Rare 2030

D5.1 Scenarios space and stories: a preliminary version

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Report Information

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Executive summary

Rare2030 foresight approach is designed to envisage alternative future scenarios and set out roadmaps for their implementation through changes in policies and strategies. This report presents the findings of the third step of this process: the so called "Building Scenarios" phase – which is consequential and builds upon the in-depth analysis of the state of art of RD policies (D.4.1) and the horizon scanning phase investigating the trends related to Rare Diseases cure, treatment and care (D4.2).

While the RARE2030 Storylines will be elaborated in the Deliverable "RARE2030 Scenarios" (May 2020), this document describes the activities carried out, the stakeholders involved and the inputs received to collectively design RARE2030 Scenarios space. In participatory foresight, the process of facilitating the understanding among experts of different disciplines and backgrounds is as much as important as the final results. Discussing the desired futures and debating the perceived threats is a way to rise the eyes above over every day work and look together the horizon in order to imagine new possible coalitions, ideas and solutions. This task requires patience, imagination and time – and it can be perceived as hard especially if it involves stakeholders engaged in emergency situations and campaigns. In the light of this, we have made our best to represent all different contributions gathered so far and would like to heartily thank the hundreds of participants for sharing with us their expertise, experiences and insights.

The first section describes the results of survey "What trends will change the future for people living with rare diseases in the next decade?" which aimed at ranking by importance and uncertainty the 11 trends identified as relevant for the future of Rare Diseases. The consultation offered the respondents the opportunity of commenting the trends description and proposing wild cards. Wild cards are defined as disruptive events with low probability to happen but with expected high impact. Out of the 50 wild

cards proposed, “Epidemic illness” and “economic crisis” are the ones that we are now, unfortunately, are due to be taken into consideration in the drafting of the RARE2030 Storylines.

The findings of the conference “Validation of Trends to Build Future Scenarios in Rare Disease Policy”, held in Brussels on November 7th, 2019, are presented in second part. In the morning session, opened by Mrs Ries (European Parliament), the Research Advisory Board experts and the project partners reviewed trends and offered insights on emerging futures for Rare Disease governance. In the afternoon session, participants worked in ten small groups, and carried out three exercises designed to move from the trends ranking toward the building of the RARE2030 scenario space.

The third and fourth sections, building on the insights accrued throughout the partners’ interviews and an expert workshop, sketches radically different visions of how Rare Diseases cure, care and treatment could be in Europe at 2040. It is important to note that in presenting the entire set of remarks and comments offered by partners and stakeholders we might incur in some inconsistencies. In the next report (D5.2), we will systematically review all the inputs received during the different consultations in order to confer coherence and plausibility to the storylines.

The breadth of scope of the Rare2030 project is one of its major strengths and the source of significant added value; however, herein lies one of the greatest challenges. To enable a sweeping review of the status quo in European rare disease activities and policies, and to work on this to identify trends and build consensus around scenarios space, it was necessary to consult as wide a body of stakeholders as possible. Pivotal in this process has been the establishment of a Panel of Experts (PoE), to gather a broad range of stakeholders with expertise in numerous topics of relevance to the diagnosis, treatment, management and care of rare diseases. All along the project development, the Panel of Experts has played a key role supporting the project team by offering a variety of forward views and applying the insights to depict possible RD futures. The project team has dedicated much attention to ensure a balanced and comprehensive representation of the wide range of stakeholders involved in RD governance. Indeed, the Panel of Experts includes more than 183 members from over 33 countries in Europe and beyond and it is formed by stakeholders with different backgrounds representing – among others - patient advocate (56), national and regional Competent Authority (24); ERN Coordinators/HCP representatives (23); pharmaceutical Industry and other health-related industries (17); social care and social innovation experts (9). All the members of the Panel of experts were invited to take part to the forward looking activities described in this report and approximately the 70% took part to the RARE2030 survey and conference.

Due to the intrinsic nature of foresight activities, the evaluation of the policy impacts of RARE2030 scenarios will be possible only with time. However, the project has achieved, in its development, the process objective of creating bridges between the technical fields and connecting stakeholders to discuss policy changes, challenges and possible futures.

1 The RARE2030 Survey: "What trends will change the future for people living with rare diseases in the next decade?"

1.1 The survey approach

The RARE2030 survey "What trends will change the future for people living with rare diseases in the next decade?" was launched on 29th October 2019 and remained on-line until the 7th of November with the aim of eliciting stakeholders' contributions on the identified trends and their implications for Rare Diseases.

Commented [lgs1]: farei riferimento alla deliverable precedente "on the 12 trends identified in deliverable…."o incollerei la tabella dei trend

Scenarios are built around trends that are considered highly important for the sector at study but also unpredictable, as changes that policy-makers and stakeholders consider uncertain (how will they evolve? which effects will they have in the future?) are more suitable for the identification of anticipatory strategies and actions able to influence them. Accordingly, the aim of the survey was to identify those trends that are deemed more:

- Important: as any change in/deviation from the trend will have a visible effect on the outcome.
- Uncertain: as difficult to predict, and in principle amenable to changes according to strategic choices, investments, R&D activities.

Specifically, the survey asked experts their educated guesses to the following questions, for each trend:

- **Looking ahead to 2030/2040, how important do you think this trend will be for the rare disease field?–** evaluated according the qualitative scoring system: (1) critically important, (2) very important, (3) important, (4)of medium importance, (5) of low importance;
- **How predictable do you consider the evolution of this trend to be at 2030/2040?** – evaluated according to the following scoring system: (1) unpredictable, (2) partially predictable, (3) predictable, (4) mostly predictable, (5) fully predictable

In the analysis of survey results, we took into consideration the responses weighted average[1]. In relation to the first question, **stakeholders evaluated the trends proposed between 'critically important' and 'very important'** – the weighted average of all trends varying between 1,51 for the trend ranked as most important and 2,51 for the trend evaluated as relatively less important. The responses were very consistent with a standard deviation ranging from 0.84 to 1,04.

With regard the second question, **respondents considered the trends proposed between "partially predictable" and "predictable"** - the weighted averaged of all trends varying from 2,61 for the trend ranked as more unpredictable and 3,51 for the trend evaluated as relatively more predictable. The

[1] Survey instrument Survey Monkey calculates the weighted average as follows – where W stands for the weight of the answer choices and X response count for the answer choice $\frac{X_1W_1 + X_2W_2 + X_3W_3 \ldots X_nW_n}{\text{Total response count}}$

answers were more scattered with a standard deviation rate varying from 0,99 to 1,12. The survey findings are analyzed in section 2.3.

In addition, the survey included two open questions to elicit:

- comments and suggestions for the improvement to the trends description – briefly summarized in section 2.4.
- the identification of wild cards: those are surprise events and situations characterized by low probability and high impact. These situations tend to alter the fundamentals, and create new trajectories which can then produce a new basis for additional challenges and opportunities that most stakeholders may not have previously considered or be prepared for. The wild cards proposed by stakeholders are presented in section 2.5.

1.2 Who answered the survey?

One hundred and thirty-four experts with different backgrounds responded to the RARE2030 survey, offering inputs and ideas for the ranking the trends. The survey completion rate was very high – approximately 89%.

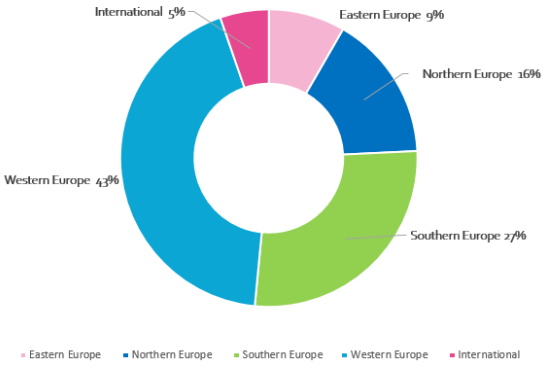


Figure 1 Survey respondents by EU Regions

In terms of the geographic origin of the participants, experts from 33 European countries participated in the workshop, including 4 non-EU countries (North Macedonia, the Republic of Serbia, Norway, Switzerland, United Kingdom), and representatives from United States, Canada and Singapore.

Adopting the UN geo-scheme for European subregions[2], the majority of participants (43%) were from Western Europe (Austria, Belgium, France, Germany, Luxembourg, Netherlands, Switzerland) followed by 27% from Southern Europe (Bosnia, Croatia, Cyprus, Greece, Italy, Malta, North Macedonia, Portugal, Serbia, Slovenia, Spain), 16% from Northern Europe (Denmark, Ireland, Latvia, Norway, Finland , Sweden, United Kingdom) and only 9% from central Eastern Europe (Bulgaria, Czech Republic, Poland, Romania, Slovakia). Figure 2 below shows the detailed representation of the survey respondents by country.

[2] UN, Statistics Division. Geographic Regions. Available at: https://unstats.un.org/unsd/methodology/m49/ with Cyprus considered Southern Europe.

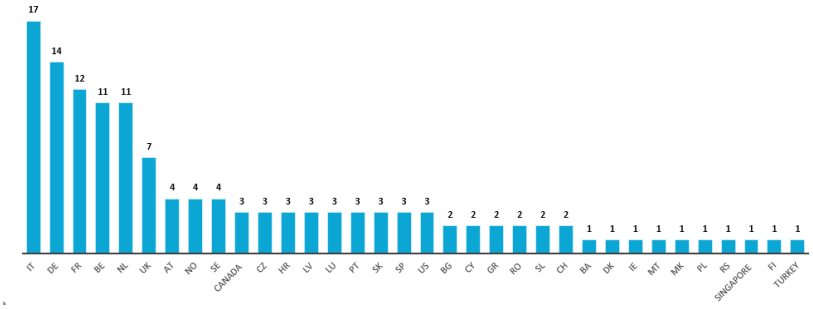


Figure 2 Survey respondents by countries

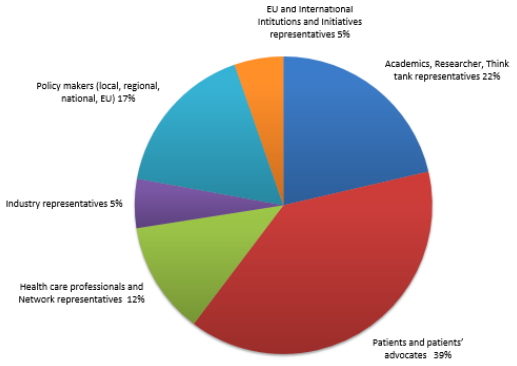


Figure 3 Survey respondents by affiliations

Respondents included primarily patient advocates and representatives from civil society organizations (39%), while researchers and policy makers were represented respectively by 22% and 17% of respondents. Notwithstanding the efforts to have the quadruple helix fairly represented among the survey respondents, the industry sector and the healthcare professionals turned out to be under-represented.

1.3 Trends' level of uncertainty and importance

The table below reviews the level of importance of each of the considered trends, derived from the answers to the first question. To facilitate the reading weighted averages are grouped according to the following colour classification – bearing in mind that score 1 corresponds to the "highest importance":

- Red: those trends with a weighted average of response from 1,50 to 1,80
- Orange: those trends with a weighted average of response from 1,80 to 1,90
- Dark yellow: those trends with a weighted average of response from 1,90 to 2,50

Looking ahead to 2030/2040, how important do you think these trends will be for the RD field?	**Weighted average**	**Colour coding**
11. New technologies and advanced therapeutics	1,51	

1. Rise of pan-European multi-stakeholder networks to advance diagnostics, treatment and care for rare diseases	1,70	
3. Greater variation in access to treatments and care resulting in more inequality across Europe for people with rare diseases	1,71	
12. Application of Whole Genome Sequencing from the research to the clinical sphere	1,80	
2. Strains on the health care budget and the emergence of new care delivery models	1,80	
7. Rise in innovation-oriented, multi-stakeholder, needs-led (patient-led) research	1,86	
9. Increased potential for large sets of standardised and interoperable data	1,87	
6. Increasingly empowered rare disease patient and the patient advocacy evolution	1,89	
8. Facilitation of knowledge exchange and local care delivery through digital health	1,94	
5. Threats to solidarity equity, and the prioritization of rare diseases	2,16	
10. Rise in the use of AI for diagnostics, treatment and care, opening-up the potential of 'big data'	2,24	
4. Demographic change of RD patients introducing new challenges	**2,40**	

Table 1 Trends – level of importance

The ranking of unpredictability is shown with a similar colour coding – taking into consideration the maximum and minimum of the average weighted response for the second question.

- Red: those trends with a weighted average of response from 2,50 to 3,00
- Orange: those trends with a weighted average of response from 3,00 to 3,20
- Dark yellow: those trends with a weighted average of response from 3,20 to 3,50

How predictable do you consider the evolution of this trend to be at 2030/2040?	Weighted average	**Colour coding**
5. Threats to solidarity equity, and the prioritization of rare diseases	**2,61**	
10. Rise in the use of AI for diagnostics, treatment and care, opening-up the potential of 'big data'	2,74	
7. Rise in innovation-oriented, multi-stakeholder, needs-led (patient-led) research	2,74	
2. Strains on the health care budget and the emergence of new care delivery models	2,83	
3. Greater variation in access to treatments and care resulting in more inequality across Europe for people with rare diseases	2,88	
11. New technologies and advanced therapeutics	3,05	
9. Increased potential for large sets of standardised and interoperable data	3,06	
1. Rise of pan-European multi-stakeholder networks to advance diagnostics, treatment and care for rare diseases	3,09	
12. Application of Whole Genome Sequencing from the research to the clinical sphere	3,23	
8. Facilitation of knowledge exchange and local care delivery through digital health	3,26	

6. Increasingly empowered rare disease patient and the patient advocacy evolution	3,27	
4. Demographic change of RD patients introducing new challenges	**3,51**	

Table 2 Trends – level of unpredictability

From the cross-comparison of the ranking results by importance and unpredictability – shown in the table below – it stands out that the following five trends have been considered as most important as well as unpredictable:

- Greater variation in access to treatments and care resulting in more inequality across Europe for people with rare diseases
- Strains on the health care budget and the emergence of new care delivery models
- New technologies and advanced therapeutics
- Rise in innovation-oriented, multi-stakeholder, needs-led (patient-led) research
- Rise of pan-European multi-stakeholder networks to advance diagnostics, treatment and care for rare diseases

Looking ahead to 2030/2040, how important and unpredictable do you think these trend will be for the RD field?	**Importance**	**Unpredictability**
3. Greater variation in access to treatments and care resulting in more inequality across Europe for people with rare diseases		
2. Strains on the health care budget and the emergence of new care delivery models		
11. New technologies and advanced therapeutics		
7. Rise in innovation-oriented, multi-stakeholder, needs-led (patient-led) research		
1. Rise of pan-European multi-stakeholder networks to advance diagnostics, treatment and care for rare diseases		
12. Application of Whole Genome Sequencing from the research to the clinical sphere		
5. Threats to solidarity equity, and the prioritization of rare diseases		
10. Rise in the use of AI for diagnostics, treatment and care, opening-up the potential of 'big data'		
9. Increased potential for large sets of standardised and interoperable data		
6. Increasingly empowered rare disease patient and the patient advocacy evolution		
8. Facilitation of knowledge exchange and local care delivery through digital health		
4. Demographic change of RD patients introducing new challenges		

Table 3 Trends – level of importance and unpredictability – survey results

In fact - and somehow predictably - it turns out that all trends have been considered important and should be taken into consideration for the RD strategies and measures. For the scope of the foresight exercise, however, attention will be placed on those changes – in the upper right quadrant in the figure below - for which it is still not possible to foresee a clear development in the medium-long run.

