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RARE DISEASES

Value-based healthcare, screening programs and policies

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Editorial

NEW HORIZONS IN RARE DISEASE CARE IN EUROPE: WHERE ARE WE AND WHERE ARE WE GOING?

ALEXANDRA IVANOVA AND ÁLVARO HIDALGO

Weber Foundation

We are at a significant turning point from a legislative perspective in the pharmaceutical sector. The European Parliament voted last April in favor of European pharmaceutical reform, which could drastically change the framework for innovation. This raises the need to understand and assess the proposed changes in relation to the risks and opportunities they might pose for patients with rare diseases. Another notable item within this new regulatory framework is health equity in Europe and how to mitigate inequalities. The importance of working to achieve quick diagnosis with equal access to patients across countries and regions is highlighted.

One of the priorities in the current political context is ensuring that Europe can be seen as a leader in rare diseases. To this end, efforts must be made toward an EU Action Plan on Rare Diseases that combines the strengths of all nations, thereby placing rare diseases at the forefront of national and European political agendas. All of this aims at one ultimate goal: finding ways to provide better care for patients with rare diseases.

In this current landscape, the second international issue of the newsRARE journal is born, with the primary focus on reviewing pharmaceutical policies and the evaluation of innovative medicines from 2021 to today; analyzing the differences between countries and regions in terms of neonatal screening and early diagnosis; and lastly, but no less important, exploring the possibility of evolving toward value-based healthcare systems for patients with rare diseases and their families.

Public Policies Aimed at Improving Access to Innovation and Providing Comprehensive Care

Caring for rare diseases (RD) is complex due to their heterogeneous and multidisciplinary nature, geographic dispersion, and low prevalence. In this context, the implementation of effective comprehensive care policies becomes crucial to improving the quality of life for patients.

Rare diseases affect a relatively small percentage of the population, which often results in a lack of recognition and resources dedicated to their care. However, the chronic nature and, in many cases, progressive nature of these diseases demand continuous and specialized care. Detection policies must focus not only on early diagnosis but also on identifying at-risk patients, thus facilitating quick and effective access to treatments and ensuring equity.

Coordination between different levels of the health system, as well as between various disciplines and sectors, is essential for adopting comprehensive care policies. This includes collaboration between geneticists, pediatricians, primary care physicians, and other health professionals, who must work together to share knowledge, experiences, and resources. It is also crucial to promote the creation of reference networks that facilitate access to specialized centers, ensuring that patients can receive high-quality care regardless of their location.

Furthermore, the inclusion of measures that promote research and the development of new treatments is essential. Policies should encourage collaboration between academic institutions, the pharmaceutical industry, and patient organizations to promote innovation and the search for effective solutions. The creation of incentives for rare disease research can facilitate the discovery of new biomarkers, therapies, and diagnostic approaches that are accessible to patients.

It is also important to highlight the relevance of the active participation of affected communities in the design and implementation of policies. Patient organizations should be seen as key allies in the process, providing valuable information about their needs and priorities. This collaboration not only enriches policy development but also empowers patients and fosters a sense of solidarity in their community.

Early Diagnosis: Moving Toward New Horizons

One of the major challenges in rare diseases is the delay in diagnosis. On average, it can take several years between the

appearance of the first symptoms and the precise identification of the disease, leading to severe consequences for both patients and health systems. This delay not only affects the quality of life of patients but also significantly increases costs due to inadequate treatments or repeated consultations.

Thanks to recent technological advances, especially in "omic" sciences such as genomics, proteomics, and metabolomics, it has been possible to accelerate and improve diagnostic accuracy. These technologies have transformed the approach to rare diseases, allowing for more precise identification of the genetic variants underlying many of these conditions. However, the effective implementation of these techniques still faces obstacles, including a lack of trained specialists and the limited availability of specialized reference centers, which restricts universal access to early diagnosis.

Neonatal screening is one of the main strategies for the early detection of rare diseases, especially those of genetic origin, allowing treatments to begin before clinical symptoms appear, significantly improving long-term health outcomes.

Looking to the future, one of the most promising advances in early diagnosis of rare diseases is neonatal genetic screening based on next-generation sequencing (NGS). This method has the potential to increase detection capacity and cover a broader spectrum of preventable or treatable genetic diseases in childhood. Global pilot studies, such as BabySeq, Screen4Rare, and BabyDetect, are already exploring the feasibility of this approach in different regions, which could radically change how rare diseases are detected and treated in the first days of life.

However, its widespread implementation poses important ethical, logistical, and financial challenges that the international community must address. The diagnostic accuracy of NGS must be balanced with the protection of genetic privacy and informed consent. Furthermore, the long-term implications for health systems must be considered, as broader screening will require additional resources for the follow-up and treatment of diagnosed patients.

Despite these challenges, neonatal genetic screening represents a revolutionary advance in the fight against rare diseases. As technology evolves and global health systems adapt, the promise of earlier and more accurate diagnosis could transform the quality of life for millions of people affected by rare diseases worldwide. International collaboration will be key to maximizing the benefits of these advances and ensuring that all countries, regardless of their development level, can access the innovations that are changing the paradigm of rare diseases.

