on the interpretation of hospital exemption legislation with impact on patient access to available treatments. • ATMPs Accessibility – clinical expertise, ICU and other resource requirements and the short shelf life of ATMPs require patients to be treated in specialist centres that require manufacturer and, increasingly, country level .
	From Research to Access:	• Lack of trust between stakeholders. • Too little use of public-private partnership (PPP). • Difficulties for data sharing due to stringent regulations that are, in some cases, impeding data sharing. • Limited data accessibility – collected still in a fragmented way.
Theme 6	*Data Management Model for AI*	• Reluctance or fears of patients/ people to share their data. • No existence of incentives for patients to share their data. • Unequal knowledge access to AI technologies and education between regions and actors (NGO vs industry actors).
	Ethical and Legal Aspects of Data	• Risk that data provided are no anonymized and that could lead to easy identification of individuals with possible discrimination when it comes to insurances, housing and employment.
	Data policies	• Following up the analysis carried out by ORCHA is possible to identify the following barriers in the use of health apps to manage the diseases. • Awareness as patients and healthcare professionals don't know about opportunities for technology support. • Access as there are barriers to access to the apps. • Trust as there are many doubts from patients and healthcare professionals on using them and sometime it is a justified concern as the app quality is low. • Governance around safety matters. • Reluctance to change of healthcare systems which are still hospital focused while 40% of our health are related to "social determinants of health". • Difference of rules on digital health apps among EU countries. • Discrepancy of rules about patients' physical lives and digital ones which create confusion and fears.
	Technology for inclusion and empowerment	• Lack of opportunities to access to "digital education" from those patients who have impairments and disabilities and who could benefit the most from technologies advancement. • Risk of marginalisation – as seen during the COVID 19 crisis – of those that haven't digital skills or digital devices.

Opportunities/pathway

Theme 1	*Diagnosis*	• Implement new genetic sequencing technology in clinical practice • Similarly bring forward and harmonise genetic screening best practices and guidelines pre and during conception across Europe
	New-born Screening	• review current policy and practice in the field of NBS, in order to develop principles for harmonious uptake/adoption of the NBS programs across the Member States with a view to delivering maximum benefit and improving outcomes for babies born with rare diseases. • Propose update of Wilson-Junger criteria for New Born Screening
Theme 2	*UHC*	• Transfer more legal power to EU in the field of health and create a EU/MS co-found for access to medicine. • Pursuing innovation, not only in innovative products but in process, pathways, data collection, genomics. Key is to build a critical mass in data collection as well as in human resources. • Create a EU Health Data Space accompanied by a big data strategy and strategic planning for infrastructures. • Ensure the proper implementation of EU legislative instruments and ENRs to address inequalities. In particular, ERNs should support to operationalise UHC. • Build action plans based on targets and identify the accountable actors and empower PLWRD to promote inclusion, awareness and collaboration and connection. • Build transparent and collaborative platforms with all stakeholders', industry, academia and government.
	Holistic care	• Support the transformation of the healthcare systems by: • analyzing the available resources, resize essential services for diagnosis, and ensure follow-up and treatment; • adopting a cross-action approach and make use of digital tools for the coordination of care; • increasing patients involvement, create multidisciplinary care teams and multi-stakeholder collaboration and implement the case manager role; • wherever possible, adding a 'rare disease perspective' into existing services (and linking rather than creating extra services) • pooling the different resources through inter-ministerial working groups.
	Equity and non-discrimination	• Promote the enforcement of EU legislation compliant with the UNCRPD and Create sanctions and penalties in case of poor MS implementation of EU legislation, i.e using sanctions for HRs infringement as economic sanction or political sanctions i.e limit voting power in EP. • Promote a focus shift from disease evaluation towards the assessment of actual lived experience. • Encourage the systematic inclusion of disability into policies and guarantee the the implementation of the article 27 of UNCRPD: right to work on equal basis with others. • Involve young patients in EPF decisions, voting rights in Board and • Promote evidence based and proactive advocacy in synergies with other patient organizations. • Promote awareness of inclusion, it could not be an easy concept for people who