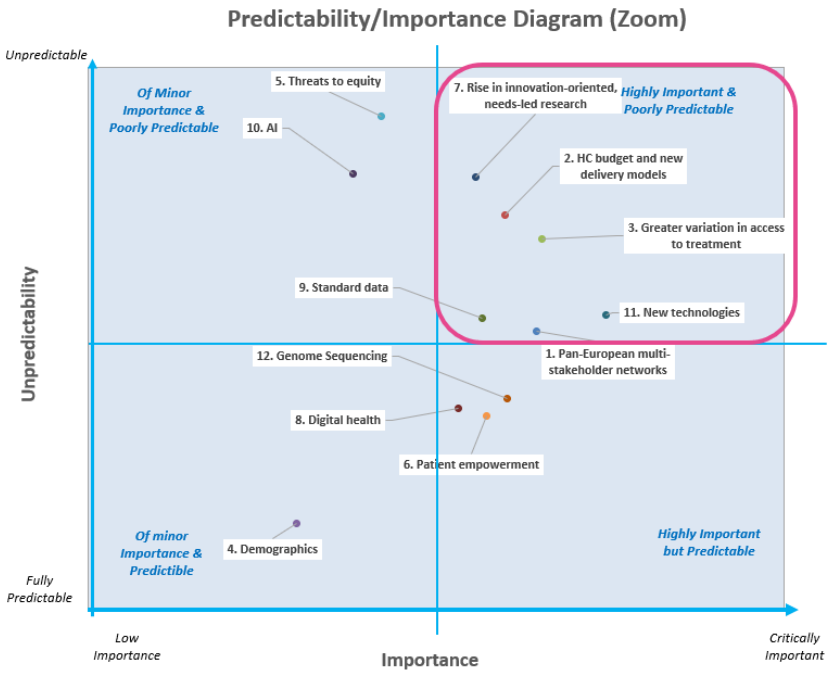


Figure 4 Graphic representation of the trends ranking by unpredictability and importance – on-line survey results

1.4 Trends comments

The last decades of economy stagnation, the linear budgetary cuts along with policy tensions pose a major threat to EU countries' capacity to sustain healthy economies addressing inequalities between countries and among countries in relation to income, education and access to care and treatment. As regards the trend "*Greater variation in access to treatments and care resulting in more inequality across Europe for people with rare diseases"* respondents' comments highlighted:

- The opportunities for measures by European lawmakers to curb the price impact of orphan medicines through cross-national price negotiations;
- The opportunity for an European Health Technology Assessment (HTA);
- The opportunity for completing the cycle of innovation for rare disease treatments e.g. introducing true biosimilar competitions for ERTs;
- The risk that in the future more orphan drugs will be produced raising questions of availability, affordability and accessibility;
- The risk of the pressure of internal migration within the EU as a counteracting force for extreme inequality. If a particular OMP "is significantly more accessible in one country, we would expect movement across the EU of patients needing that treatment, and potentially an undue burden

on that country. This seems like it might undermine individual countries covering high-cost low-volume OMPs".

With regard to the trend "*Strains on the health care budget and the emergence of new care delivery models"* one stakeholder pointed out that "The unresolved gap between general practice (proximity) and specialized care have not been addressed and is crucial in RD. The hyper specialization carries the potential risk of increase the fracture between the non-specialized medical population and the expert one, aggravating the diagnostic odyssey due to lack of correct and timely referrals". Another stakeholder stressed the need of "cooperation on a regional level for provision of treatment, care, diagnosis, social and health services" while others mentioned the urgency to rethink the healthcare system and to find a healthcare transition model built around the patients and their families. In line with this, it was mentioned that "an intervention is needed to support the families for adequate qualification paths and creation of social/work integration networks". The question of human capital was also raised as it remains of key importance to be able to select and attract new experts in the rare diseases care.

Strictly connected with the previous trends, stakeholders provided comments on "*Threats to solidarity equity, and the prioritization of rare diseases"* which was judged of relative low importance but highly unpredictable. One stakeholder highlighted that "worsening social inequalities in global health risks becoming a threat to European health systems such that rare diseases are not considered a priority anymore". Taking more an individual prospective, another stakeholder stated "I see on the negative side an increasingly difficult and hostile social environment where value of solidarity and inclusion are replaced by fear, poverty (of mind and pocket), selfishness, and ignorance". This might somehow affect the same RD community as pointed out by one stakeholder "Traditional Patient Advocacy (Self help - "Selbsthilfe") loses impact as new generations are not willing to invest the efforts and the energy needed for meetings, developing concepts, networking etc. An increase of communication through social media is likely to weaken the bond between patients and might harden the communication style between patients in a similar way as other social media communication. Having only understanding/empathy within a closed Group is likely to generate Change in the Health care System or Society".

The trends *New Technologies* and *Genomics* were combined as they both focus on the importance of offering new treatments and care to patients. Only if managed in effective, participatory and transparent ways – which is perceived as highly uncertain - innovation could play a role for improving performance while reducing costs in resources constraint future. Much will depend on the extent to which there will be a concomitant growth of the trends related to the "*innovation-oriented, multi-stakeholder, needs-led (patient-led) research*" and the consolidation of the "*pan-European multi-stakeholder networks to advance diagnostics, treatment and care for rare diseases*".

With regard to *patient-led research*, one respondent pointed out that "The enactment of the Clinical Trials Regulation EU No 536/2014 is expected to encourage researchers to conduct more clinical studies". This means that:

- Patients need to be knowledgeable and empowered to be able to catch up with this trend and be involved in the drug development process (this stresses the need for more intensive patient education);
- EU Member States will need to create national policies to ensure the access of patients to new therapies, setting eligibility criteria to ensure the effectiveness of public expenditure (thus reducing waste in healthcare).

In line with this, one respondent stressed that "patient science (patient-driven research and clinical trials networks) will make things going much faster" and another stakeholder foresaw "the creation of unpredictable socio-technological effects, like patient communities forming around ePROs, self-reported health, and advocacy. This could activate whole patient populations". Following this trend, new actors might be entering the healthcare sectors: the "Rise of industries outside the healthcare sectors (FAANG - Facebook, Amazon, Apple, Netflix and Alphabet -formerly known as Google) challenging the incumbent dominant players" is anticipated by one respondent.

1.5 Wild cards

The survey asked respondents to identify possible wild cards for the future RD diseases diagnosis, treatment and care. Wild cards are defined as disruptive events with low probability to happen but with expected high impact. More than 50 changes were suggested by stakeholders. Not all changes proposed can be considered as wild cards or 'unexpected events' since they are strictly dependent on policy choices, strategies and programming and represent more deliberative changes than unexpected surprises.

The figures 5 and 6 below map the positive and negative changes proposed in 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 figures – will be included in the scenarios as wild cards. The bubble size reflect the number of time that the event occurrence was mentioned by the survey respondents.

With regard the positive events, the two changes mentioned the most were i) the implementation of more effective International/EU/National RD policies (mentioned by 15 respondents) ii) genome sequencing at birth and breakthrough in genetic treatment (6 mentions). Among the policies put forward by respondents: a RD Solidarity fund and more RD research; joint EU HTA assessment; a common EU Orphan Drugs treatment price regulation, common EU reimbursement policies and a ELSI regulation allowing easy sharing of data and cross-border exchanges.

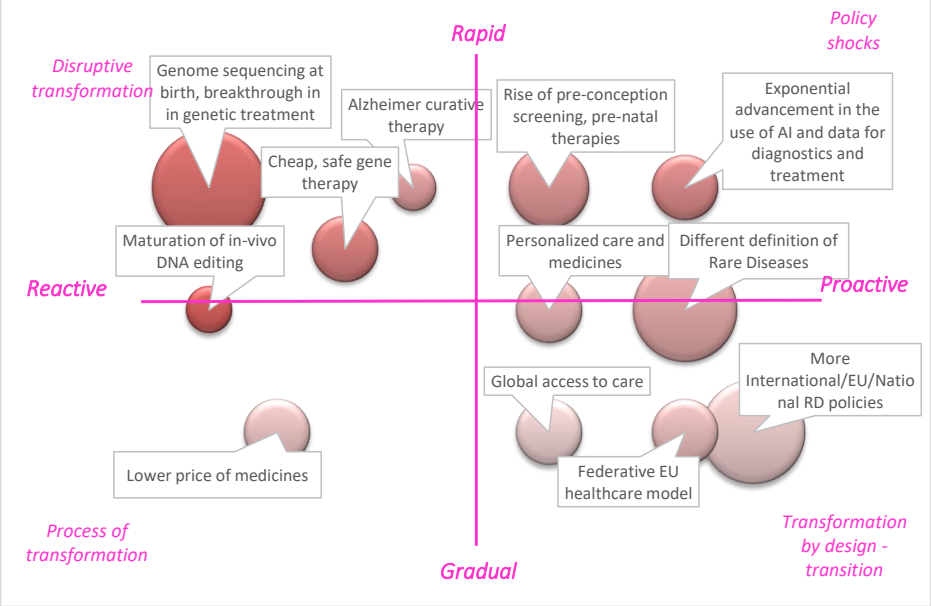


Figure 5 Positive wild cards

Under the bubble regarding the "different definition of RD diseases" we have included comments related to the fact that better diagnostic services might change the aspect of rarity. On respondent pointed out that the prevalence criterion in RD definition could become not enough and another suggested that the integration of rare diseases into mainstream medicine could lead to a loss of specialization in rare diseases. Similarly, one stakeholder highlighted the possibility of "standardization of gene therapy for a variety of diseases. This would make treatment of rare diseases "semi-routine" and change its aspect of "rarity"". Related to this, one participants highlighted that "It may be assumed that only one-half of the rare diseases have been described today. Rising to 80% (through genomics, epidemiology and AI) would have major scientific, sociological and economic impact".

Looking at the negative events, the one mentioned the most was related to the possibility of i) a new financial or economic crisis (9 mentions) followed by ii) the risk of EU collapse or fragmentation (6 mentions) and iii) the rise of political extremisms (4 mentions) in Europe.

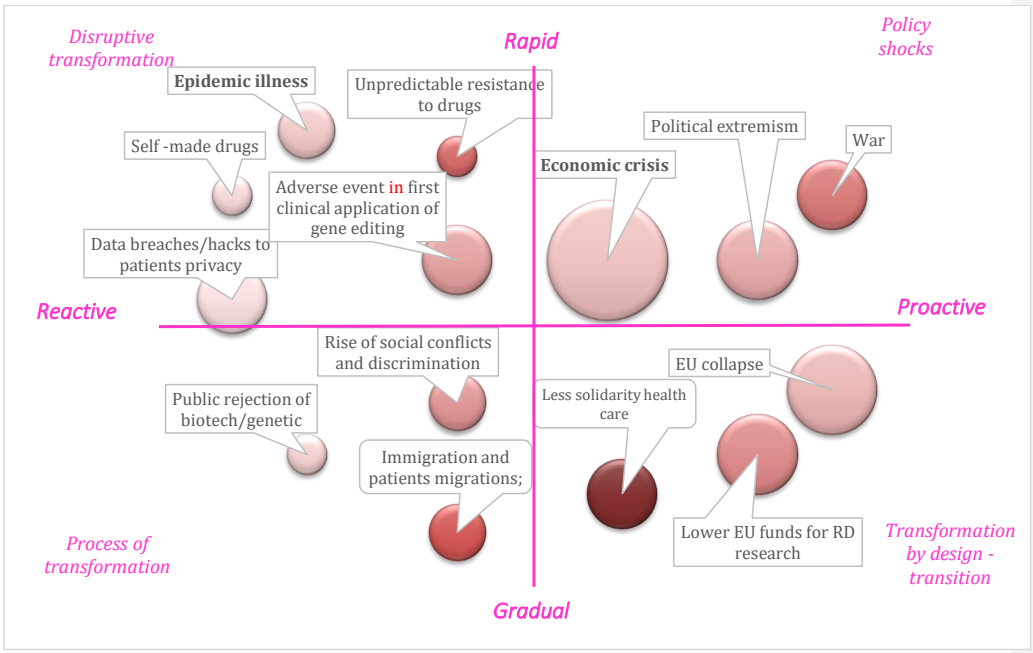


Figure 6 Negative wild cards

Epidemic illness and economic crisis were mentioned by respondents as possible wild cards and these two are now that ones we should consider in the RARE2030 Scenarios – imagining the impact they might produce in RD field and in society at large.

2 Panel of experts conference "Validation of Trends to Build Future Scenarios in Rare Disease Policy"

2.1 The conference Agenda

The final agenda of the RARE2030 event, as presented below, provides an overview of the various sessions and topics addressed on November 7th, 2019.

09.00 -09.10	Welcome: Frederique Ries (Mep Belgium)
09.10- 09.30	Review of the Rare2030: Preparing the Future of Rare Disease Policy Yann Le Cam, EURORDIS-Rare Diseases Europe
09.30 - 10.30	Rare 2030 Research Advisory Board Panel Discussion: Global insights - Moderated by Andrea Ricci, ISINNOVA ● Terkel Andersen, EURORDIS-Rare Diseases Europe Board of Directors ● Robert Madelin, FIRPA, former Director DG CNECT and DG SANTE ● Milan Macek, Chairman of the Department of Biology and Medical Genetics at the Charles University in Prague ● Rüdiger Krech, WHO Health Systems and Innovation (video)
10.30 – 10.40	Presentation of Methods and Health and Health-care trends by Giovanna Giuffrè, ISINNOVA
10.40-13.00	Presentation of RD Trends – by Victoria Hedley, University of Newcastle Institute of Genomic Medicine (interactive session). Discussants: ● Lucia Monaco - Head of Research Impact and Strategic Analysis of Fondazione Telethon ● Ana Rath – Acting Director of Orphanet INSERM ● Maurizio Scarpa - Coordinator of the MetabERN and the Chair of the ERNCG ● Charlotte Vrinten, Research Associate ICL
13.45 - 17.00	Working groups sessions – each group: ● Discussed the survey preliminary results (40') ● Reviewed interconnection among trends (30') ● Imagined possible, different futures for one pre-assigned trend (40')

2.2 Who participated to the RARE2030 Panel of Experts conference?

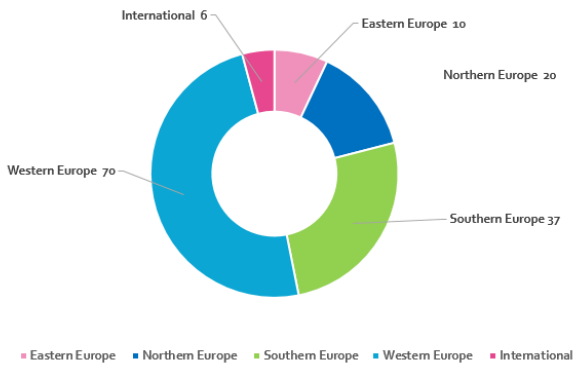


Figure 7 Workshop participants by EU Regions

One hundred and forty-five participants joined the RARE 2030 Panel of Experts Conference.