Evolution Toward Value-Based Healthcare

VBHC is a crucial pillar in optimizing clinical management and resource sustainability in the approach to rare diseases. This approach is vital due to the unique challenges faced by both patients and health systems. Since the diagnosis, follow-up, and treatment of these diseases are extremely costly, VBHC offers a way to improve equity and efficiency in resource allocation. Healthcare must be as equitable as possible, ensuring that all patients, regardless of the rarity or severity of their condition, can access treatments.

Health systems face the challenge of balancing the high costs involved in managing rare diseases with social justice in resource distribution. While strategies must adapt to the clinical variability of these diseases, there are tools that can be applied across the board, such as advanced genetics services and screening programs. The latter, particularly in specific groups like neonatal screening, have proven crucial in detecting many rare diseases early and ensuring timely treatment.

A Hopeful Future

Finally, the development of detection and comprehensive care policies for rare diseases must be accompanied by a global approach that addresses inequalities in access to care. This includes the commitment of governments and international organizations to ensure that initiatives and resources are distributed equitably, allowing all patients, regardless of their geographical or socioeconomic status, to benefit from advances in rare disease research.

We would like to thank all the experts involved in this second international issue of newsRARE and acknowledge their outstanding work. Without their contributions, it would have been impossible to meet the goal of this project, which is to generate evidence and knowledge that support informed decision-making and contribute to improving the quality of life of people with rare diseases in Europe. We also want to thank the sponsors of the journal, whose support is essential to continue working on creating this content. We fully trust that this platform will become a reference point in the field of rare diseases at the European level, aiming to improve both communication between opinion leaders at different levels and healthcare for people living with rare diseases in Europe.

UNRAVELING THE PRESENT: A TOUR OF RARE DISEASE POLICIES AND REGULATIONS SINCE 2021

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In the June 2021 issue of newsRARE, an analysis was carried out of the policies implemented in recent decades with the aim at promoting the development of and facilitating access to orphan drugs in Spain[1]. It was concluded that, although significant progress had been made in the field of policies for the promotion of rare diseases (RDs), there were still considerable needs that had not been adequately addressed. The resolution of these demands acquired particular urgemncy in a context marked by the pandemic, globalization and digitalization,

making it imperative to address the updating of existing policies as a matter of priority.

Since then, the landscape has undergone significant transformations. The restrictions that affected the healthcare field and had an impact on various sectors no longer represent an insurmountable obstacle, but rather a learning opportunity for the community as a whole. Advances have been implemented in the reform of pharmaceutical legislation, as well as in the field of artificial intelligence (AI), among others. In the political arena, new regional plans, political advocacy and awareness movements have been developed in relation to RDs, targeting not only those affected, but also their family members, caregivers and healthcare professionals.

The purpose of this article is to provide an overview of the most salient developments (or setbacks) in the policy and regulatory environment of RES-E since the June 2021 issue of our journal. The structure of the article is organized into two main sections. The first section deals with developments at the European level, including changes proposed by the European Commission (EC) in pharmaceutical legislation, changes in AI-related regulations, the mandatory joint clinical evaluation of orphan drugs from the end of this decade, and some aspects related to regulatory processes in other European countries. The second section focuses on recent changes in Spain, such as the launch of new regional strategies on RDs, the drive towards the humanization of healthcare, changes linked to therapeutic positioning reports (TPRs) and the attempt to address this regulatory vacuum by establishing a new Royal Decree on Health Technology Assessment.

EUROPEAN OUTLOOK: A SHIFT IN RARE DISEASES POLICIES AND REGULATORY FRAMEWORKS SINCE 2021

In recent years, there has been an evolution in the regulatory network that oversees pharmaceutical legislation in Europe, aimed at addressing unmet medical needs, with particular emphasis on the attention given to RDs and pediatric diseases. This process is intertwined with the Joint Clinical Assessment of Health Technologies initiative, with a particular focus on orphan drugs, vaccines and advanced therapies. As a backdrop, the proposed Artificial Intelligence Act emerges, a crucial element that redefines the regulatory guidelines in this specific field.

Reformulating pharmaceutical legislation

EU pharmaceutical legislation encompasses both general and specific provisions. Within the latter category is the legislation on orphan drugs, which was introduced in 2000 with the enactment of Regulation No. 141/2000 by the European Parliament and the Council. This regulatory framework delineates the characteristics of RDs in the EU and establishes incentives for the development of medicinal products to address these pathologies[2]. Obtaining centralized authorization from the European Medicines Agency (EMA) is a requirement for orphan drugs, while other non-orphan drugs for RDs may seek authorization through various procedures[3,4].

In the process of obtaining marketing authorization as orphan drugs, it is imperative that drugs be designated as such by the EC[5]. The criteria for such designation cover aspects such as disease prevalence, severity, unmet need, economic return and potential benefit. The underlying purpose of the regulation was to encourage research in the field of orphan drugs, ensuring the availability and accessibility of equivalent treatments. To this end, benefits were granted, such as funding for research and development, market exclusivity and reduced fees[6].