		do not live with disability. • Use European Commission Structural Reform Support Service (SRSS) to support and finance MS disability assessment and national policies of inclusive societies and labour markets. • Promote cross-budget analysis (healthcare-economic-social impact) to not be viewed as a cost.
Theme 3	*Ageing RD population*	• Collect and analyze data to get a better understanding of people needs. • Support the feel of urgency of pan-european and global collaboration to respond to public health needs provoked by COVID-19 crisis. • Establish best practices in care and research – through ERNs work - to harmonize the care in EU. • Define pathways for each condition - balancing access to centralized services (CoE) with the provision of care at local level. • Demonstrate the value of ERNs by reinforcing the monitoring and evaluation system and by ensuring their integration into the national health systems. Reinforce EU and national support for ERNs. • Strengthen country level approach to RD - with a call to renew/update their national plans. • Set investments to ensure RD training to healthcare workforce .
	ERN & CoE Accreditation	• Update national RD Plans to ensure integration of ERNs into NHS with inclusion of referral pathways and patient awareness raising activities. • Implement clear and speedy pathways of care from local, regional, national and international levels and set adequate monitoring systems. • Adopt innovation in models and tools for advance virtual healthcare and create reimbursement policies for virtual healthcare. • Advocate for EC support to the financial sustainability of CoE and ERNs. • Centralize expertise and knowledge where it is more needed and invest in CoE to fulfil the EUCERD recommendations for quality (centralized accreditation). • Reinforce patient-leadership to level out clinician ambition and to pursue high quality care " We are both stronger together, with mutual respect". • Raise patients' awareness on good quality health care in order to empower them not to be satisfied with low quality care.
	Clinic of the Future & Digital Care Pathways	• Increase research in innovative digital care pathways and in the effectiveness of virtual healthcare, as digital health can reduce costs. • Take advantage of acceleration produced by COVID 19 crisis on the use of digital health and the development of funding instruments for digital health and the technologies. • Work for building up CoF (Clinic of the future) imagined as networks of based care services, clinic-led use of genomic technologies, with a multidisciplinary team and provided with infrastructure for data crowdsourcing and an ethic framework to protect the vulnerable patients. • AI and digital health are used as cost-effective instruments for supporting physicians' clinical recommendations enabling the increased accuracy of predictions and the definition of risk profiles – opening the door toward personalised care. • Design culturally-sensitive personalized interventions and encourage patients to take an active role in their own health and health care. • Create effective and dynamic Multi-disciplinary team working with patients to

		reach shared decisions.
		• Invest in communication and soft skills. There are some very personal topics i.e. pregnancy or death that need to be dealt with on a personal level and for which human competences could be never be replaced by AI applications (i.e in breaking bad news).
	Health Workforce	• Plan for the future of work force - not only about numbers but also competences. Promoting bundles of policy interventions in supply, training and retention is needed to ensure long term sustainability of the health workforce. • Create a RD workforce engaged in embracing a true patient centred care and ready to create a dialogue with patients. • Prioritize flexibility in the ways the workforce is prepared, regulated and mobilized. Solutions linked to teams, skills mix, service redesign and relocation have to be taken into account. • Equip future healthcare workers to manage complex care and digital technologies with a focus on soft skills. • Create an attractive environment to retain and motivate workforce. • Develop a stronger EU capacity to plan and forecast healthcare workforce needs and solutions. • Develop continuous education programmes for HC professionals involved in the chain of care (within and outside) the ERNs aiming to reach out GPs and local healthcare at national level. Consider short placements exchange of experts to train others peers.
Theme 4	*Therapy development*	• Patients preferences taken into account before the trial starts (from bedside to bench) and PROs become the core of drug development • Standardization and interoperability of data of registries - Common data elements (i.e EURRECA). • Patients in charge of their own data. Collecting relevant data (PROMs), store their own clinical data from different data silos (EHR, registries and companies) decide themselves with whom to share. • Incentives to stimulate research and highly specialized settings and cross-border research. • MA more based also on adaptive trial designs RWD (e.g Interim analyses; Bayesian designs: single arm trial and external, historical controls). • Eu role in reimbursement.
	Innovation in clinical research	• Enhance the reuse of data is key. Making data FAIR is the first step to be able to reuse it. It would allow the reuse of placebo data and the use of natural history data. • Use adaptive study designs in research. • Include the information of Real World Data into CT design, pharmacovigilance, HTA and pricing and reimbursement. • Adopt the EHDEN framework to harmonise health records to the OMOP common data model (patient-centric). Create a federated data network. • Inform guidelines with large-scale observational research (RWE).