According the UN geo-scheme, the most part of participants were from Western Europe (48%), especially from Belgium, France and Germany, followed by Southern Europe (37%) as Italy, Spain, Portugal, Croatia, Slovenia and Northern Europe (20%) with the majority from Norway, Sweden and UK. International participants came from Singapore, US, Canada. The distribution of the different geographical macro-areas and countries represented is reported in Figure 7 and Figure 8.

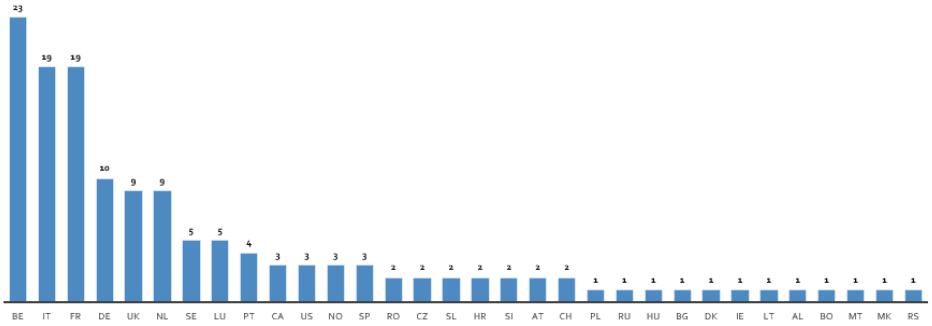


Figure 8 Workshop participants by countries

Regarding the Panel expertise, the participants that joined the Conference were mainly representatives of patient organizations (43%), followed by academic and researchers in the field of RDs but also in the wide field of regulatory issues or health economics. Concerning policy makers (16%), EU policy makers as representatives of European Commission Bodies reported the most important participation. Healthcare professionals and network representatives (as ERNs Coordinators and Hospital Managers) and industry representatives were also present (9% and 10% respectively). EU and international institutions and initiatives representatives such as the Canadian Organisation for Rare Disorders, the

Indian Organization for Rare Diseases, the Global Alliance for Genomics and Health (GA4GH) and the European Space Agency, among them, completed the participants list.

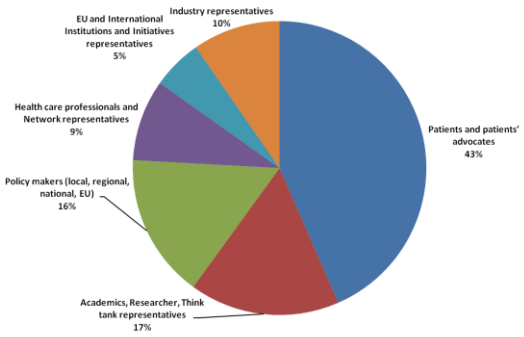


Figure 9 Conference participants by affiliation

2.3 Welcome and introduction

Frédérique Ries (Mep Belgium) opened the conference illustrating the role and the importance of the RARE2030 project for the future of RD policy governance.

She stressed how "Rare2030 is an opportunity to press pause…to sit down for a moment, brainstorm, consult and prioritise… to see what these special patients need and the trailblazing ideas and policies that will have the best impact."

As one of the main promoters of the project, she highlighted the efforts done and the long work lying behind the launch of RARE 2030, that she considers one of her European Parliament (EP) best achievements. The approval of the initiative was not easy; the effort to reach consensus started in 2016 by meeting with, discussing and persuading EP members about the enormous value of the project, competing with equally valuable projects. She praised the role of the European Commission in supporting the RDs initiative giving feedbacks and reviews.

Dr. Ries then stressed that reflections that are coming out from RARE 2030 play already a key role in the current policy discussion, as for the Artificial Intelligence (AI) and digital transformation in healthcare trend, a topic on which she is currently drafting a resolution. AI and digital health are potentially disruptive innovations also for RDs, allowing to put patients at the center of research. To realize this

huge potential, a continuous training of patients and healthcare practitioners is needed in order to manage the opportunities but also the risks. In this field, the standardization of data across Europe could also speed up the research and the results, but the increase of data sharing and exchange must respect privacy and security. She also expressed the intent to launch an EU debate on the effects of digitalization in healthcare stressing that AI should not de-humanize health. She concluded by wishing a fruitful work and collaboration with the EP towards the most effective exploitation of the outputs of the RARE 2030 Project.

Yann Le Cam, (CEO EURORDIS) introduced the objectives and methodology of the project, based on an approach that integrates the qualitative inputs and discussion to build Storylines (scenario narratives) and generates policy recommendations (backcasting) which is the final, concrete, aim of the project.

In line with the fundamental ambition of foresight, he stressed that we cannot predict the future for RDs but we can explore different possible futures. The health of RDs patients "has not to be left to chance or luck, the more we are prepared, the more we have chance to anticipate". Preparedness in this regard is the analysis of what exists today, the identification of the drivers of change and of the different possible future scenarios, trying to simplify the complexity to better work on it".

He underlined that the project starts from the need to devise an updated policy framework on rare diseases, some important steps were represented by the EP Regulation on Orphan Drugs (1999) and by the RD strategy set in 2008/2009 but "things are evolving, the environment is evolving and we need a policy to address the needs of the people based on the current situation".

"One of the key recommendations of the European Auditors report on the cross-border healthcare (CBHC) directive is that the European Commission needs to review, adopt and potentially replace the framework on RDs before 2023", he added. The work of RARE 2030 is in this line, representing a bridge for a new framework of EC and Member states on RDs.

Yan Le Cam further introduced the Research Advisory Board and the Panel of Experts composition and the partners of RARE 2030 with their specific expertise and tasks in the project. He gave also some anticipations on the next RARE 2030 consultation steps as the online survey with 10,000 RDs patients and families, the Young Citizens Conference and the six Regional workshops that could help RARE 2030 to "consolidate" their project results and move towards effective policy recommendations.

Dr. Le Cam finally focused on the 12 trends identified in the previous steps, emphasizing the aim of the day that is reviewing, validating and ranking trends by importance and uncertainty to start moving towards building the scenarios for the future. He stressed the importance to get a better understanding of the interaction between the PEST (political, economic, social, technological) dimensions of the trends in order to provide the best strategic policy recommendations.

2.4 The RARE2030 Research Advisory Board: insights from emerging futures

Rüdiger Krech, WHO Health Systems and Innovation and member of the Research Advisory Board of the Project shared his insights on the project through a video. .

He offered positive comments on the trends identified in the Project and focused his attention on the role of the "new technologies" trend for the diagnosis and treatment of RDs. In this regard he stressed that "I would include innovation in communication technologies as they may have an important impact in networks of global centres of excellence…". His main desire for the next 10 years is to see the achievement of a network of centres of excellence for RDs with the best worldwide experts, virtually linked and "present at the bedside of the patients". These should represent top-notch places for research in innovation in diagnosis and treatment and training centres for international healthcare professionals, funded through international agreements. The structuring of this network will reduce the time to diagnose, will improve a patient-centered care and, optimistically, will decrease the number of RDs patients because more RDs patients will have the opportunity to be treated. He also referred to the WHO Global Programme of Work as an operative 5-years programme in line with the Sustainable Development Goals to "leave no one behind".

Regarding PEST categories he stressed that all categories and the interdependence between them are important to drive the implementation of policies. Focusing on specific topics he underlined that the availability of drugs has not been a "charity matter"; RDs drugs have to be part of a transparent pricing system and this calls for a serious commitment of everyone to transparency. WHO has already started a dialogue with industries and stakeholders for a fair pricing of drugs to provide medicines for all, but only if we are aware of the interdependences between political, societal, cultural values and we take an ethical dimension "we will be able to reach realistic goals".

The discussion then revolved around the following 3 main questions that Andrea Ricci from ISINNOVA asked to the RAB members: Terkel Andersen, EURORDIS-Rare Diseases Europe Board of Directors, Robert Madelin, FIRPA, former Director DG CNECT and DG SANTE, Milan Macek, chairman of the Department of Biology and Medical Genetics at the Charles University in Prague.

Question 1. You have the chance to meet a clairvoyant that knows what will happen in 2040, what will you ask?

Terkel Andersen: "Since we have to leave no one behind…**who is being left behind in 2040 in RDs?** Who does not have access to diagnosis and treatment? Furthermore, "how do we see RDs in 2040? More individualized, more focused on genetics and personalised intervention or more as groups as right now?".

Milan Macek: "I will ask if **we will be so interdependent** as now. If the world **will remain human**, if we **will value the community**, a strong community with solidarity which takes care for marginalized populations". "Technologies will continue to develop, but it is not the answer…machines have no emotions, technology could be a good servant but also a bad master".

Robert Madelin : "Maybe the best option will be a machine that works on data sets…and gives the **trade-off of our desires**, **showing the sustainability implications** and helping us **to think as a whole**, driving back empathy in the world. For instance highlighting that each rare disease patient not adequately treated and cared means a social loss, an economical loss, a human loss."

Other comments by the Panel:

- Technology does not provide the outcome, thanks to technology we could have some new accessible effective solutions but none *de facto* available owing to high prices. We do not have to focus on technology, we have to focus on the societal context, on what we want.
- We also have to be honest and transparent on what technology could do and cannot do.
- The setting of an ethical European framework, which recognises our interdependence and is based on the value of solidarity is key for promoting sustainable development.

Question 2. Back to present, we are endowed with all powers to orient policy, initiating investments without constraints, what will you do to improve the situation for RD?

Milan Macek: "**not to leave ultra-rare diseases behind**, invest in ultra-rare diseases that could help us to understand also mechanisms of others diseases as chronic diseases. I will link rare diseases initiatives to other initiatives and research".

Robert Madelin "Maybe I will ask about the **"known unknown"** .Will there be consensus in 2040 that no one has to be left behind? **Will there still be consensus on solidarity, collective provision of health?** And then, which is the winner strategy in research and innovation for RDs? To have a **narrow or a broader label of RD in research and innovation?"**

Terkel Andersen: "strengthen the pathways for diagnosis". He stressed as it is important to increase integration and dialogue in a coordinated action between patient organizations, information systems, ERNs, ORPHANET. **The main fear is to lose coordination**, to forget ethical issues and input of patients: "I miss the fact that we have no European Committee organising a dialogue amongst all stakeholders … to design policies where we not only depend on accidental progress but actual design what kind of future we want."

Other comments of the Panelists:

- We have to remark that we need a success by design not an accidental progress.
- We can ensure good networking of patients and families using EU online platform i.e DG Santé, to promote the dialogue not only between disease groups but also across geographical, socially, economically different groups.
- We need to stress the added value of the European collaboration. We already do it with ERNs but we can do it better to ensure quality care for all, regardless where we live. This is the main vision, we must not underestimate the principles and values of solidarity and of free movement of citizens.
- We have to think about the intra-Europe migration and about the demographic change of the future and we don't want to leave Eastern and southern Europe behind.

Question 3. *Which are the most urgent barriers to remove to achieve your goals?*

Robert Madelin: "We are a society without strategy, working with "slices of the salami", we have to adopt **the perspective of interconnections** between humans and humans and the planet, we need to think as a whole, even if we are interested in only one of the slices. This is also valid for RDs."

Milan Macek: "We have to support our values, values that made us strong..as solidarity, family, health, education"

Terkel Andersen: Some of the institutions are underfunded and at risk to close, "**we have to find funding models for institutions and infrastructure"** and to study how to include RDs in the health budget of the future to build a sustainable ecosystem around RDs.

Questions and comments from the audience:

- Role of the human perspective in AI: AI needs human perspective, wrong concepts and inadequate training could generate distortion; AI could help, being an "augmented reality" but must constantly be monitored by humans.
- Difficulty to transpose policy recommendations in the real world of the different countries, there are no strict and legal binding regulations that clearly say what to do.

2.5 Validation of trends level of uncertainty and importance

Giovanna Giuffrè (ISINNOVA) presented the findings of the RARE 2030 literature review on health and healthcare trends, to help kick starting participants reflection on – and recognition of - the trends that influence RD policy the most.

Victoria Hedley (UNEW) presented the twelve RD trends emerged in the Panel of Experts calls and moderated a interactive session of panel of experts composed by RARE2030 partners to offer the audience insights on each trend possible evolution and impact.

Adopting the same approach of the survey launched before the conference and described in section 2.1, Victoria asked participants to vote on each trend importance and predictability. For each trend, the "live survey" asked experts their educated guesses to the following questions:

- Looking ahead to 2030/2040, how important do you think this trend will be for the rare disease field?– evaluated according the qualitative scoring system adopted in the pre-conference survey (section 2.3): (1) critically important to (5) of low importance;
- How predictable do you consider the evolution of this trend to be at 2030/2040? – evaluated according to the following scoring system: (1) unpredictable to (5) fully predictable trends;

In line with the survey results presented in section 2.3, stakeholders evaluated the trends proposed between 'critically important' and 'very important' – the weighted average of all trends varying between 1,53 for the trend ranked as the most important and 2,40 for the trend evaluated as relatively less important. With regard the second question, respondents considered the trends proposed between "partially predictable" and "predictable" - the weighted averaged of all trends varying from 2,52 for the trend ranked as more unpredictable to 3,49 for the trend evaluated as relatively more predictable.

The table and diagram below represent the live survey results using the same colour coding and graphic representation followed in section 2.3. Generally, it can be noted how this live survey was consistent with the results of the previous consultation offering consolidated findings to RARE2030 partners on which trends should be considered as 'critical uncertainty' for building the RARE2030 Scenarios space.