According to an EC report published in 2020, this regulation has had a clear positive impact in terms of designations, approvals, as well as aspects related to research and company creation, among others[7]. On the other hand, the following shortcomings were identified in the legislation on RDs and pediatric medicines[8]:

- The medical needs of patients with RDs and children are not sufficiently met.
- The affordability of medicines is a growing challenge for healthcare systems.
- Patients have unequal access to medicines in the EU.
- The regulatory system does not sufficiently take innovation into account and, in some cases, creates an unnecessary administrative burden.

Over time, the EC undertook a review of pharmaceutical policies, culminating in the formulation of the new European Pharmaceutical Strategy, which was adopted in 2020. This document had the

primary objective of establishing prospective regulation that would support research and technologies aimed at meeting the therapeutic needs of patients[9]. Specifically, a reflexive process was triggered, based on this strategy, focused on adapting the incentive system established by the EU regulatory framework for pharmaceuticals. The purpose was to stimulate innovation in areas where unmet medical needs persist, such as in the RDs[10].

This reflection has led to the formulation of a proposal, in April 2023, for the revision of the European pharmaceutical legislation. This proposal envisages the repeal of Regulation No. 141/2000, with the consolidation of existing regulations related to orphan drugs and pediatric medicinal products. This approach seeks to promote greater consistency and simplification in the relevant regulations[8].

According to this document, drugs intended to treat RDs and children will remain subject to the same provisions that apply to any other drug in terms of quality, safety and efficacy. This includes aspects such as marketing authorization procedures, pharmacovigilance and quality standards. However, specific requirements will be maintained for these types of drugs in order to support their development. This is justified by the realization that market forces alone have not proven to be sufficient to stimulate adequate research and development processes for medicines for children and patients affected by RDs[8].

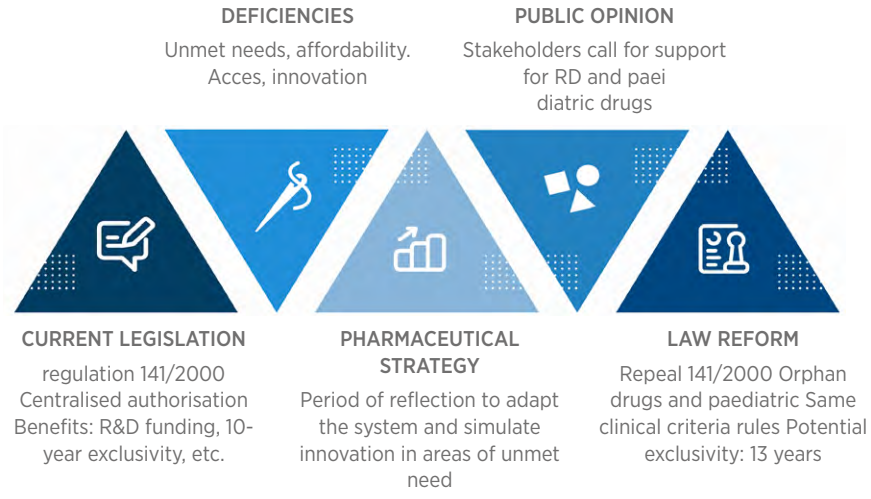
All parties involved in the process of developing the proposal[I] highlighted the need to provide greater support for medicines that address the unmet medical needs of patients, both in the case of RDs and pediatric medicines[8].

As a key outcome, a variation in the length of the market exclusivity period for orphan drugs is proposed, setting terms of ten, nine and five years, depending on the category of orphan drugs in question, whether it is intended to address a large unmet medical need, involves new active substances or has well-established use applications. An additional one-year extension of market exclusivity is envisaged, based on patient accessibility in all relevant Member States[8]. In addition, they could have market exclusivity for up to 2 more years if they develop new therapeutic indications for an already authorized orphan drugs. In sum, market exclusivity for orphan drugs could reach 13 years[11] (compared with 10 under current legislation [12 if for pediatric orphan drugs][2]) (Figure 1).

Towards a harmonized evaluation

Another relevant aspect is Regulation (EU) 2021/2282 on health technology assessment, approved by the EC at the end of 2021. This Regulation aims to ensure the proper functioning of the market for medicinal products, medical devices and in vitro diagnostic medical devices[12]. This document

FIGURE 1: THE PATH TOWARDS PHARMACEUTICAL LEGISLATIVE REFORM



Source: *European Commission (2023)*[11].

I *With regard to the revision of the legislation concerning pediatric drugs and those intended for use in RDs, specific consultation activities were carried out as part of the impact assessment procedure. A public consultation was carried out between May 7 and July 30, 2021. Specific surveys, including one on costs addressed to both pharmaceutical companies and public authorities, were carried out between June 21 and July 30, 2021, with late responses accepted until the end of September 2021 due to the summer recess. At the end of June 2021, a program of interviews was implemented with all relevant stakeholders, such as public authorities, the pharmaceutical industry (including SMEs), academia, civil society representatives and healthcare providers. In addition, focus groups were convened on February 23, 2022 to address some of the key issues related to the reform.*

establishes a framework to support collaboration between Member States and the necessary measures to carry out Joint Clinical Assessment (JCA) of health technologies at European level.

Although the Regulation entered into force in 2021, its effective application will not begin until 2025. According to the Regulation, joint clinical evaluations will begin to be mandatory that year for oncology drugs containing new active ingredients and advanced therapies, such as gene therapy, cell therapy and tissue-engineered products. Subsequently, in January 2028, it will be extended to orphan drugs, and from 2030 it will be mandatory for all drugs (Figure 2)[13].