	Advanced therapy medicinal products	• Explore with openness any partnership to co-fund clinical researches • Develop new forms of business and partnership oriented to results as example the one between Telethon and San Raffaele Academic Hospital (SR-TIGET) and GSK that was crucial for the MA approval). • New Intellectual property right development and definition of Agreements with industrial partners e.g. Telethon IP policies protection that implies return of any IP and results co-developed in case partners do not pursue therapy development until access to patients. • Using EMA support early, before, during and after MAA. • Using EMA incentives as ATMP classification (free of charge procedure) ,Scientific Advice (reduced fee) EMA innovation task force, Certification of ATMPs, MAA for ATMPs (centralised procedure with all regulatory tools available). • Encourage developers to present alternatives to animal testing (i.e organoids). • Continue looking efficacy and safety long term after the product is approved, therefore faster access to patients.
	Life into therapeutic development	• Better incentives and funding for patient groups to become professional in research and development to push patient-led development (as in the drug repurposing arena where repurposing of off-patent drugs through social impact bond save costs for the development of new drugs). • Financing of European and international project such as IMI projects (PARADIGM, PREFER) – to avoid silo thinking promoting PO engagement. • Develop of valid and reliable PRO measure and use it in clinical trials. • Better define PRO objectives (to avoid the lack of standardisation mentioned above) – First critical step in assessing the patient perspective in CTs. • Patients are already involved in CTs but they should be involved in the design of QoL endpoints – what is the relevant issue we should measure in a CT. • QoL measures for children: ongoing work.
Theme 5	*RD in numbers*	• As regard Rare Diseases in Numbers: What do they mean? • It is essential to generate data globally, across sectors and coded in the same way (Orpha codes) both at clinical level (health and social sector) and at research level (through registries and data repository). • It is key to develop new knowledge on the basis of medical, social and patients collaboration for a better evaluation of the burden of diseases – this could be achieved also through the use of RWD. • It is key to develop tools to allow healthcare systems to gather evidence based data for research and identify economic indicators – also on the cost of well-being for RD patients. • Account for patient and societal value into OMP development and review how OMP development could contribute to promote the creation of health innovation ecosystem in Europe.
	New disruptive technologies	• ATMPs Assessment – EMA, in collaboration with HTAs, issue guidance on ATMP assessment with a focus on methodological uncertainty. • ATMPs affordability: education of stakeholders on the ATMP development cycle, costs and incentives. • ATMPs Availability: Development of formal guidance on cross-border. pathways at EU level to facilitate access to different ATMPs. In addition, it should be clarified at EU level the use of hospital exemption in the ATMP regulation is appropriate-

		• ATMPs Accessibility – EU certification of treatment centres to reduce administrative burden and ensure consistency across MS.
	From Research to Access:	• Stronger regulatory science, improvement on government processes (agency and countries collaboration) and on codified methods of collaboration/partnership between stakeholders (academic, industries and patients). • Development of outcomes based agreements (e.g Italian experience); • Roll out of awareness raising and educational campaigns on new treatments. • Improved synergies between OMP and paediatric legislation. • Setting of investments for creation of long term infrastructures.
Theme 6	*Data Management Model for AI*	• Collect data following FAIR principles as guarantee for standardisation. • Develop a new model for data sharing which includes incentives to patients/people. • Follow- up the examples set by concrete initiatives on the AI use in the area of ophthalmology and dermatology. • Improve collaboration among players. • Look at initiatives led by industries such as Novartis program "Data42".
	Ethical and Legal Aspects of Data	• Create greater coordination between GDPR norms and the deontology rules of medical professionals. • Experiment new business model such as FINDATA (top down example) or SALUS COOP (more bottom-up case). • Increase the role of patient organisations on advocating for data sharing and on awareness raising on what data are important to share, why and which are their rights they can demand for. • Work on building trust – which is the underneath success factor for many initiatives - and promote a culture of change.
	Data policies	• Develop a common understanding and a minimum set of requirements for digital health apps at EU level and leave the possibility to MS to establish additional rules and procedures. • Following up the analysis carried out by ORCHA is possible to identify the following enablers in the use of health apps to manage the diseases: a. Accreditation of products b. Promotion c. Integration d. Prescription
	Technology for inclusion and empowerment	• Education campaign for people with disabilities in order to guarantee them access to the available technological support. • Change reimbursement procedures.

Inspiring projects, best practices and niche innovation showcased throughout ECRD