Trends	Importance	Unpredictability
2. Strains on the health care budget and the emergence of new care delivery models	1,57	2,8
3. Greater variation in access to treatments and care resulting in more inequality across Europe for people with rare diseases	1,69	2,56
11. New technologies and advanced therapeutics	1,53	3,15
5. Threats to solidarity equity, and the prioritization of rare diseases	1,86	2,63
9. Increased potential for large sets of standardised and interoperable data	1,69	3,06
1. Rise of pan-European multi-stakeholder networks to advance diagnostics, treatment and care for rare diseases	1, 73	2,37
10. Rise in the use of AI for diagnostics, treatment and care, opening-up the potential of 'big data'	2, 48	2,52
7. Rise in innovation-oriented, multi-stakeholder, needs-led (patient-led) research	1, 91	2,37
12.Application of Whole Genome Sequencing from the research to the clinical sphere	1, 82	3,12
8. Facilitation of knowledge exchange and local care delivery through digital health	1, 92	3,39

6. Increasingly empowered rare disease patient and the patient advocacy evolution	1,95	3,28
4. Demographic change of RD patients introducing new challenges	2,06	3,49

Table 4 Trends – level of importance and unpredictability – live survey results

Color coding legend:

Importance	Unpredictability
• Red: those trends with a average of response from 1,50 - 1,80 • Orange: those trends with a weighted average of response from 1,80 - 1,90 • Dark yellow: those trends with a weighted average of response 1,90 -2,50	• Red: those trends with a weighted average of response from 2,50 - 3,00 • Orange: those trends with a weighted average of response from 3,00 - 3,20 • Dark yellow: those trends with a weighted average of response 3,20 -3,50

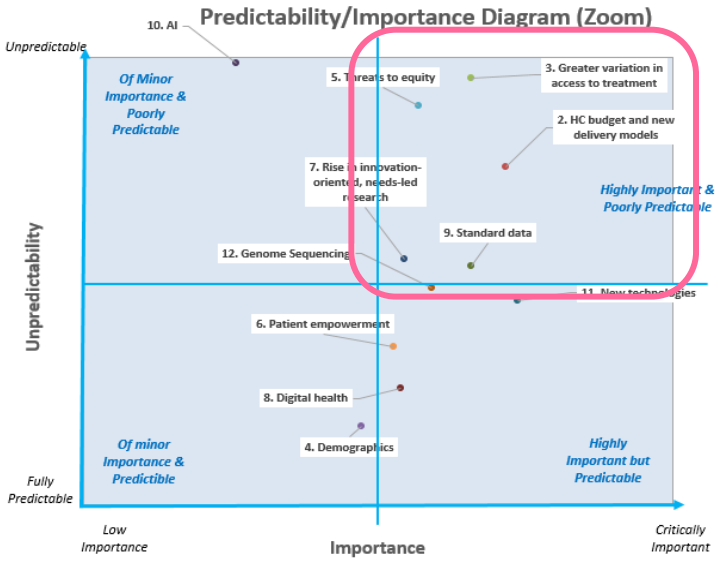


Figure 10 Graphic representation of the trends ranking by unpredictability and importance – live conference results

2.6 Working groups findings:

In the afternoon, the PoE Conference staged a working group session articulated around three exercises designed to move from the trends ranking toward the building of the RARE2030 scenario space. Starting from the confirmed list trends emerged in the morning, participants were split into 10 groups,

preassigned by the Consortium so as to guarantee mixed expertise and country representation in each group. Each group was assigned a facilitator from EURORDIS, UNEW or ISINNOVA. Time available was not enough to allow for a plenary discussion of working groups' results and moderators where tasked to summarise working tables' findings, which are presented in the sections below following the chronological sequence of the three exercises, respectively aiming at:

- validating the ranking of the survey results;
- analysing the interconnections between trends;
- eliciting qualitative comments and insights useful for the building of the scenario space.

In carrying out the exercises some hurdles have been met – mainly owing to the limited time available, so that most groups run out of time before completing the third exercise. However, in each different group, the discussion saw the active participation and the face-to-face exchange of comments and ideas among the Panel of Experts – thus enriching the previous, extensive engagement on-line.

2.6.1 Trends' ranking validation

The first exercise was designed to validate and consolidate the survey ranking of trends by importance and uncertainty. Given the list and the factsheets of the 12 trends, produced throughout the literature review and reported in 4.2 deliverable, participants were asked to select and write down the most important and most uncertain trend (1 preference only) and to start-up the discussion in the group by explaining their choice.

Eighty-one preferences were collected from the different working groups. As shown in Figure 9 below, the following five trends received the most preferences:

1) Greater variation in access to treatment and care (19,8% preferences),
2) Strains on health care budget and the emergence of new care delivery models (17,3%),
3) Rise of pan-European multi-stakeholder networks (17,3%),
4) Threats to solidarity equity and the prioritization of rare diseases (14,8%)
5) New technologies and advanced therapeutics (11,11%).

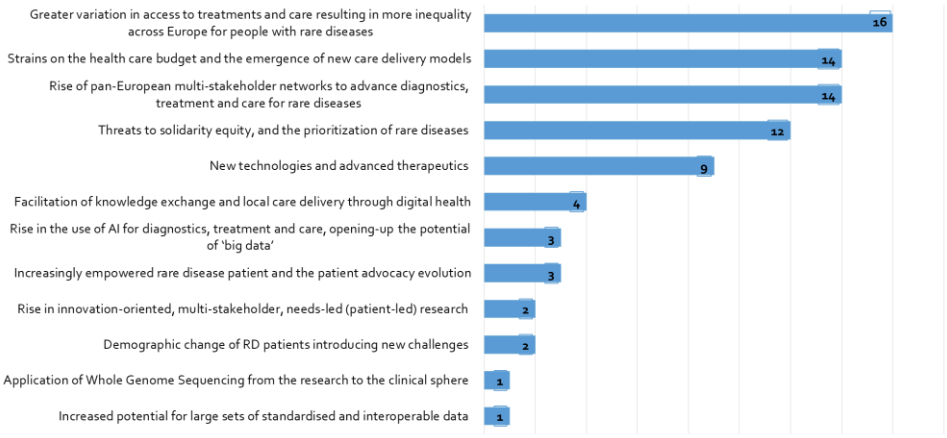


Figure 11 Workshop- Ranking of trends results

This ranking turned out to be consistent with the survey ranking results reported in section 2, thus providing clear indications to the RARE2030 consortium on what trends the PoE deems most relevant when building the Scenarios space.

In the intra-group discussion some interesting insights emerged on each of the identified top five trends:

Greater variation in access to treatment and care resulting in more inequality across Europe for people with Rare Diseases:

- The greater variation in access to care strongly relies on budget, solidarity and political will of Member States – MS- (main factors of unpredictability);
- Inequalities in access to care could also be seen within the same country between rare diseases and other diseases or across rare diseases themselves;
- A strong role of EU in RD pricing could improve the availability of treatments;
- Variation in access to treatment and inequalities between countries may derive from the different availability and accessibility of Orphan Medicinal Products (OMPs), the different competence and healthcare capability to swiftly intercept RD patients to provide a timely diagnosis, the different culture of Member States in providing access to an holistic care (not only to medicines).

Strains on the health care budget and the emergence of new care delivery models

- More transparency in allocating the healthcare budget is needed;
- The implementation of tools such as Health Technology Assessment could help in the programmatic choices;
- Including social and psychological care as central pillars of an holistic model of care for RDs, adopting a multidisciplinary approach is desirable;
- New healthcare delivery models have to fit with the health systems capabilities and culture;

- New healthcare delivery models could increase costs in the short-time but decrease them in the long-term with remarkable outcomes for patients in terms of compliance to treatment, quality of care and quality of life.

The rise of pan-European multi-stakeholder networks to advance diagnostics, treatment and care for rare diseases

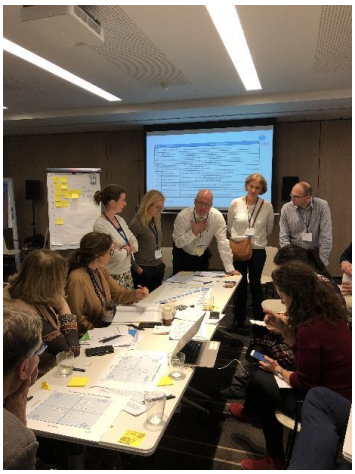
- Plays a stronger role in avoiding duplication in research and produce innovation;
- More needs-oriented networks of patients- and more integration between research networks and care networks is desirable;
- Commitment of EU and the allocation of funding to ensure networks sustainability in the long term are central aspects of uncertainty.

Threats to solidarity equity and the prioritization of rare diseases

- Solidarity is heavily threatened by the rising of European and international waves of nationalism that could endanger the access to care for vulnerable groups.

New technologies and advanced therapeutics

- Could play as enablers as well barriers for equity and efficiency, depending on how they are integrated in the current healthcare systems, how equally they are distributed and how both the healthcare workforce and patients are confident with their use;
- It is urgent to strictly regulate their use taking into account ethical and social issues;
- Ethical framework is also important in digital health and Artificial intelligence. Even if their importance turned out to be undoubted, concern about the use of data and the privacy protection in data sharing is a central pillar of uncertainty.



2.6.2 Analysis of interconnections between trends

The second exercise focused on the analysis of the interconnections between trends with the aim of underlining those interconnections which could facilitate the scenario space construction (e.g. by combining trends that are strongly correlated) while providing insights for the storylines development and enhancing their internal consistency.

Working on a matrix of the 12 trends, in each group participants were asked to use dots to highlight the most important interconnections between trends (up to 3 preferences for each participant). Each "dot" in a given cell of the matrix indicated the existence of a link between the trend described in the row and the one presented in the column. The overall number of "dots" was ultimately rather high, illustrating the complexity of the interplay between trends and the numerous feedbacks.

An online tool[3] was used by the Consortium to perform a quantitative graphic analysis of the interconnections reported in the exercise. The graphic analysis of the interconnections of the 10 groups has allowed to easily:

- Underline the most cited interconnections;
- Show all the relevant interconnections reported by participants;
- Identify single trends with the highest number of interconnections;
- Identify clusters of trends.

Figure 12 shows all the interconnections collected in the exercise. Trends are represented by dots, and the thickness of lines reflects the frequency of citation. To facilitate the reading of the graph, trend titles are shown in condensed wording.

[3] "Graph online" tool. Available at:HYPERLINK https://graphonline.ru/en/

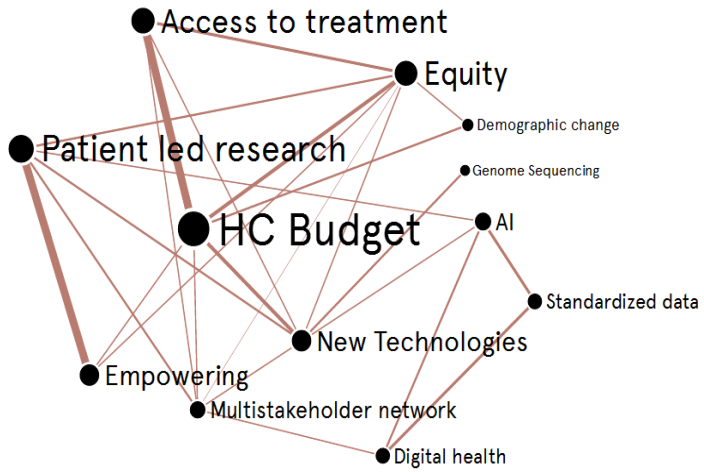


Figure 12 Total interconnections reported in the 10 groups

Note:Preferences were included if reported at least twice. The thickness of link between dots reflects the frequency of the participants choice.

As shown in Figure 12, the interconnection between *Healthcare (HC) budget constraints and the emergence of new healthcare delivery* ***and*** *the variation in access to treatment* resulted to be the most cited interconnection.

Strains on the health care budget and the emergence of new care delivery models ***and*** *threats to solidarity equity and the prioritization of rare diseases* turned out to be the most important trends in terms of interconnections with the others (see number of lines that branches out from the dots in Figure 12). Both of them, for instance, are linked with:

- greater variation in access to treatments and care resulting in more inequality across Europe for people with rare diseases,
- new technologies and advanced therapeutics,
- rise of pan-European multi-stakeholder networks to advance diagnostics, treatment and care for rare diseases.

Analyzing all the interconnections, three specific dimensions (**clusters of trends,** connected to each other)**,** have clearly emerged (Figure 13) thus helping define the scenario spaces:

1) **access to treatment** (linked with healthcare budget and equity trends);
2) **new technologies and advanced therapeutics** (linked with the rise of pan-European multi-stakeholders networks and of an innovation-oriented, multi-stakeholder, needs-led (patient-led) research);
3) **digital health** (linked with AI and standardized and interoperable data);

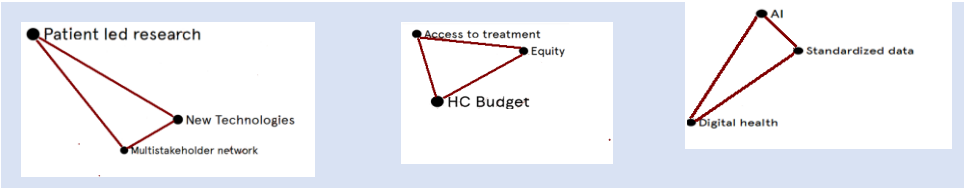


Figure 13 Trends clusters identified.

Participants also offered insightful qualitative comments on the identified clusters:

- access to treatment is strongly linked with the solidarity value of MS that could also influence the allocation of HC budget for RDs,
- needs led (patient led) research has a strong role to promote new technologies; patients should be involved in the development of new technologies and advanced therapeutics, possibly in an early phase,
- standardised and interoperable data is the key to advance in digital health and AI since the cross-country exchange of data allows to obtain a huge amount of high quality data useful to speed up research.

Other qualitative comments received addressed:

- the role of budget in promoting the innovative research,
- the link between new technologies and advanced therapeutics that could lead to the development of new healthcare delivery models.

2.6.3 Imagining different futures and ways to measure change

The third exercise was the first step towards the storyline development. Participants were asked to imagine and provide different, contrasted futures for the 12 trends and to identify possible indicators to measure trends dynamics under the imagined futures. Each group was assigned one or two trends to analyse.

Group works turned out to be rather heterogeneous in the approach to the indications – and expected output- of the exercise. The limited time available to carry out the exercise contributes to explain the diversity of results obtained: while some groups focused on indicators (table 5 below) others concentrated on the development of a backbone for the storylines (tables following table 5).

Overarching Trends in RDs	Indicators to measure change	
2 Strains on the health care budget and the emergence of new care delivery models	• % of research funds allocated in RDs • % of health and social services dedicated to RDs patients • Length of time for a diagnosis / for the right diagnosis • % of RDs patients who receive an available treatment • Length of time to access an available treatment	• % new devices on the market • % new treatments and advanced therapeutics available • Number of services and projects promoted by associations of patients • Quality of life of RDs patients (even if QoL is considered to be too subjective) and satisfaction of RDs patients
3 Greater variation in access to treatments and care resulting in more inequality across Europe for people with rare diseases	• Payment models • Collection of data across Europe • Member States to enable (cross border) mobility of patients • Supporting network • Early diagnosis (NBS) • More information about treatment options (NCPs, Doctors, Patients)	• Improve pathways to care (global to local • For very to ultra rare diseases (no definition given) centralised authorisation, followed by joint assessment and appraisal at European level could reduce inequality • Rare diseases could be identified as a pilot programme for this increased cooperation • Sovereignty vs solidarity = megatrend identify that might increase inequalities
4 Demographic change of RD patients introducing new challenges	• Length of life for RDs patients • Fertility rate of RDs patients : N. of children per woman affected by RDs (n.of children per man could be missed if not adequately recorded in healthcare IT systems)	• % of RDs patients at high functional status (identifying a new specific evaluation scale of functional status or customising evaluation scales already existing) • % of RDs patients in working age employed and % of RDs patients who received a disability allowance
5 Threats to solidarity equity, and the prioritization of rare diseases	• Quality of life • Accessing healthcare service	• Regional and cross-border collaboration (shared guidelines) • Doctors -Patients collaboration (join shared decisions)
7 Rise in innovation-oriented, multi-stakeholder, needs-led (patient-led) research	• Education of both doctors and patients • Overall change in attitudes within the society (how do we perceive patients, doctors and the industry) • Social care/ human rights/employments • Rule of transparency, legal framework for collaboration (conflict of interest, etc)	• Impact on care and healthcare • Quality of life • Access to treatment • Culture of investigation: what are we looking at? • Informed consent • Need for intermediate (role of patient organisations) • Clinical trials, treatments available and value of treatments

	• Equity (Could increase gap between trained and not-trained patients)	
8 Facilitation of knowledge exchange and local care delivery through digital health	• Measuring patient generated data	
9 Increased potential for large sets of standardised and interoperable data	• MS survey of standards used (ELIXIR, IRDiRC) and % of healthcare providers using usable dataset – national database • % of patients in standardised registries • % HCP using EHR (e-Prescription)	• Accessibility of data from human, political and legal (GDPR) side • Measuring the sustainability of datasets (maintenance issues) • Coding of reason mortality for RD patients
10 Rise in the use of AI for diagnostics, treatment and care, opening-up the potential of 'big data'	• Patient satisfaction with use of AI (asking them if they are comfortable with the use of AI) • Accuracy of algorithms	• N. of diagnoses reached (correctly) with AI • Alignment of training (BPG) datasets for algorithms.
12 Application of Whole Genome Sequencing from the research to the clinical sphere	• Technical/medical performance (i.e % of patients getting diagnosis) • GS Data (i.e n. of registered people, n. of gene sequencing and gene editing treatments etc	• Governance/management (i.e the establishment of ethical committees and of regulations).