A Coordination Group will play a key role in conducting joint clinical evaluations of medicinal products, seeking to replace the parallel evaluations of clinical data performed by various national evaluation bodies with a single harmonized evaluation. It should be noted that these joint assessments will be non-binding, so that conclusions regarding the efficacy and safety of medicines, issued by each member country, will remain independent of the results obtained through the JCA process. It is also important to note that the conclusions derived from the CABs will not influence national decisions regarding the pricing and reimbursement of medicines[12,14].

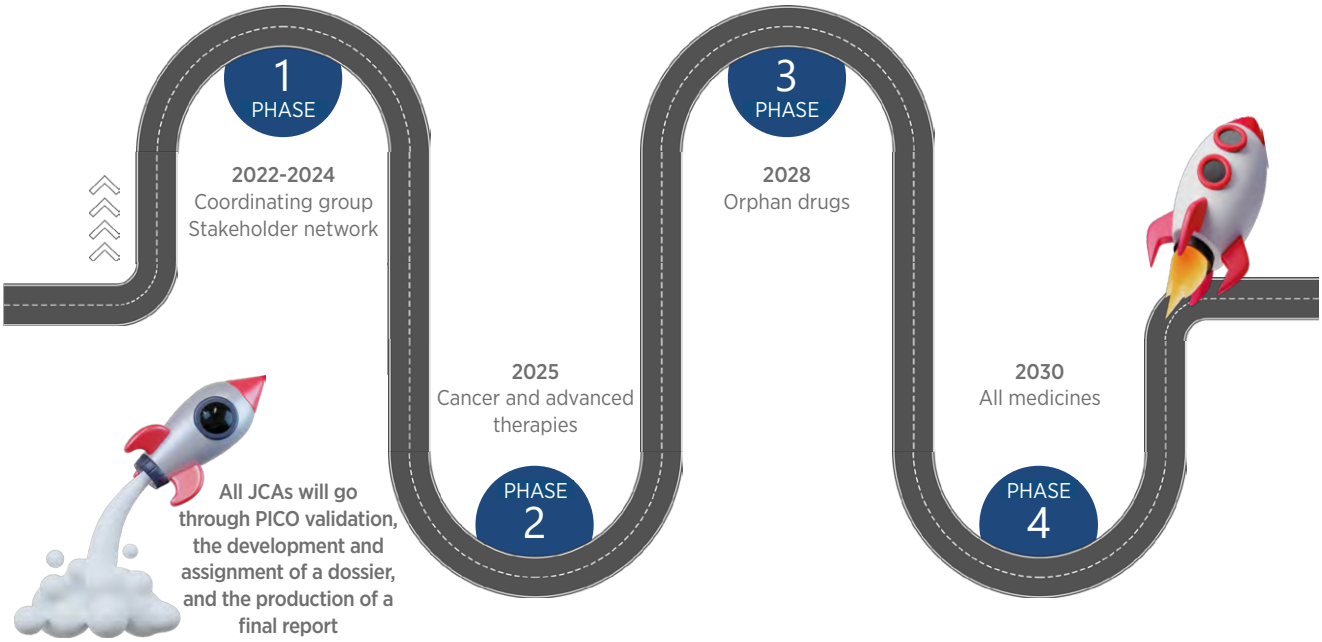
In a targeted approach, the Coordination Group will consider the inherent particularities of the health technology subject to assessment, with a special focus on orphan drugs, vaccines and advanced therapies[12]. In order to ensure inclusiveness and transparency in this collaborative process, the Coordination Group will conduct consultations with a wide range of stakeholders, including patient organizations, health professionals, clinical and academic societies, health technology developers, consumers and other non-governmental health organizations. A stakeholder network will be established to facilitate ongoing dialogue with the Coordination Group, and external experts with relevant expertise will contribute to the process[12].

The joint assessment process can be broken down into four distinct phases[15]:

1. **Scoping phase:** comprises the development and validation of the PICO scheme (patient population, intervention, comparator(s) and outcome variables).

2. **JCA dossier development phase:** involves the compilation and development of the dossier necessary to carry out the joint assessment.

FIGURE 2: THE PROCESS TOWARDS HARMONISATION OF HEALTH TECHNOLOGY ASSESSMENT



Abbreviations: ***JCA:*** *Joint Clinical Assessment.* ***PICO:*** *patients, interventions, comparators and outcome variables.*
Source: *Global Legal Insights (2023)*[13].

3. **JCA dossier assignment phase:** refers to the process of assigning specific dossiers to JCAs, considering the nature of the health technology in question.

4. **Publication of the final report of the CAB:** the process concludes with the disclosure of the final report resulting from the joint evaluation.

Pioneering regulation: the Artificial Intelligence Law

Last December 8, 2023, the EU has reached a landmark agreement on a comprehensive law to regulate the development and use of AI in the EU. The legislation, known as the Artificial Intelligence Act, still needs to be voted on by the European Parliament. This vote is expected to take place in early 2024, with an effective date two years after approval[16].