(Medics for Rare Diseases) **M4RD**	Education/ Training	Project	M4RD provides education in the Rare Disease field for medical students and doctors.
Clinical information point for RDs for clinicians	Education/ Training	Practice	The Centre for RDs of Tubingen provides advice on management and treatment of RD to clinicians (overcoming the lack of sufficient time and/or knowledge of non RD expert healthcare staff)
Dx29	Diagnosis	Tool	The Dx29 is a diagnostic decision support platform developed by Foundation 29 in collaboration with patients, physicians and researchers. An AI algorithm based on phenotype and genotype analysis provides a ranking of possible RD diseases.
SemioTIC platform	Diagnosis	Tool	SemioTIC platform aims to accelerate the diagnosis for RD patients by developing the doubt culture among the health primary care actors (GPs and Private specialists). Based on clinical signs and symptoms SemioTIC alerts the GPs about a potential risk of RD, prequalifies the potential subtype of RD and gives information about the closest RD expert center.
"Solve RD solving the unsolved rare diseases"	Diagnosis	Research project	"Solve RD -solving the unsolved rare diseases" is a research project funded by the European Commission for five years (2018-2022). Main ambitions are to solve large numbers of RD, for which a molecular cause is not known yet, by applying sophisticated combined omics approaches. In addition, the project aims to improve diagnostics through the implementation of a "genetic knowledge web" which is based on shared knowledge about genes, genomic variants and phenotypes unlocking the collective intelligence of clinicians, researchers and bioinformaticians.
Solve –RD	Education	Practice	Under the Solve RD Project a study lasting 18 months was set in two genetic services (UK, CZ). Researchers carried out observations of clinical appointments and interviews with families and health professionals to identify priorities to improve the communication of genomic results using a Evidence Based Co-Design (EBCD) approach.
CPMS	Diagnosis	Practice	ERN Clinical Patient Management System Platform uses collective intelligence for diagnosis of rare disease patients. The European Reference Network on Intellectual Disability, TeleHealth and Congenital Anomalies (ERN ITHACA) reported the first year results of the CPMS use as an example of a telemedicine strategy that facilitates the access to diagnosis and the management of patients with rare developmental disorders.

OMIM (Online Mendelian Inheritance in Man)	Diagnosis	Tool	OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. OMIM focuses on the relationship between phenotype and genotype. OMIM contains information on all known mendelian disorders and over 15,000 genes.
Treatabolome	Treatment	Tool	The Treatabolome concept aims to build a genetics-based decision-support systems to increase treatment rates for treatable conditions. It acts through a systematic review of the evidence for treatment for each condition/gene variant to develop a computer-aided system to enable clinicians to gain easier access to information about the best treatment for the treatable variants. Pilot testing was performed with neuromuscular disease by SOLVE-RD and EURO-NMD.
WHO CGN4RD	Networking	Tool	**WHO CGN4RD** (WHO Collaborative Global Network For Rare Diseases) is a collaborative global network to strengthen healthcare systems competency for rare diseases. It connects hospitals, major academic health organizations around the world, the regional level and the global level.
EU RD Platform	Data	Tool	European Platform on Rare Disease Registration (EU RD Platform) developed by the Commission's Joint Research Centre (JRC) in collaboration with DG SANTE, copes with the fragmentation of rare disease patients data across Europe making single RD registries' data searchable and findable while the registries remain the owners of their data.
RARE clinic	Treatment	Practice	RARE clinic in Sweden (located near a university hospital) is an academic specialized center, built together with patients organizations, that brings together several services. The center offers to patients a) a common general platform for documentation and care of all diagnoses combined with diagnosis specific surveillance, treatment and care b) Digital solutions combined with physical visits d) cross-border and stakeholders collaboration
WAYS (Work and Youth Strategy)	Employment	Project	WAYS (European Patients' Forum Youth Group) explores the specific barriers and needs of young employees with chronic diseases in different countries across Europe to collectively reflect on actions needed to promote awareness in employing young patients with chronic diseases in the EU.
Health 29/Duchenne Data Platform	Data	Tool	Health 29 by Foundation29 is a patient data platform that digitizes, processes, centralizes and protects the user's health data helping patients to safely and securely choose how they share data and to whom. It also empowers clinicians to leverage that data to make accurate diagnoses for patients. Duchenne Data Platform is the fruit of the

			collaboration between Health 29 and Duchenne Parent Project.
IMI ROADMAP	Data	Project	The ROADMAP project aims to deliver a series of methods and tools that will allow the scalable and transferable integration of data on patient outcomes in the real world. The tools will be developed and tested through pilot projects and will lay the foundations for a Europe-wide platform on real world evidence in Alzheimer's disease. The project will also deliver tools for patient engagement and address the ethical, legal and social implications of adopting a real world evidence approach to Alzheimer's disease.
IMI PARADIGM	Patients engagement	Project	The PARADIGM project aims to provide a framework for structured, effective, meaningful and ethical patient engagement and demonstrate the 'return on engagement' for all stakeholders. The project will develop a comprehensive set of tools and practices to support the integration of patient perspectives into drug development and enhance trust among different stakeholders.
IMI-PREFER	Patients engagement	Project	PREFER looks at how and when it is best to perform and include patient preferences in decision making during the medical product life cycle. The project includes patient stakeholders at every level of the project. The end-result will be recommendations to support development of guidelines for industry, Regulatory Authorities and HTA bodies.
EURECCA (EUropean REgistry of Cancer CAre or EURopEan CanCer Audit)	Treatment	Project/Tool	EURECCA started in 2007 as an ECCO/ESSO initiative. EURECCA is an international multidisciplinary platform of clinicians and epidemiologists aiming to improve the quality of cancer care by data registration and feedback, forming plans for improvement and sharing knowledge of performance and science. EURECCA is registered as a foundation, based in Leiden.
EHDEN (European Health Data & Evidence Network)	Data	Project	EHDEN was launched to address the challenges in generating insights and evidence from real world clinical data. It will achieve this by harmonizing the health records to the OMOP common data model, by developing an EU infrastructure for federated analysis of real world data, and through the, collaboration on research methodologies and the education in an open science collaboration.