Table 5: indicators to monitor changes over time

Tables below report the most prominent elements of the contrasted scenarios - for six single of the 12 trends – analysed by the participants .

Rise of pan-European multi-stakeholder networks to advance diagnostics, treatment and care for rare diseases	
Less Successful networks	**More Successful networks**
ERNs no longer exist. Healthcare issues, even for RD, are handled at national level alone, as governments become more inwards-facing	ERNs are thriving – they are the centrepiece of RD and specialised healthcare scene in Europe
Inadequate funding for ERNs. No national support for healthcare practitioners (HCPs) and their coordination to support the participation in the ERNs.	Plentiful and appropriate funding for ERNs, for coordinating centres and for HCPs.National government funds the national centres of ERNs. Sustained European funding for the central services e.g. the Clinical Patient Management System (CPMS)
Underused or no use of CPMS: return to one-to-one exchange of patient notes and files, for informal review of cases.	Well used CPMS, which functions well for each ERN, collects customised datasets, can manage large files/images/ latest medtech
No virtual reviews or consultations because there is no way to recover the cost of the clinician/other professional time spent on these activities and	Well-functioning system to reimburse professionals for the time spent on virtual panel reviews. Cross-border Healthcare or the country of patients could be used for

countries decide to not allow clinicians to spend time on this.	this reimbursement, it may be necessary to think of GDP-related brackets of pricing.
The 'geographical lottery' becomes worse, as lack of proximity to an expert centre means very difficult to access top advice and opinion.	Patients are not disadvantaged by not living close to the top experts in their field. Patients are well-engaged in case reviews: for instance joining the real-time reviews, or sections of them.
ERNs are not involved in research. This is impossible without a proper engagement with Industry. Some countries are too cautious about enabling public-private partnerships for the ERNs and choose to downplay the research responsibilities.	ERNs play a key role in advancing various types of RD and specialised research. They engage with Industry, for a range of research-related activities, in win-win public-private partnerships. Companies provide funding for registry platforms.
ERNs are unable to demonstrate tangible benefits. ERNs and HCPs are not inclined to provide metrics data, making a demonstration of impact impossible. National support dwindles and patients lose their trust in the ERNs.	ERNs demonstrate concrete added value, in terms of networking and collaboration and in improving clinical outcomes and quality of life. Appropriate metrics are used. National health systems support the ERNs more and more, as they see the tangible benefits.
People do not really commit to their ERN participation. Under-resourced and under-supported, many HCP staff suffer burn-out. The setting-up of the networks attracted a lot of energy and goodwill, but sustaining them, when no improvements are seen, led to disenchantment	People contribute to ERNs with pride and HCPs are excited to participate – the administrative burden is minimal, time spent on core activities is recouped, and people live with a good work-life balance. Lots of younger people are attracted to work in RD, and have healthier careers.
Patients become disillusioned with ERNs. They receive no support or financial compensation for the time spent on activities and struggle to fund participation	Patient support for ERNs grows stronger. European Patient Advocacy Group (ePAG) and patient representatives formally engaged with the ERNs are properly supported to participate, not only in expenses but in terms of time commitment.
No centres or professionals outside the member of HCPs know about ERNs and no integration to national systems. No rules and no clarity exist to guide patient movement (physically or virtually) within the institutions of each country and abroad.	ERNs are fully integrated to national health systems. Patient pathways are clear for all rare disease groups with referral links between ERN HCPs and non-ERN centres of expertise in the country. Primary and secondary care professionals know how/where to refer patients to tertiary centres.
Orphanet no longer exists, or is now an archived site. No sustainable funds could be found. No national support to participate and contribute data. The orphaned nomenclature is outdated and information no longer accurate. There is no replacement resource, reducing our knowledge base for RD disastrously.	Orphanet as a pan-European (indeed Global) network of national teams, is thriving. It has sustainable funding, the national teams contribute regularly and actively to the central database (supported financially by their national governments/health systems)
Data reuse is hampered because of overly strict interpretation of the need for consent for all activities. Too strict definition of data ownership was applied, with disastrous consequences.	Countries remember that data can be collected without explicit consent for certain purposes, under the 'public good' and research umbrella. This enables research to flourish.

Demographic change of RD	
Increase of DALYs	Increase of average life in a good functional status
Patients are institutionalized	Patients are more productive for society and could stay at their home
Increase of economic burden	More financial balance
Family planning is more difficult	Family planning opportunity and support
Worst quality of life	Better quality of life
	Patients are more productive for society and could stay at their home

Threats to solidarity equity, and the prioritization of rare diseases	
What happens if equity is under increased threats?	**What happens if equity is at the centre of EU RD policies?**
RD patients face bleak and painful life, filled with fear, isolation and hopelessness about his/her life in the future	Patients have (good &safe) treatments choices that work for them personally & lead a normal quality of life with no guilt or feeling that are societal burdens
Worsen of the quality of life (economics): no work (discrimination too handicapped); no budget from the state; dependant on family;	Quality of life: appropriate work for specific patient, budget from the state, opportunity to be independent
Lack of money connected with a reduction of equity and political dimension	-
Lack of healthcare professionals – limited access to mean counselling	Investment in system/profession and number of providers: better knowledge about diseases – multidisciplinary collaboration
No funding, no research budget in Europe – explosion of public bodies	Reorganisation of the healthcare: education and reformation
Even further complexity and opacity in HTA used as subterfuge for reducing access and quality through Europe	Harmonisation of HTA and resulting transparency leads to more equal access to treatment across Europe
Cooperation (network) between diseases collapses under financial strain, leading to a free for all	Greater collaboration leads to more advanced tools to evaluate efficiency and better decisions on what works
Barriers between countries are established in order to avoid persons moving and accessing to healthcare in other countries	Similar healthcare services are guarantee across EU countries
EU falls apart and cross-border collaboration stops	The EU harmonisation in RD guarantees equal access to healthcare
Genomics becomes mandatory and RD patients are disadvantaged by the system – (penalised for not connective genes)	Genomics goes well and used for treatment and prevention but not politicised
RD is an outlier and therapies continues to be an expensive outlier – efficiency?	RD becomes a new modus operandi of healthcare – new delivery, reimbursement and business model. Effectiveness!
Segmented sources of information for patients	National contact points -well established information to patients

Some MS with strong economics and financial capacities will foster development of new therapies and research n the field of RD, while other MS will stay behind	EU voice in RD strengthen and equity is harmonised in all EU MS
Broad/wide national screening available in some MS but not in others; All orphan drugs accessible in some MSs but not in others FoM restricted by communicable epidemic with drug resistance	Agreed jointly basket of care includes RD diseases treatments

Increasingly empowered rare disease patient and the patient advocacy evolution	
What happens if patients are less empowered?	**What happens if patients are more empowered?**
● Less empowered patients are "easier to deal with" ● Less empowered patients can be considered "cheaper" if you only look at the healthcare and treatment costs	● Can be considered more "expensive" because they demand more but actually save money because they focus costs on their real needs and expectations ● More plugged into networks and associations ● More educated about managing their disease ● More knowledgeable on the ecosystem which requires a more reactive system ● More sustainability required of patient organisations ● Empowering patients saves money because patients are more active in their own health and help others. ● Patients have (good &safe) treatments choices that work for them personally & lead a normal quality of life with no guilt or feeling that are societal burdens

Facilitation of knowledge exchange and local care delivery through digital health	
Digital health managed in the worst way	**Digital health managed in a successful way**
Data manipulated by corporate interests	Patient generated data increase personalised care
No trust and no change in mentality, patients are not opened to use wearable technology, eHealth tools	Mutual trust for interoperability and exchange of data
Using CPMS increases burden on healthcare professionals	Digital health facilitates the work of healthcare professionals

New technologies and advanced therapeutics	
New therapeutics managed in the worst way	**New therapeutics managed in a successful way**
Technologies that cover unmet needs, including diseases that are typically underserved because very rare or because no investment in research has been made.	Concentration of innovation on small number of RDs the "usual suspects" that often do have already treatments available

Good redistribution across the EU territory.	Availability of new technologies in a limited number EU countries
More effective (quasi curative but often more expensive) treatments are available and refunded by the healthcare systems	Traditional pre-existing treatments (as often cheaper) chosen are more affordable for the healthcare system.
Patient relevant outcomes and experiences are essential part of the development and of clinical trials	Patient relevant outcomes and experiences are not part of the development of the therapies/technologies.
Development occurs in a pre-competitive space where data is shared amongst developers within agreed outcomes	No data sharing in a pre-competitive space, companies work in isolation.
Evidence generation is linked to market price of product	No link between the product's price on the market and evidence generation
Clear ethical rules and processes are in place.	New technologies are introduced with no clear legal/ ethical framework regulating their use
New therapies (especially referring to gene therapies but also gene editing) are provided with genetic counselling included in the guidelines of care	No genetic counselling is offered
Common clinical guidelines are available to all healthcare centres where the treatment/technologies are administered	New therapeutics are administrated in healthcare centres with no clinical guidelines shared across centres
Health workers involved in the delivery of new technologies are equipped with appropriate skills and competences	Health workers involved in the delivery of new technologies did not receive appropriate training and are not equipped with appropriate skills and competences.
New therapeutics managed in the worst way	New therapeutics managed in a successful way

3 RARE 2030 Scenarios Space proposal

3.1 From trends to Scenarios Spaces

In December 2019, EURORDIS and ISINNOVA reviewed the survey and conference's results to consolidate the structure of the scenario space around trend-related axes that capture the outcome of the discussion on trends at best. The RARE2030 scenarios axes must be independent in order to allow the foresight of truly alternative, contrasted futures, and promote discussion by highlighting possible trade-offs and synergies. On the other hand, scenarios axes should be intuitive and easily understandable by different stakeholders. The analysis focused on the following seven trends, all of them with high impact on the future of RD and a high degree of uncertainty:

- Greater inequality in access to treatments
- Threats to solidarity, equity and the prioritisation of rare diseases
- Strains on health budgets
- The emergence of new integrated care delivery models
- New knowledge, technologies and advanced therapeutics
- Rise of multi-stakeholder networking
- Rise in needs-led research

The trends were reformulated in two clusters to become the “lens” through which the future of RD and the evolution of the other trends are envisioned. A preliminary proposal of Scenario space was then built upon:

- **Societal attitude toward solidarity** (horizontal axis), capturing the first trends reported above and featured by higher public intervention pursuing 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), representing the other trends reported above, featuring population needs-led innovation on the top and technology-led innovation on the bottom

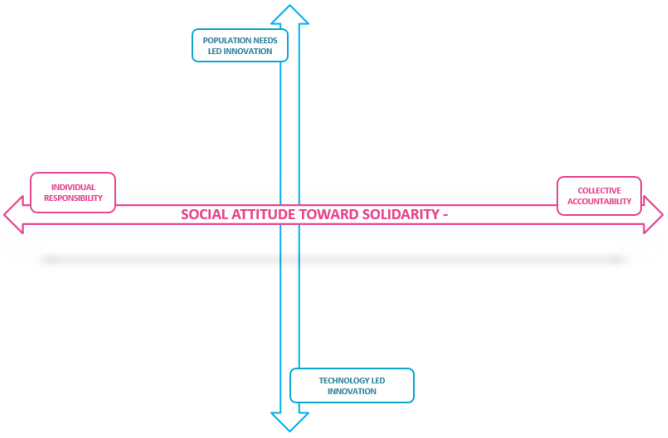


Figure 14 Proposal for Scenarios axes

To test the validity of the axes, EURORDIS has further elaborated their definition and ISINNOVA has run a preliminary test by imagining how the seven key trends could evolve under the four different quadrants identified (graph and table reported below).

Axis 1 - Social Attitude toward Solidarity (horizontal axis) One of the key question that this dimension underlies is Who is responsible for the health and well-being of people living with rare diseases? Government? Healthcare employers? People living with rare diseases themselves? Their families? People living with rare diseases may not only be physically disadvantaged but also socially not because of the individual's inability to fit in with their surrounding environment, but because of society's inability to include them.

- Individual Responsibility - Out of necessity, people living with rare diseases have often been required to take matters into their own hands? Is this ideal? In what circumstances is it "okay"?
- Collective Accountability - Equity means giving everyone a chance to achieve the greatest possible health and well-being. This is possible only if there is a collective responsibility to grant people living with rare diseases the same chance to achieve their greatest possible health and well-being.

Axis 2 - Type of Driver of Innovation (vertical axis) Innovation describes new, better, more effective ways of solving problems - in this case, related to the health and well-being of people living with rare diseases and to the systems that make it possible. Innovation can include policies, systems, technologies, ideas, services, and products (e.g. surgical innovations, epigenetics, CRISPR-mediated DNA modification, cooperation in healthcare delivery actors...) that provide solutions (e.g. to improve quality of care and patient autonomy, reduce harm, improve access, increase efficiency, eliminate waste, and lower costs...) to existing problems for people living with rare diseases.

- Technology-led Innovation We usually think about innovation in the life sciences as being technology-driven where innovation originates from scientific discoveries. When new technologies make it possible to move from the scientific domain to technology implementation, inventors and corporate R&D groups and companies compete to develop commercial applications. Across university research laboratories and throughout the biotech and pharma industries, scientific breakthroughs have been the launching point for major product developments in the traditional bench-to-bedside trajectory.
- Needs-led Innovation Over the past decade, however, a focus on needs-based innovation has emerged as an alternative strategy for innovation, particularly in the domain of biomedical technology (medical devices and diagnostics). Innovators are beginning to focus on developing a deep understanding of needs as the starting point of the invention process. In contrast, the technology-led approach first creates the technology innovation, then seeks out its market.

3.2 Partners feedbacks on the Scenarios space

ISINNOVA circulated a short note with the scenarios space proposal to RARE2030 partners in order to gather comments and suggestions. EURORDIS and ISINNOVA then held 7 bilateral calls with partners which allowed clarifying and refining the scenarios space features. The findings of these conversations are briefly summarized below in the form of 'questions and answers'.

1. **Which is the territorial level/ boundaries of the Scenarios?**

Rare2030 Scenarios adopt a European perspective. However, the regional workshops - planned from May to September 2020 - will articulate and test the scenarios in different national and regional

contexts. Besides, the Scenarios will look at international experiences and will coordinate with the vision and goals set at the international level – such as the International Rare Diseases Research Consortium.