Although this law may be subject to additional amendments during its finalization, when passed, it will be the first comprehensive law in the world regulating AI. It adopts what some consider a "risk-based assessment" approach to regulating AI: the higher the risk of a tool, the stricter the rules governing it. Although it is not specific to the healthcare sector, it will certainly impact it[17,18].

Under the proposed Act, AI systems that present limited risks would be subject to minimal transparency obligations, such as disclosing that content is AI-generated. Meanwhile, high-risk AI systems would be allowed, but would be subject to requirements, including a "fundamental rights impact assessment" before deploying the tool on the EU market. High-risk AI systems include applications related to transportation, education, employment and welfare. Finally, AI systems deemed to be an unacceptable risk would be banned in the EU. These systems include those used for cognitive-behavioral manipulation and emotional recognition in the workplace. Violations of the AI Act could lead to severe penalties for organizations, with fines reaching up to 7% of global sales[17,18].

Socio-health care coordination and citizen participation are common objectives, seeking to optimize patient autonomy and facilitate their social reintegration process, giving rise to the need to address regulatory gaps

Regulatory developments in European countries: the French case

In 2021, France transformed its Temporary Authorization for Use (ATU) system through a new early access model. This change sought to simplify and harmonize processes, ensure immediate access for patients and guarantee the financial sustainability of the system. The reform introduced two mechanisms for drugs subject to authorization[19]:

- "Early access" for innovative drugs targeting unmet therapeutic needs, with commitment to commercial authorization or request for reimbursement.

- "Compassionate access" for medicines that are not necessarily innovative, with no initial intention of commercial authorization, but effective in unmet therapeutic needs.

Early Access" applies mainly to innovative drugs, requiring applications to the High Health Authority (*Haute Autorité de Santé* or HAS), which issues a decision within 3 months. The manufacturer must guarantee availability two months after authorization. The advantage lies in the standardization of the clinical data collection process, speeding up the evaluation and possibly accelerating reimbursement[19].

One novelty is the presumption of innovation vis-à-vis comparators, allowing the laboratory to set prices freely. If the final negotiated price is lower than the early access price, the manufacturer must reimburse the difference[19].

For "Compassionate Access", the absence of commercial clinical research is required, i.e., no pharmaceutical laboratory is conducting any clinical research for commercial purposes. The laboratory follows a clinical protocol, and the price and reimbursement depend on whether the product is reimbursed in another indication. If so, the price is maintained; otherwise, the laboratory sets the price freely[19].

An appeal from the global RDs community to UN Member States

On September 21, 2023, Member States gathered at the United Nations Headquarters to accelerate the achievement of Universal Health Coverage by 2030. In parallel, the International Association for Rare Diseases (Rare Diseases International), the European Association

Artificial Intelligence Law: diversification of regulations according to the level of risk[17,18]

The recent regulation establishes responsibilities for providers and users according to the risk associated with AI. Although many AI systems present minimal risks, it is crucial to assess each of them.

Unacceptable Risk

AI systems considered unacceptable risk, threatening to people, will be prohibited and include:

- Cognitive manipulation of the behaviour of vulnerable individuals or groups, such as voice-activated toys that induce dangerous behaviour in children.
- Social scoring based on behaviour, socio-economic status or personal characteristics.
- Real-time and remote biometric identification systems, such as facial recognition, except in cases of "ex-post" identification with judicial approval to prosecute serious crimes.

High Risk

AI systems that adversely affect security or fundamental rights fall into two categories:

- Systems used in products regulated by EU product safety legislation, such as toys, aviation, automobiles, medical devices and lifts.
- Systems belonging to eight specific domains that must be registered in an EU database, ranging from biometric identification to legal interpretation assistance.

All high-risk AI systems must be assessed before they are placed on the market and during their lifecycle.

Generative AI

Generative AI, such as ChatGPT, must comply with transparency requirements including:

- Disclose that the content was generated by AI.
- Design the model to avoid illegal content generation.
- Publish summaries of copyrighted data used in training.

Limited Risk

Limited risk AI systems must meet minimum transparency requirements, allowing users to make informed decisions. After interacting with AI applications, users should decide whether they wish to continue using the service, being aware of their interaction, including systems that manipulate image, audio or video content.

for Rare Diseases (EURORDIS), the Spanish Federation for Rare Diseases (FEDER) and Ågrenskall[II] organized an event entitled "A plan to leave no one behind". This event highlighted the need to include the 300 million people worldwide living with RDs in universal health coverage. The participation of international leaders and the insistence on concrete actions at global, European and national levels reflect the growing political commitment to address the complex needs of the RDs community[20].