GSK-Telethon-OSR	Partnership	Practice	GlaxoSmithKline (GSK), Fondazione Telethon (Telethon) and Ospedale San Raffaele (OSR) collaborated to the development of Strimvelis, the first ex-vivo stem cell gene therapy to treat patients with a very rare disease ADA-SCID (Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency).
EORTC item library	Clinical research	Tool	The Item Library provides users with tools to create custom-made ad hoc item lists of quality of life instruments to be used in conjunction with the standard core questionnaires and modules. Users are able to browse through existing measures (including other custom-made item lists) and search for items that meet the needs of their research questions in order to design their own item list of research related questions.
SISAQOL	Clinical research	Project	The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium has been convened by the EORTC with the aim to develop recommendations for standardizing the analysis and interpretation of patient reported outcomes and quality of life data in cancer randomized trials.
HERCULES	HTA	Project	Project HERCULES aims to develop a disease level economic model and other tools to better demonstrate the real value of new treatments for Duchenne Muscolar Dystrophy for Health Technology Assessments and reimbursement decisions.
EPTRI (European paediatric transnational infrastructures)	Drug development	Project	ID-EPTRI project, coordinated by CVBF and funded within the H2020-INFRADEV-01-2017 programme, aims to create the framework for a new Research Infrastructure (RI) intended to enhance technology-driven paediatric research in drug discovery and early development phases to be translated into clinical research and paediatric use of medicines.
RARE IMPACT	Treatments access	Project	The project aims at optimizing patient access to effective gene and cells therapies in the EU. The project has provided already guidance to 10 countries with regard to different policy dimensions.
IMPACT HTA	HTA	Project	IMPACT HTA is a research project looking at new and improved methods across ten thematic areas aiming at: i) understanding variations in costs and health outcomes within and across countries, and ii) integrating clinical and economic data from different sources to improve methods in economic evaluation in the context of HTA and health system performance measurement.
EJP RD	Policy	Project	The European Joint Programme on Rare Diseases (EJP RD) brings over 130 institutions (including all 24 ERNs) from 35 countries to create a

			comprehensive, sustainable ecosystem allowing a virtuous circle between research, care and medical innovation
Data42	Data	Tool	Novartis program leveraging the power of data science to reimagine research and development.
FINDATA	Data	Practice	FINDATA is a Health and Social Data Permit Authority, a one-stop shop for the secondary use of health and social data.Findata operates under the performance guidance of the Finnish Ministry of Social Affairs and Health and the Ministry appoints both a separate director for the organisation and a steering group. Main objectives are: improve data security and the data protection of individuals; speed up and streamline the utilisation of social welfare and health care data resources. Decrease the duplication of work in permit processing. Develop data descriptions for the social welfare and health care sector together with the controllers.
SALUS COOP	Data	Practice	Salus Coop is a cooperative that aims to legitimize citizens' rights to control their own health records while facilitating data sharing to accelerate research innovation in healthcare.
ORCHA	Digital Health	Tool	ORCHA is a health app evaluation and advisor organisation. The system helps governments, health and social care organisations to choose and deliver health apps that will safely make the biggest impact in terms of improving outcomes. The tool help health professionals to prescribe and monitor the usage of health apps.
EXOSKELETON	Wearable technology	Tool	Proving Walking assistance for adults and children in a learning process driven by AI.
SEIZURES TRACKING TECHNOLOGY	Wearable technology	Tool	Devices (i.e. bracelets, watches) Support patients with epilepsy detecting and alerting them and people around them that the patient is having a seizure. Data can be also collected to give physicians an accurate picture of the situation, Also no wearable devices exist for the same scope.
EYES TRACKING TECHNOLOGY	Technology	Tool	Allows you to use technologies with your eyes. It enables people with disabilities to express themselves