2. **How should the term 'individual responsability' be interpreted? Does it just refer to the individual or does it also embrace a single company, organisation, country?**

Responsibility is considered individual when individualistic attitudes prevail, and this actually holds at different levels of society: from private citizen to organizations and countries. It aims to capture the rising trend of people and patients being more centred on themselves rather than on the society of which they are part – with the related positive and negative consequences. During the calls, a partner mentioned the work of Prof. Michael Schlander on social preferences as relevant for characterising the individual responsibility *vs* collective responsibility axis. *'A person exhibits social preferences if the person not only cares about the material resources allocated to her but also cares about the material resources allocated to relevant reference agents"* (E. Fehr and U. Fishbacher 2002[4]). This axis includes possible considerable change in society as well as a possible shift inside the RD community, foreseeing the risks of 'competition among diseases'. Also, this axis aims to record the level of collaboration between MS at EU level for RD strategies, actions and measures exploring a future with increased coordinated policy *versus* one where little progress is made in this area. One partner suggested characterizing this axis of social attitude as "fragmented vs coordinated" already capturing the consequences of the social and political changes. After discussing with the consortium it was decided to keep the original extremes providing a more precise definition of the concepts.

3. **Should the social attitude axis refer to equity more than solidarity?**

One partner suggested that the term *equity* would be preferable to *solidarity* as it would better capture the aspects related to healthcare[5]. Among others, partners suggested the work of John Rawls "Justice as Fairness: Political not Metaphysical[6]" to support the framing of the discussion. Other partners, however, consider that the term *solidarity* better describes a broader societal landscape entailing both individual and collective perspective as defined by Durkheim[7]

- the kind of solidarity practiced by peers within a family or a tribe, which they dubbed organic solidarity;
- the kind of solidarity binding very diverse members of a heterogeneous community based on relations of interdependence and complementarity, known as functional solidarity. Unlike the former kind, this solidarity is not automatic but the product of a members' awareness of the need to build it in order to ensure the community's survival. This is the kind of solidarity that

[4] Fehr, E., Fischbacher, U. The nature of human altruism. Nature 425, 785–791 (2003). https://doi.org/10.1038/nature02043

[5] WHO defines equity as "Equity is the absence of avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically. Health inequities therefore involve more than inequality with respect to health determinants, access to the resources needed to improve and maintain health or health outcomes. They also entail a failure to avoid or overcome inequalities that infringe on fairness and human rights norms". https://www.who.int/healthsystems/topics/equity/en/

[6] John Rawls (1985) Justice as Fairness: Political not Metaphysical Philosophy & Public Affairs Vol. 14, No. 3 (Summer, 1985), pp. 223-251 https://www.jstor.org/stable/2265349?seq=1

[7] Émile Durkheim, The Division of Labour in Society, Basingstoke, Palgrave Macmillan, 1984 (orig. ed. 1893) mentioned by SOLIDARITY 2.0 Marjorie Jouen | Adviser, Jacques Delors Institute policy paper

characterises the European Union. In order to last, its justification needs to be constantly renewed over time.

Even if the idea of equity is not explicitly mentioned in the axis, all partners agreed on this trend's relevance and on the importance of stressing it in the Scenarios Storylines.

4. **What do you mean with the term innovation? Is there any innovation which is not needs driven?**

It is important to note that the term innovation includes not just technology changes but also social and process related innovation. According to the definition provided by the WHO Health Innovation Group can be adopted: "*Health innovation is to develop and deliver new or improved health policies, systems, products and technologies, and services and delivery methods that improve people's health. […] Health innovation can be in preventive, promotive, therapeutic, rehabilitative and/or assistive care*[8]".

As a useful reference to investigate this axis, the work of Mariana Mazzucato[9] was suggested as it clearly diagnoses the problems of the current health innovation system and outlines the principles for how it can be better designed to deliver public health. "*A thriving health innovation system should generate new health technologies that improve public health and ensure access to effective treatments for the people who need them. However, our current health innovation system fails to direct innovations towards the greatest health needs, and is fraught with inefficiencies: when innovation happens, it happens more slowly and at great cost. Driven by profit rather than public health, the pharmaceutical sector is incentivised to set high prices and deliver short-term returns to shareholders, rather than focus on riskier, longer-term research which leads to critically needed therapeutic advances. The high prices of medicines are causing severe patient access problems worldwide, with damaging consequences for human health and well-being*"[10]. Even if Mazzuccato work refers to health innovation in general and not specifically to RD innovation – it offers a solid basis for framing the Scenarios.

During the interviews with project partners, it emerged how technology/innovation can improve treatment of rare diseases but can also hinder it. One example mentioned is that of the Orphan Drugs available for Fabry disease – for which we already have therapies but maybe not the best ones. In this case the availability of the current therapy is *de facto* hindering future basic research.

Another ideas collected was characterized the extreme of the innovation axis with *the profitability of investment vs the consideration if treatment is useful and sustainable for the health system*. Example: a company may decide to invest in product X because it is profitable, it covers a lot of patients or because the market is «ready» (for example the patients have been identified) without an evaluation of usefulness or sustainability of the product. However these aspects emerge clearly enough through the "needs led and technology led axis extremes characterization" provided in the scenario proposal.

5. **Who should be considered as an RD patient?**

More than one partner underlined the importance of clarifying, under "the RD needs led innovation", who exactly should be considered as an 'RD patient". The necessity was mentioned to also include under this definition under-diagnosed patients, ultra-rare diseases and diseases for which there is still no knowledge and research – thus innovation.

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[8] World Health Organization (2018) Promoting health through the life-course [Online]. http://www.who.int/life-course/about/who-healthinnovation-group/en/ (Accessed: 18 September 2018)

9 Mazzucato The people's prescription (October 2018) Re-imagining health innovation to deliver public value

10 Mazzucato The people's prescription (October 2018) Re-imagining health innovation to deliver public value

6. **How to define the needs under the 'population needs-driven innovation"?**

Partners proposed to refine the innovation axis to better account for the diverse perspective of the main actors at play when identifying the needs and setting innovation priorities. Accordingly, the axis would focus on 'innovation priorities", with one extreme featuring "needs definition and priorities setting carried out by patients and healthcare providers – or by multi-stakeholder collaboration', and the other featuring "needs definition and priorities setting carried out predominantly by profit/market". One of the reasoning behind this, is the consideration that the current needs spectrum may not reflect the actual patient needs and that technologies solutions are overestimated over social ones. What is the actual patient and family burden of the disease beyond clinical needs? Social needs? Psychological needs?

7. **To what extent is the education of doctors and healthcare professionals included into the innovation axis?**

One partner stressed the need to include how education and human capital development would change under the different Scenarios. The emergence of new mentality about treating people with RD would not be possible without new doctors trained to work in multidisciplinary team and able to use all of the ICT and web-based diagnostic tools. It was proposed to design the «Rare Disease doctor in 2040» with all the new skills needed to provide truly integrated and modern care. The future of healthcare professionals will require more and more to work with diverse, dispersed, digital, dynamic teams (4-D teams) in order to be able to attain high performance[11,12]. The idea is to include "human capital development" as a cross-cutting issue to be considered under the different storylines.

On the other hand, the importance to create a knowledge 'critical mass' and promote the creation of RD specialised institutes was also pointed out: specialised institutes should be able to work across basic research all the way to clinical spheres – avoiding fragmentation of expertise. Examples were made from cancer experiences which could also provide the economic case for supporting this evolution – a specialised institutes would allow quicker diagnosis and ensure better treatment according to agreed-upon standards of care – avoiding unnecessary medical tests or uneffected treatments. This allows laboratory diagnostics to be more centralised as well optimising the resources available.

[11] Haas M, Mortensen M. The Secrets of Great Teamwork. Harv Bus Rev. 2016 Jun;94(6):70-6, 117.

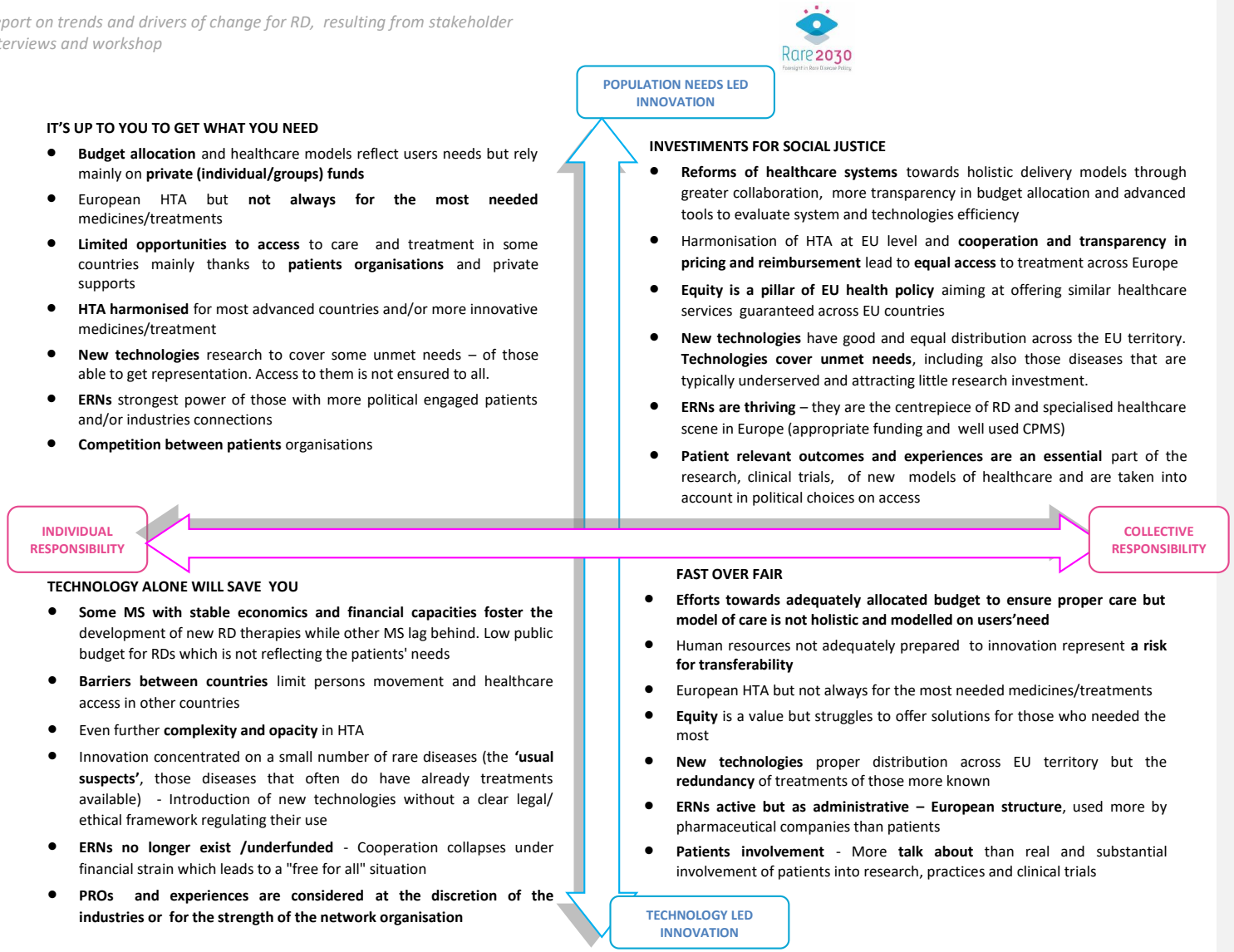
[12] Georgia Hay ."What diagnosing rare diseases can tell us about the future of work" [Online]. https://www.ted.com/talks/georgia_hay_what_diagnosing_rare_diseases_can_tell_us_about_the_future_of_work_jan_2018

3.3 Populating the scenarios space with RARE2030 partners

During the bilateral calls, EURORDIS and ISINNOVA gathered suggestions and ideas from RARE2030 partners on how the specific 7 trends reported in 3.1 section could evolve under the four different Scenarios. The graphs below were elaborated by ISINNOVA for promoting the partners discussions while the ideas collected in the calls and are summarised in the four storylines drafted below (sections 3.3.1 to 3.3.4.) These inputs will be further reviewed and refined in D5.2 where the final storylines will be presented.

Scenarios	***Equity***	***Access to treatment and care***	***Budget and new delivery models***	***New technologies***	***Multi-stakeholder networks***	***Patients led research***
Collective accountability and population needs-led innovation	Health - high EU policy priority – MS cooperation toward harmonisation and regulating the market and ethical framework	EU rule for HTA, greater transparency for price and reimbursement for treatment related to significant outcomes for patients	Successful reform of healthcare budget, transparency, equity and efficiency in allocation and new holistic delivery models set in most MS	Technologies oriented towards the most needed medicines/ treatment for patients	ERNs work effectively reflecting users' need	Patient relevant outcomes and experiences are an essential part of the research, clinical trials, new models of healthcare and are taken into account in political choices on access
Collective accountability and technology-led innovation	High EU priority – solidarity among MS, the ethical framework does not always take into account patients needs	European HTA but not always for the most needed medicine/treatments	Some MS succeed in transforming healthcare, others fail and do not manage to respond to population need	Innovation and technologies oriented towards the most profitable medicines/treatments for companies	ERNs more as administrative structure	More talk about than real and substantial involvement of patients into research, practices and clinical trials
Individual accountability and technology-led innovation	Crisis of solidarity between the EU, up to individuals find and pay for medical services	Opacity and MS' differences in HTA and access to care, barriers for accessing healthcare in other MS	Budget is not adequately allocated, low budget public resources for all and not allocated for users'need	New technologies are not modelled on user needs and are available only for those few groups that can afford	ERNs no more exist, collaboration is left to a few auto-organised groups and does not reflect users'need	Patient relevant outcomes and experiences are considered at the discretion of the industries or for the strengths of the network organisation
Individual accountability and population needs-led innovation	Empowered individuals and networks work with privates companies set innovation rules and framework (equity could be not fully ensured)	Limited opportunities to access to proper care and treatment in some countries mainly available thanks to patients organisations and private supports	Budget and healthcare models reflect users needs but rely primarily on private (individual/groups) funds and satisfy only group that can afford	New technologies reflect the user needs of only several influential groups, inequity in access for these innovations is seen	ERNs most active power of those with more political engaged patient and industries connections	Competition between patients organisations

Table 2 First testing of the RARE2030 Scenarios Space



IT'S UP TO YOU TO GET WHAT YOU NEED

- **Budget allocation** and healthcare models reflect users needs but rely mainly on **private (individual/groups) funds**
- European HTA but **not always for the most needed** medicines/treatments
- **Limited opportunities to access** to care and treatment in some countries mainly thanks to **patients organisations** and private supports
- **HTA harmonised** for most advanced countries and/or more innovative medicines/treatment
- **New technologies** research to cover some unmet needs – of those able to get representation. Access to them is not ensured to all.
- **ERNs** strongest power of those with more political engaged patients and/or industries connections
- **Competition between patients** organisations

INVESTIMENTS FOR SOCIAL JUSTICE

- **Reforms of healthcare systems** towards holistic delivery models through greater collaboration, more transparency in budget allocation and advanced tools to evaluate system and technologies efficiency
- Harmonisation of HTA at EU level and **cooperation and transparency in pricing and reimbursement** lead to **equal access** to treatment across Europe
- **Equity is a pillar of EU health policy** aiming at offering similar healthcare services guaranteed across EU countries
- **New technologies** have good and equal distribution across the EU territory. **Technologies cover unmet needs**, including also those diseases that are typically underserved and attracting little research investment.
- **ERNs are thriving** – they are the centrepiece of RD and specialised healthcare scene in Europe (appropriate funding and well used CPMS)
- **Patient relevant outcomes and experiences are an essential** part of the research, clinical trials, of new models of healthcare and are taken into account in political choices on access

TECHNOLOGY ALONE WILL SAVE YOU

- **Some MS with stable economics and financial capacities foster the** development of new RD therapies while other MS lag behind. Low public budget for RDs which is not reflecting the patients' needs
- **Barriers between countries** limit persons movement and healthcare access in other countries
- Even further **complexity and opacity** in HTA
- Innovation concentrated on a small number of rare diseases (the **'usual suspects'**, those diseases that often do have already treatments available) - Introduction of new technologies without a clear legal/ ethical framework regulating their use
- **ERNs no longer exist /underfunded** - Cooperation collapses under financial strain which leads to a "free for all" situation
- **PROs and experiences are considered at the discretion of the industries or for the strength of the network organisation**

FAST OVER FAIR

- **Efforts towards adequately allocated budget to ensure proper care but model of care is not holistic and modelled on users'need**
- Human resources not adequately prepared to innovation represent **a risk for transferability**
- European HTA but not always for the most needed medicines/treatments
- **Equity** is a value but struggles to offer solutions for those who needed the most
- **New technologies** proper distribution across EU territory but the **redundancy** of treatments of those more known
- **ERNs active but as administrative – European structure**, used more by pharmaceutical companies than patients
- **Patients involvement** - More **talk about** than real and substantial involvement of patients into research, practices and clinical trials

3.3.1 Investments for social justice

New Delivery model. Under this Scenario, most of national healthcare systems are successfully reformed toward models able to ensure holistic and patient-centered services. The transition has been achieved thanks to:

- Greater collaboration between institutions and stakeholders,
- More transparency rules in budget allocation,
- The systematic adoption of advanced tools to evaluate process and products efficiency.