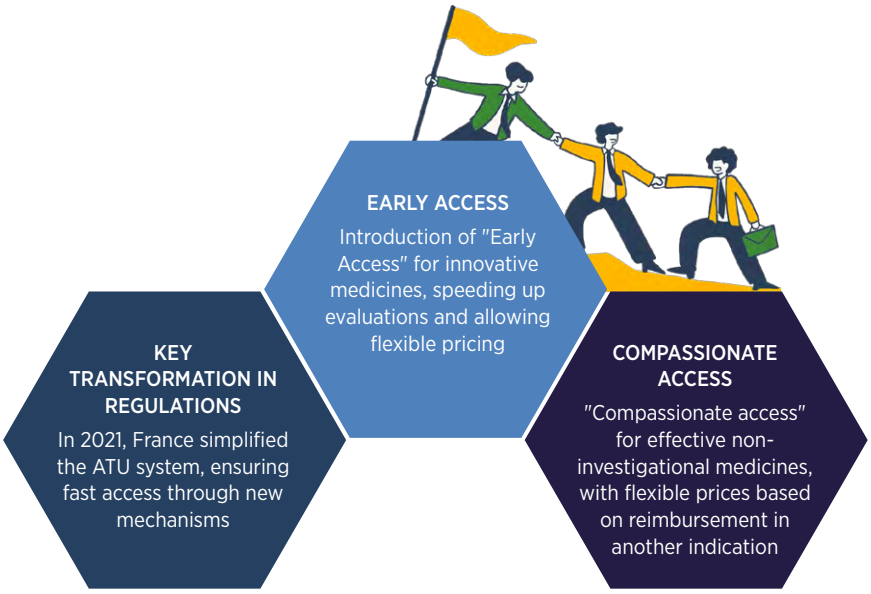
The call to action included mobilizing efforts to establish a global framework through the adoption of a World Health Assembly Resolution on RDs. The urgency is highlighted by addressing challenges such as late diagnosis, lack of access to essential services and high treatment costs. Spain, with its previous leadership in passing the UN Resolution on RDs in 2021, is at the center of these efforts, supporting the updating of national and European strategies to improve the reality for people with RDs[20].

TRANSFORMATIONS IN SPAIN: POLITICAL AND REGULATORY DEVELOPMENTS AND TRENDS IN RES-E AFTER 2021

The evolutionary dynamics of regulations focused on RDs in Spain reveals a convergence between the Autonomous Regions in terms of regional strategies and aspects linked to the humanization of the health care setting. However, this period has also been characterized by legal challenges with respect to the health technology assessment

II Ågrenska is a Swedish competence center for RDs and other disabilities.

FIGURE 3: TRANSFORMATION IN ACCESS TO MEDICINES IN FRANCE



Abbreviations: *ATU*: *autorización temporal de utilización*. Source: *Rudd (2023)*[19].

process, giving rise to the need to address regulatory gaps. In this context, the harmonization of political and legal objectives emerges as an unavoidable task, the purpose of which is to ensure the coherent evolution of these policies.

Convergence of Regional Strategies (2021-2023)

In the June 2021 issue of newsRARE, it was highlighted that Spain had established a strategic framework for RDs through the National Strategy on RDs of the NHS, published in 2009 and updated in 2014. This framework covered seven areas and guidelines with information on RDs, prevention and early detection, health care, therapies, social-health care, research and training21. At that time, 5 Autonomous Communities (ACs) (Andalusia, Madrid, Extremadura, Navarra and Murcia) had already approved specific plans for RDs, while another 4 (Catalonia, Basque Country, Valencian Community and Castilla la Mancha) had incorporated specific measures for RDs in their health plans[22].

Since 2021, 3 ACs (Galicia[23], Canary Islands[24] and Castilla y León[25]) have launched their own RES-E plans. Madrid[26] and Andalusia[27] announced that they will update their plans in 2023. However, as of the writing of this article, these updates had not yet been published.

The strategies outlined by Galicia, the Canary Islands and Castilla y León in Spain reveal a notable convergence in their approach to RDs. First, all regions recognize the need to develop specific information systems and registries for RDs, with the aim of standardizing and recording epidemiological data, thus providing a solid basis for understanding the incidence and prevalence of these diseases. Convergence is manifested in the priority assigned to primary and secondary prevention, where the 3 ACs share the objective of avoiding hereditary transmission, guaranteeing neonatal screening tests and reducing diagnostic times[23-25].

In the area of health care organization, the strategies converge in the definition of new care models that address the fragmentation of knowledge and the difficulties in identifying initial suspicions of rare pathologies. Likewise, they all agree on improving access to pharmacological and non-pharmacological treatments, including orphan drugs, advanced therapies and medical devices. Socio-health care coordination and citizen participation are common objectives, seeking to optimize patient autonomy and facilitate their social reintegration (Figure 4)[23-25].

The evolution of humanization in healthcare in Spain (2021-2023)

The drive towards the humanization of healthcare has experienced notable growth over the last few decades. By 2020, 8 ACs had specific plans aimed at the humanization of healthcare (Valencia in 2001; Asturias in 2004; Baleares in 2004; Extremadura in 2007; Madrid in 2016; Castilla-La Mancha in 2017; Navarra in 2017 and Galicia in 2019)[28].

In the period between 2021 and 2023, 2 additional ACs (Andalusia and Castilla y León) have submitted new humanization plans, while another 4 ACs have carried out updates of their preexisting plans (Asturias in 2021; Baleares and Madrid in 2022; and Castilla-La Mancha in 2023). This phenomenon is evidence of a sustained trend toward strengthening initiatives aimed at improving the quality and humanistic orientation of health care at the regional level[28].

Among the strategic lines of action defined and updated by the ACs (2021-2023) to promote humanization in healthcare, key elements can be identified that reflect their commitment to continuous improvement and quality in healthcare. A summary of these lines of action is presented below:

1. Generate a culture of humanization: promote an organizational culture that permeates all healthcare with a human and patient-centered approach.