ERN. ERNs work effectively reflects users' needs and are well integrated in the national health care systems

Innovation and equity in access. New technology therapeutics and diagnostics are distributed equally across nations - regardless of where patients live in the EU- and ensuring equal access to treatment is a top policy priority at all government levels (regional, national, EU). This is also due to the progress made in the harmonization of HTA at EU level and the greater consideration for "societal aspects" in the score assessment for HTA. In addition, a unique EU body is now responsible for pricing negotiation and it guarantees enhanced cooperation and transparency in pricing procedures and in reimbursement procedures.

Research and Knowledge creation. Most of healthcare systems have established specialised RD Centresand have created "healthcare pathways" specifically for RD patients. Centres of Expertise are connected by well-funded networks, cover most rare diseases, and adopt a multidisciplinary and transnational approach. They centralise the knowledge around diseases in one place creating a critical mass of patients needed for research and clinical trials. This results in faster diagnosis, better – improved as well as integrated - quality of care. Patient relevant outcomes and experiences are an essential dimension of research, clinical trials and their inputs are key for designing new models of healthcare. There is great investment to create knowledge able to cover as many diseases as possible – and not just focusing on the "low hanging fruits". There is greater awareness of rare disease as a concept at all society levels: from citizens to academics and policy makers.

The academic system has gone through a fundamental reform oriented to create incentives for collaboration and sharing of data. Clinical research is rewarded only if all data to accomplish it are shared too. Within time, researcher behaviors shifted from competition to cooperation.

Research priorities. Research health priorities are mission-oriented and set by multi-stakeholders consultations in which citizens and patients inputs are highly evaluated.

Data. Resources have been made available to facilitate data collection and data sharing and agreement signed for data standards across countries. Data are currently collected by multiple stakeholders, including patients, using more mobile apps and personal apps. These applications represent collaborative resources to exchange and collect data together and in the same way. There isn't, however, a single standard for data collection but a single model for enabling different standards to link data together. The following two actions have allowed for this change at the EU level (ie. MS have to agree):

- *Common infrastructure:* Funding agencies grant a small percentage of their budget into a common pot to sustain data infrastructures (eg. ELIXR, Orphanet) which are indispensable for innovation and research.
- *Education and training*: EU funds trainings and supports patient registries, i.e. JRC and standardised capacity building and EJP to interoperate the existing registries.

3.3.2 Fast over Fair

New delivery model. Under this Scenario, national healthcare systems have adopted different processes and solutions to ensure proper treatment and care to all citizens. However, most systems are facing difficulties to adopt new long-term organisational models and simply respond to the most pressing needs and challenges as they emerge.

ERNs are solid administrative structures but achieve limited impact in patient's life. Often the network strategies are limited to promote cross-border health.

Innovation and equity in access. Generally, the dynamics of innovation ensure sporadic results in the most profitable areas which, once available, are distributed equally across member states. Pricing negotiation is still managed at national level and EU policies play an important role in reducing inequity by promoting healthcare reforms and supporting cross-national healthcare access. Innovation and technologies are oriented towards the most profitable medicines/treatments for companies. The stock exchange seems to exert the greatest influence in deciding which products to develop and market. As a result, even if progress is made for the European HTA – it does not always affect the most needed medicine/treatments.

Research and Knowledge creation. Many healthcare systems have set specialised RD Centers, but those often focus on few, well-advanced disease areas (example of cancer clinics). The creation of "healthcare pathways" specifically for RD has achieved mixed results depending on the local context and on the human resources preparation. In fact, healthcare professionals are highly specialised but not always adequately prepared to make the best use of innovation technologies or work with trans-disciplinary teams. Competition is high between centers and researchers, which significantly limits the sharing of knowledge and data. The academic system partners with large industries and adopts typical traditional rewards to motivate academics, which do not always factor in public benefit or strategy. Genomics is developing dramatically and it is perceived as a commodity, used by individuals at their own will and commercially exploitable.

Many structures have developed and adopted guidelines for stakeholders' involvement, but in many cases it corresponds more to a policy declaration than to a real and substantial involvement of patients into research, practices and clinical trials. In some countries, distrust toward science and researchers increases.

Research. Health research priorities are primarily set by public-private partnerships with the occasional and voluntary consultation of citizens and patients' inputs.

Data. Big platforms for data collection exist but they are not directly populated by patients. There are no public strategies on what kind of data should be collected and little attention is dedicated to quality of life indicators.

ERNs collect only data from those patients visiting their hospitals and data entry for rare diseases is made by «professionals» but not so much by patients. Generally, patients have little control over their own health records. The data collection product is of high quality but managed primarily by private companies, and patients are not consulted on the development process. Some companies have adopted ethical frameworks on data use and protection and in some exceptional virtuoso cases they collaborate in data sharing to advance research and innovation.

Example. Global Commission (public/private partnership between Microsoft, Shire/Takeda and EURORDIS) to speed up diagnosis and therapies. This coalition works because it includes multinational frameworks that already have data sharing agreements across boarders… "Freedom to 'link' data".

3.3.3 It's up to you to get what you need

New delivery model. Under this Scenario, national healthcare systems are not always able to offer care adapted to the patients' needs for financial as well as organisational reasons. On the other hand, private healthcare systems are blooming and provide a holistic approach and advanced care to those who can afford it. Better opportunities to access to integrated care and treatment are available in some countries and the EC supports patients' cross-border access to care.

ERNs develop along differentiated paths, as those with more politically engaged patients, better industry connections or larger partnerships with chronic or communicable diseases have assumed strongest relevance and powers. Patients organisations are competing for funding, policy support and for attracting talents.

Innovation and equity in access and equity in access. There are great advancements in new technologies and research in specific fields, which lead occasionally to great benefits to the whole population. However, innovations are irregularly distributed. This is due also to the progress made on the harmonisation of HTA at EU level and to the greater consideration now placed on "economic aspects" in the score assessment for HTA. Pricing negotiation is still managed at national level even though patients' movements played an important role in reducing inequity and in promoting healthcare reforms. Diagnosis and care pathways are optimised only for some patients' groups while patient's organizations and private supports play a key role in designing pathways for the less known diseases and ensuring funding for those who need it most. This scenario features high competition between universities and exponential growth of private institutions. Medical attention is focused on the most profitable diseases while no progress is made on advancing awareness and knowledge of RD.

Research. Health research priorities are driven by collaboration between the private sector, the public sector and the most powerful patients' and organised groups.

Data. Only some citizens/researchers/companies that are conscientious are keen to organise data, registries and collaboration with other industries. Due to a lack of public response or «out of necessity» only some disease groups/areas thrive and become game-changers and exceptional innovators. For a minority of rare diseases, data collection initiatives like registry platforms for Duchenne muscular dystrophy or *Cystic fibrosis* are greatly advanced. In these cases, patient organisations have managed to acquire substantial resources and expertise to create infrastructure and seamless routes to be used by patients.

3.3.4 Technology alone will save you

New delivery model. The majority of healthcare systems have failed to change and now are facing a crisis due to the budget constraints and a growing older and sick population. Treatments are more and more expensive, there is a low public budget for RDs not reflecting the needs.

ERNs no longer exist; collaboration is left to few auto-organised groups. The big nine corporations--Amazon, Google, Facebook, Tencent, Baidu, Alibaba, Microsoft, IBM and Apple—though extensive use of AI offer some kind of healthcare support information and use the data acquired for their benefits.

Equity in access. Innovation is rather sporadic in this scenario, with significant inequalities across MS. The majority of Centers of Expertise for Rare Diseases are privately funded and not connected by Networks. Only few MS with strong economic and financial capacities have established care pathways, specialised centers and are fostering the development of new RD therapies while other MS will stay behind. There is no harmonisation of HTA among EU countries, and neither cross-border access to treatment nor internal movement of workers are allowed.

Research. Health research priorities are set primarily by collaboration between private interests.

Data. MS have developed their own bespoke registries and e -health record platforms with hardly any awareness of what other MS are doing. There is no coordination on data standards, and data linking platforms (RD Connect and Match Maker) have disappeared after a major breach/scandal in data privacy. The world is back in the time of "data silos". Without ERNs support, registries are run by individual clinicians and are local. Patients aren't really able to access the data to amend it or share it across boarders/clinics/research purposes.

On the other hand, companies are collecting a multitude of data on patients without their knowledge or without their full understating the ramification of handing their data over.

Example: *23 and Me* service and other direct-to-consumer testing. How informed are the patients? They have freedom to use their data but are not well informed of how they are used by the service provider. This could be true for genetic data but also for any data.

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4. Reviewing the scenarios space with partners and external experts.

4.1 Agenda and participants

On February 6th, 2020, EURORDIS organised an event with RARE2030 partners and a number of external experts in order to present the Scenarios axes and gathers a first round of ideas and contributions. The final agenda of the event, as presented below, provides an overview of the various sessions and topics addressed.

6.02.2020	**Topic**	
09.00 - 09.10	Introduction and welcome addresses	Yann Le Cam EURORDIS
09.10 - 09.30	Tour de table	All participants
09.30 – 10.10	RARE2030: project results and next activities and ECRD2020 Conference	Anna Kole EURORDIS
10.10- 10.40	Open discussion: RARE 2030 Scenario space	Anna Kole EURORDIS and Giovanna Giuffrè ISINNOVA
10.40 – 11.00	Coffee break	
11.00 – 12.20	World café: RARE2030 Scenarios (4 tables, 20min each)	ISINNOVA AND EURORDIS
12.20- 12.40	Table reporting	ISINNOVA AND EURORDIS
12.40-13.00	Wrap up and Closing	EURORDIS

In addition to eighteen project partners, nineteen external experts participated in the RARE2030 workshop discussing, from their own expertise perspective, the challenges and opportunities arising from the possible Rare Diseases futures. All the external participants are actively involved in the organisation of the 10th European Conference on Rare Diseases and Orphan Products (ECRD) that given the current pandemic will be held online in May, 2020 with the theme "The journey of living with Rare Diseases in 2030". The following organisations were represented – providing a truly multi-disciplinary and trans-national discussion group:

Chiesi Farmaceutici	ENDO ERN	MedTech Europe
Chronic Myeloid Leukemia (CML)	European Joint Programme on Rare Diseases	Rare Disease Sweden
Committee on Orphan Medicinal Products, European Medicines Agency	European Medicines Agency	Rare Diseases UK
DIA	EURORDIS	SANOFI
Dravet Syndrome European Federation	Institute of Biomedical Sciences, Vilnius University	World Duchenne Organisation

Table 3 Organizations represented at the RARE2030 event

4.2 The introduction

Yann Le Cam, (CEO EURORDIS) opened the meeting introducing the RARE2030 team and the representatives of ECRD. After a tour de table which gave the opportunity to each participant to briefly present his/her background, the speaker reminded the importance of producing anticipatory and 'future proof' policy recommendations for RD governance in the upcoming years. In order to do so, it is critical that all experts promote and support the policy dialogue at different territorial levels – global, European as well as national and regional. In light of this, Yann recalled the forthcoming events organised in the framework of RARE2030 to engage stakeholders in the policy discussion – focusing especially on the regional workshops planned between May – Nov 2020 in those countries that will hold EU presidencies in the upcoming years.

Anna Kole (EURORDIS) presented the workshop agenda and the event threefold objectives:

- Understanding the Foresight process and outcomes of Rare 2030 reflections in more detail – bridging the gap between Rare 2030 partners/experts and the ECRD programme committee;
- Developing future scenarios from the expert point of view;
- Considering how RARE2030 narratives could be included throughout ECRD 2020.

The speaker introduced the ECRD Agenda and themes, highlighting for each session the possible contributions that the RARE2030 project could provide:

- Theme 1: The future of diagnosis: new hopes, promises and challenges
- Theme 2: Our values, our rights, our future: shifting paradigms towards inclusion
- Theme 3: Share, Care, Cure: Transforming care for rare diseases by 2030
- Theme 4: When therapies meet the needs: enabling a patient-centric approach to therapeutic development
- Theme 5: Achieving the Triple As by 2030: Accessible, Available and Affordable Treatments for People Living With a Rare Disease
- Theme 6: Future direction in digital health: hype vs reality

It was reminded that a webinar to bridge the project work and the conference discussion will be organised on April, 23rd from 14.00 to 15.00 CET. The webinar – that will then be available on-demand on the project website, will be the opportunity to hear the latest outcomes of the project and understand how the study lays a foundation for policy discussions throughout each theme of the ECRD.

Anna then gave an overview of the project phases reviewing the results achieved in each phase: from the 12 trends selection to the trends ranking and concluded with the presentation of the RARE2030 Scenario Space proposal. The discussion was opened and participants were asked to review the Scenarios axes by answering to the questions:

- To what extent do you think the two proposed axes are 'independent' one from the other and able to capture the trends which were considered most important and uncertainty for the future of RD?
- To what extent do you think the axes and their proposed "extremes" are clear and can be easily understood by different EU, national and local stakeholders and policy makers?