2. Infrastructures and human resources: improve infrastructures, spaces and technological resources to guarantee respect for patient dignity and support the work of healthcare personnel.

3. Personalized and comprehensive care: to promote quality and personalized care that covers all dimensions of the person, providing tangible results for the patient.

4. Patient-centered relationship: focusing health care on active listening, effective communication, shared decisions and co-responsibility between the patient and the health system.

5. Active listening and communication: encourage active listening, proactive treatment and effective communication as fundamental elements in the interaction between health professionals and patients.

6. Support for the pursuit of professional excellence: to provide support to health professionals in the pursuit of excellence in their performance, recognizing their crucial role in humanization.

7. Active social participation: to actively involve society in the health care process, recognizing the importance of citizen participation.

8. Warmth, comfort and accessibility: prioritizing warmth in the healthcare environment, ensuring patient comfort and improving accessibility to healthcare services.

9. Equity in access and transit: guarantee equity in access to the health system and facilitate the transit of people through the system, prioritizing patient autonomy.

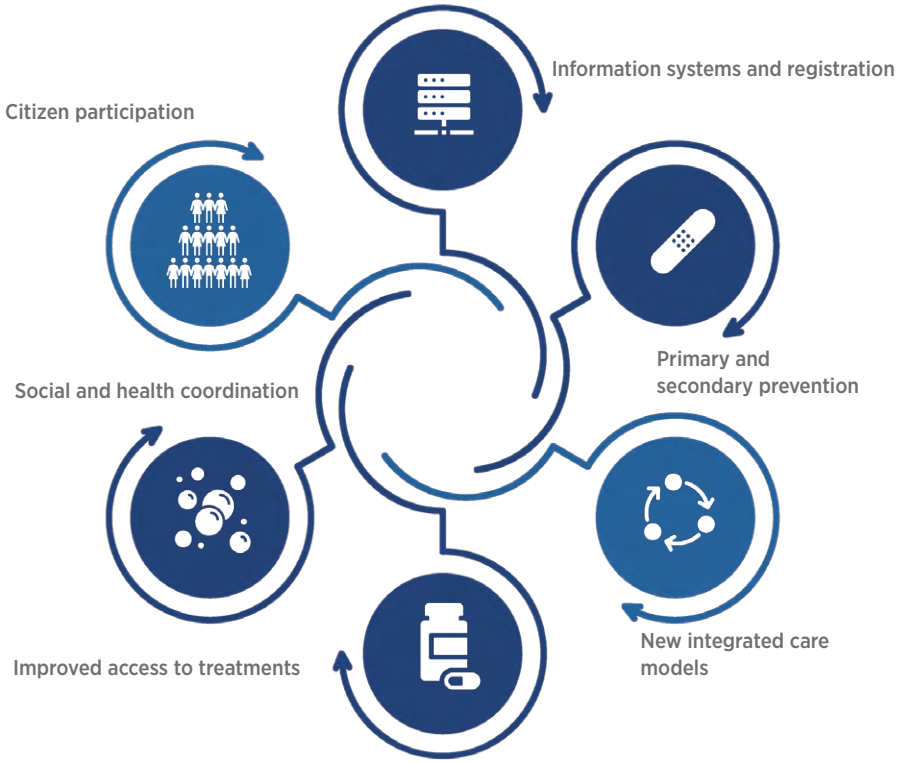
10. Effective information: provide effective information to strengthen the patient-health system relationship.

11. Sustainability of the healthcare system: advocate for the sustainability of the healthcare system, recognizing the importance of a change in the organizational model and the essential contribution of healthcare professionals.

Annulment of the Therapeutic Positioning Report Consolidation Plan: a legal setback in the evaluation of drugs in Spain.

In the June 2021 edition of the newsRARE publication, mention was made of the launch in 2013 of TPRs,