Below a short summary of some of the many comments related to the scenarios space:

- Regarding the definition of the innovation axis, the possibility of renaming it "innovation

priorities" (instead of "innovation types") was suggested, in order to take a perspective that stresses the role of actors who set R&D priorities and incentives;

- As for the terminology used in the innovation axis on the lower extreme, the possibility to use the term "market-led innovation" rather than "technology led innovation" was raised. It was also suggested to reflect on conditions under which patients can best lead innovation and evaluate the capacity of the healthcare system to evolve and adapt.
- Regarding the solidarity axis definition, the need to include a country and corporate perspective through the imagination of dominant culture that could be more competitive/fragmented vs collaborative was mentioned
- It was asked to what extent social aspects (e.g. insurance) are included into the solidarity axis and suggested to better define to what extent this axis is specifically focused on healthcare or encompasses societal aspects more broadly.
- It was asked to also consider the difference between equality and equity as possible extremes of the solidarity/fairness axis.
- The need to include healthcare skills and capabilities as cross-cutting issues of the Scenarios development was also observed.
- the opportunity to liaise the RD Scenarios with broader healthcare economic and political changes was raised, also to take into account how the RD Scenarios would be linked with overall patients' needs.

4.3 Session "World café: RARE2030 Scenarios"

Participants were divided into four tables representing the four different futures of RARE2030 Scenarios Space and were asked to answer the following question:

- *We are in 2030. What do you think has changed fundamentally in institutions, techniques, infrastructures under the proposed Scenarios?*

The sections below present the participants' interactive group work results on the four Scenarios as reported by the four group tables moderators. Group participants post-it and inputs were revised only to ensure storyline style and some comments received after the event were included. It is important to note, however, that in presenting the entire set of remarks and comments offered by stakeholders we might incur in some inconsistencies. In the next report, we will systematically review all the inputs received during the different consultations in order to confer coherence and plausibility to the storylines.

4.3.1 Investments for social justice

The Rare diseases community has moved forward from explaining the needs of RD patients to implement solutions that could best address those needs. Solutions are tailored to the needs of the different diseases and take into consideration the different local context. Major investments have been made by governments to ensure people's health and well-being in a social justice principles scenario. There is great awareness of rare diseases in society. National and regional governments collaborate together to gather as much information and tools to understand and provide the best care for people living with rare disease (PLWRD) in Europe.

The role of EU. The EU has increased legislative power. Theh the reconsideration of common values facilitates MS benchmarking and the monitoring for free rider MS, reducing the risk of a two-speed EU, with some coalition of countries moving toward a transformation while others lag behind.

Multi-stakeholder fora and partnerships, which are the norm in the different fields (regulatory, research, organizational), have been pivotal in promoting change thanks to the increased decision power they accrued over the years (no longer purely advisory).

The Market (for healthcare products, pathways, systems) is shaped by multidisciplinary fora/settings always involving patients, regulators and companies. A "Check and balance approach" is widely adopted in order to ensure equal (opportunities for) representation among all groups of citizens/stakeholders/companies. "Leaving no one behind" is a must for health policies at all territorial levels (Theory of justice, Rawls, distributive justice). This has led to an increased recognition for RD, including for ultra-rare RD. Communities and networks of rare diseases are active at different territorial levels and especially at global level for ultra-rare diseases. These networks play a key role for informing policies and strategies in a more complex and rapidly changing world.

EU Healthcare systems (Super-max Model) are needs-led, outcomes-driven systems thanks to the strengthening of our capacity 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. There is a greater societal responsibility and regulatory powers. Healthcare systems management is effective, budgets transparent, interventions evidence-based and data protected. Optimal outcomes are based on a growing evidence-based achieved through greater collaboration. Regulations balance market incentives in order to drive down service-costs and incentive innovation system responsiveness/flexibility.

Research. Multi-stakeholders initiatives steer decisions on the priority of investments on rare diseases that allow to obtain the biggest advantages of advanced technologies for the development of therapies as well as diagnostic tools, specifically meaningful for rare diseases patients. Research is increasingly mission/solutions oriented and research organizations are able to collaborate across countries and diseases. Teams are trained to collaborate in complex processes – sharing and building up on discoveries and knowledge. Many organizations share 'common incubators'. A new culture paradigm bridges between specialties, sectors, stakeholders with the aim to improve and accelerate organizational and technological innovation as well as transfer. The results/discoveries achieved in the RD field are increasingly transferred to tackle more common diseases (model of solutions) while the process offers a learning area for new ways of working and collaborating. This is the result of the 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.

Innovation. There is a greater transparency, accountability and cost-effectiveness evaluation of budget spending. New technologies are evaluated for their effectiveness to respond to needs. The innovation is organizational (process-related) as well as technological (products and services). Diagnostic and evaluation are made by one team in one place. The outcome leads to access the best available

treatment and to the provision of all other supporting services in society –- Cross budgetary Holistic care is provided and there are less inequalities between MS.

Healthcare model. Most healthcare systems have adopted a personalized approach and are structured around networks of services. RD healthcare has become a model for other services by experimenting and validating pathways that offer 'individualized, holistic outcome' in one time and in one place in structured network of services. "Rare is somehow not rare anymore" because there are professionals able to understand the diseases and offer the best available care, cure and treatments. The definition of rare is now including those patients most in need and vulnerable. Well-developed networks of doctors who compile their patient's data into common and open databases that include health and genetic data of people living with the same disease allow a quick and accurate diagnosis. Doctors can also quickly and easily ask the opinion of other experts across Europe through virtual consultations. PLWRD are less burdened with the need to find their own solutions to faster and better diagnosis and treatments and can meet their needs in specialized centres of care that consider all health and social needs together. As these centres are connected across Europe, the new technologies that are available for someone living with a rare disease in one country are therefore available for those living in another country ensuring equity to access to care between MS. Support services as school-labor and insurance (BIG 5) are provided by society. Cross-programmes and cross-budget initiatives deliver holistic care ensuring the best quality of care.

Data. Production and collection of big data goes beyond consumer and profit-driven companies. National healthcare systems and health insurers collect sensitive health data showing a strong societal responsibility with good data governance and protection.

4.3.2 Fast over Fair

Health is managed by the public system but also by the teaming-up of many different actors who work together when they have common goals. Advanced technologies for improved diagnosis and treatment are available and see the collaboration between multiple private and public stakeholders, but only when they share the same interests. These new advances however are possibly limited in ethical/social oversight of their implementation. 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.

EU Healthcare systems (Federated Model) are payment led and characterized by greater interoperable system and streamlined, mature regulation. A greater collaboration of different stakeholders and better interoperable system, enriched with data, are used to inform better health decision. Driven by budget constrain, services are prioritized and reduced but remain free at the point of access. However, 'top-up payments' are increasing for new innovation and therapies for those how can afford to pay.

Innovation ensures the fast identification of tailor-made treatments for each individual. Companies and regulators decide what is profitable and a small group of decision makers agree that certain groups will be "left behind". Major risks in leaving certain PLWRD behind results from a lack of discussion/reflection of what kind of society people want. Incentives are set for intermediate steps (e.g natural history studies) to support the successful market launch of products. The innovation is often based on existing knowledge thus shortening the cycle of research and development. Progressively increased pressure on

containing public cost of innovation drops and shortens the length of IP (intellectual property). This pathway runs the risks of saturating certain diseases areas (e.g. metabolic diseases) or to create a stagnation for new more advanced technologies. Generally, innovation aims to "faster commoditization" and is more focused toward efficiency rather than piloting breakthroughs. Innovations are pushed to "proof of concept" in the easiest way therefore often going to the "lowest hanging fruit".

New technologies: the speed of new technologies is what has allowed more rare diseases to have treatments developed for them. This scenario encourages new treatment: rare diseases are researched and OMPs are rewarded as long as their orphan status is recognized as profitable. Direct to Consumer testing companies continue to proliferate outside of any healthcare system. These tests yield people knowledge of their genetic predisposition but since health systems struggle to "manage and rule" this scenario, this testing introduces risks of privacy and of correct information for patients and consumers.

Access to care. Diagnosis and care are facilitated by technologies and multi-stakeholder mechanisms are in place to assess, select and develop innovation assets with the potential to benefit the most vulnerable. Ineffective healthcare is dismissed for saving on effective innovation, especially in health care service provision. Those who have access have better health outcomes but the risks are that services would only be the ones that are profitable and skills and knowledge are only those considered 'productive' (loss of knowledge and skills when it comes to healthcare).

Education. Access to education on products/services related to rare diseases is rather harmonised across all stakeholders to ensure that all users are prepared to actually use new technologies. Patient organizations often work together across countries and diseases to empower and focus on the unmet needs of PLWRD in different EU countries.

Data. The IT revolution has allowed structured data collection but there isn't a common agreement on the ethical framework (e.g. like in the film GATTACA: future society driven by eugenics where potential children are conceived through genetic selection to ensure they possess the best hereditary traits of their parents). Patients, healthcare professionals, researchers and companies see the value of collecting data on a large scale and in a common way and share their data for the "greater good". The technologies needed to do this is in place but respond to the market needs and pressures and are not designed to be sustained on the long term. Data governance and protection are, somehow, ensured but data management may become exclusive (ie. only certain groups can afford and are able to access data and others cannot).

4.2.3 It's up to you to get what you need

This scenario is characterised 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 a half revolution. The limited resources and the lack of coordination among MS have created wide disparity between patients depending on their country, type of diseases, knowledge, social networks and economic resources. Due to a weakening of the collective vision and strategy, competition is growing between diseases and intra-rare diseases groups. You can access the care you need, if you can make it.

Healthcare systems (Two-tier model) are price-led, demand driven. Main characteristics are the greater prioritisation of services against population needs with the 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 stretched leading to limited flexibility for innovation except for those new models of care and service improvements that drive cost-containment/savings. Top- up payments for new innovation and therapies are privileged and available for those who can afford to pay. The increased bureaucracy and regulation make meeting needs even harder.

Multi-stakeholder networks do not exist or only in a bureaucratic way as there is less investment in networking and cooperating at European level.

Research is characterized by "silos" reflecting the interests of the more represented and powerful groups. Private research funding increase and competition is on the rise. As consequence, great advancements are hampered by the lack of sharing and cooperation between researchers. Some coalitions between research groups are however established to increase their political power.

Innovation. Under this Scenarios, there are limited incentives and a slower approval system of innovation to manage budget exposure and associated costs, general innovation focuses on process and systems, not on drugs or technologies.

New technologies and therapeutics are developed with the active role of patients in a co-creation process, shaped by their needs. There is a flourishing of biotech industries and digital health companies which are highly specialized only on specific needs of specific groups of patients.

Access to treatment and care. Access to treatment and care is guaranteed only to the most powerful groups that can see their needs met. Inequities persist and increase. The deployment of the potential for holistic care and for personalized medicine occurs only for the most important diseases and the most represented diseases' groups.

Data. Data sharing is fragmented. A market of data is established especially to drive research for particular diseases groups, creating strict link between private companies and patients' associations. Data sharing is an individual/ single groups choice. Data protection is not ensured, patients have to take their personal responsibility and risks.

Empowerment and engagement. Only those patients empowered and engaged to advocate for their health and to express their needs manage to be listened to and included in the healthcare systems. It's left to patients' individual responsibility to acquire those skills (education/training) which would 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 people living with rare disease but they do not necessarily work together to achieve common goals on the European level. For example some networks of patient organizations, researchers and doctors manage to cooperate in collecting information around a disease to make advancements but this progress is random and irregular. As such there is much competition between disease areas, both rare and common.

4.3.4 Technology alone will save you

Under this Scenario, the market leads the choice, only few people have power and many are left behind. Only the strongest survive: huge inequalities between rich and poor / educated and not educated people are seen. Private companies have a greater role in managing the health of people living with rare diseases. Technology advances are quite developed enabling a full personalized healthcare or "designed treatment". These innovations can help PLWRD in their everyday life but leave them largely responsible for their health and the protection of their rights.

Healthcare Systems and access to care: Private Insurance-based, market-led, profit-driven system (US private-model, with limited free-access of care. 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.

Multi-stakeholder partnership: Google (health) replaces ERN.

Research is fragmented and not coordinated at global level. Questions arise about the type of research and treatments under development as decisions are driven by the social and financial power of few better-off individuals (including groups of stakeholders). Research efforts are duplicated with strong inefficiency which leads to the delay in meaningful results for care.

Innovation and new technologies. The market chooses treatments available/under development focusing on the more profitable products. Treatment prices increase as an effect of the decision taken by companies also influenced by the stock exchange market. Direct to consumer gene testing are widely accessible with increased risk of abuse. Unauthorized treatments are quite common.

Data are commercialized and new types of businesses arise such as the explosion of consumer genomics. People can enter their personal health data and independently participate in research but data are used by private research groups and companies under limited data protection and high personal risk.

Patients organizations have been replaced by technologies that allow patients to manage their own needs and those that have access are at times sufficiently empowered to develop breakthrough technologies themselves.

The role of EU: the European Union still exists but only as a formal union of states, without concrete power to influence national health decisions and global policies.

Conclusion and next steps

In the upcoming month, the project team will review and finalize RARE2030 Scenarios ensuring plausibility and consistency to each storyline. Then, in the fourth and last step of the foresight process, stakeholders will be invited to define policy options, strategies and targets. In this "the back-casting phase" (May-December 2020), we will combine a normative and a preparedness approach. The first one aims to find a consensus on the most desirable Scenario and identify the most impactful policies to move toward the identified vision. Stakeholders will collaborate to draft a roadmap by setting priorities and goals, gathering examples of best practices and niche experiments and spotting major gaps in research that should be filled now to develop innovative and effective future policies. Conversely, the "preparedness approach" aims to evaluate strategies and actions direct to react to the less favorable RARE2030 scenarios. It highlights "reactive strategies" that could respond and mitigate risks due to global changes or events outside policy control.

In line with the participatory dimension of the project, events will be organized at European and national level so to ensure the inclusion of wide and diverse views in drafting the RARE2030 policy recommendations. Among the planned activities, the European Conference on Rare Diseases and Orphan Drugs (ECRD), held on streaming from 15-16th of May 2020, will serve as an opportunity to evaluate the plausibility and consistency of proposed scenarios and brainstorm on policy priorities and actions. The citizens' conference (July 2020) will bringing together 30 young citizens from 28 EU member in order to gather opinions and fresh look into actions and options to move toward the future we want. Then, four regional workshops will be organized between May and November 2020 to down-scale the scenarios description to different territorial contexts and include national policy and actors into the European perspective.

At the time of writing this report, Europe has become the epicentre of the Coronavirus pandemic with daily death rate in Italy, France Spain, and the UK. The coronavirus has changed the way we all live, work and interact and rise an up enormous uncertainty – political, economic, social and technical – on what the world and European society might look like in the next decade. The project team will review the current foresight news and articles in order to get insights on how the foreseen global landscape shifts might interact with RARE2030 Scenarios and get a better understating on the risks and opportunities the rare disease community might face. The final aim will be to produce 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"[13].

[13] M.Friedman (1962) "Capitalism and Freedom" (strangely) quoted by Naomi Klein in the "Coronavirus Capitalism": Naomi Klein's Case for Transformative Change Amid Coronavirus Pandemic" https://www.youtube.com/watch?v=IFqNAEx1Im4&feature=youtu.be&t=52