FIGURE 4: CONVERGENCE POINTS IN THE REGIONAL STRATEGIES ON RDS, 2021-2023

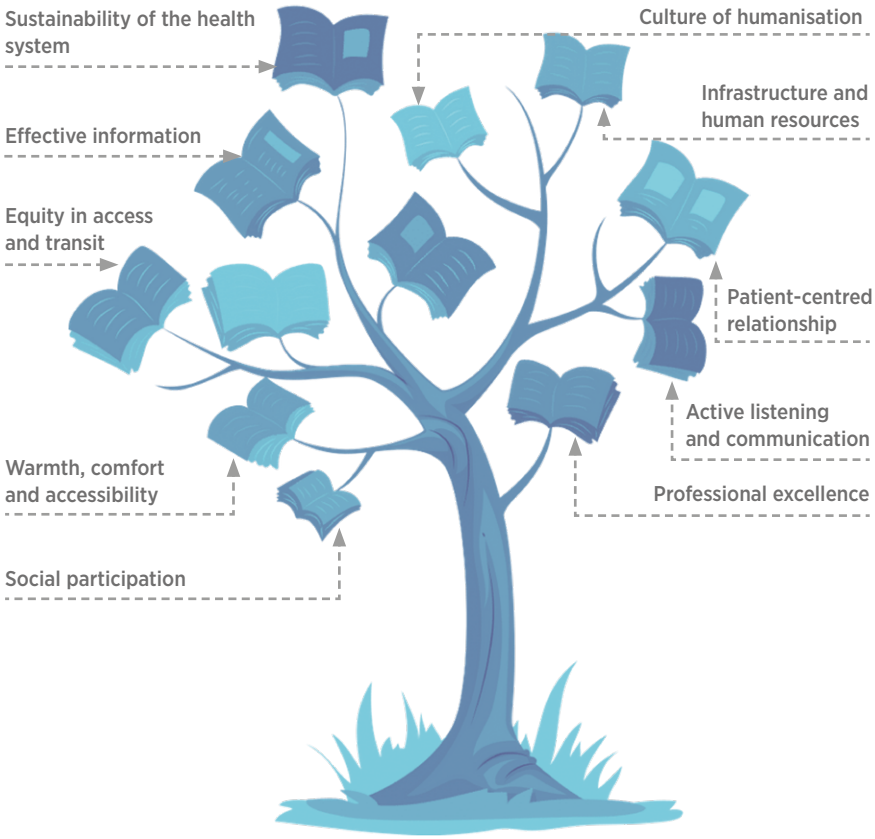


Sources: *Servicio Gallego de Salud (2021)[23], Gobierno de Canarias (2022)[24] and Junta de Castilla y León (2023)[25].*

with the aim of alleviating disparities in access to treatment between various regions by fostering greater coordination and collaboration. It was emphasized that in November 2020, the Ministry of Health presented a plan to consolidate the TPRs[35], aimed at improving the evaluation process through adjustments in governance (REvalMed network evaluation; evaluation nodes, one of them in non-oncological RDs) and in the tools used in the preparation of the aforementioned reports (prioritization matrix; incorporation of economic evaluation in the reports; scorecard for control and follow-up)[1].

However, the TPR consolidation plan was challenged in court by Farmaindustria. In June 2023, the National High Court annulled the plan[34] on the grounds that it contravened the legislation by attributing powers to bodies other than those designated by law. The judgment noted that the plan was a general provision, not an internal instruction, as it developed existing legislation, was addressed to independent bodies and was intended to modify the regulatory framework. The Audiencia Nacional held that the plan violated the law by requiring an economic content for TPRs, in contradiction with the provision that specified an exclusively scientific content[34,36].

FIGURE 5: KEY ASPECTS OF THE AUTONOMOUS COMMUNITIES HUMANISATION STRATEGIES, 2021-2023



Sources: *Junta de Andalucía (2021)[29], Junta de Castilla y León (2021)[30], Gobierno del Principado de Asturias (2021)[31], Gobierno de las Islas Baleares (2022)[32], Comunidad de Madrid (2022)[33], Consejería de Sanidad de Castilla la Mancha (2023)[28].*

The Ministry of Health chose not to appeal the National Court's ruling. The absence of an appeal led to the sentence becoming final, which strengthened the competence of the Spanish Medicines Agency (AEMPS) in the evaluation of drugs. According to the Ministry of Health, this annulment of the plan does not affect its plans to promote an independent and transparent evaluation system, highlighting the processing of the Royal Decree on the Evaluation of Health Technologies[37].

A key step towards regulation of Health Technology Assessment

In February 2023, the Spanish government presented its Legislative Plan for the months leading up to the elections of the same year. The measures focused on health included the Royal Decree on the Evaluation of Health Technologies, which would regulate the financing and pricing of drugs and their incorporation into the pharmaceutical provision[38].

Subsequently, in October 2023, the Ministry of Health initiated the process of processing the aforementioned Decree[37]. During this phase, a public hearing period was opened, with the aim of gathering opinions from various stakeholders in the sector. The main points mentioned in the public consultation document[39] are detailed below:

- **Background to the regulation:** the document presents a prior public consultation on a draft Royal Decree that will regulate the evaluation of health technologies in Spain. It stresses the importance of evaluating these technologies to ensure an efficient and equitable healthcare system and men-

tions the creation of a European network for health technology assessment (EUnetHTA).

- **Problems to be solved with the new regulation:** problems such as the regulatory vacuum in the regulation of health technology assessment in Spain, the lack of certainty for developers and economic operators, and the need for clarity in governance and participation are identified. In addition, the recent annulment of an existing plan is highlighted, underlining the urgency of a new regulation.

- **Necessity and timeliness of its approval:** the need for the regulation is presented as crucial, especially after the recent cancellation of an existing plan. The complexity of the pharmaceutical sector at a global and local level is highlighted, highlighting that inaction or delay in the approval of the regulation could have negative consequences on research, development, patient access to medicines and the sustainability of the healthcare system.

- **Objectives of the regulation:** the objectives of the draft Royal Decree include the regulation of an independent, transparent and participatory system for the evaluation of health technologies in Spain. It seeks to align national regulation with the European Regulation and to develop complementary national aspects. It is intended to provide certainty, predictability and reduce the administrative burden for developers.

- **Possible solutions, regulatory and non-regulatory alternatives:** the proposed solution is the approval of a new Royal Decree that comprehensively addresses health technology assessment in Spain, complementing the provisions of the European Regulation. It is emphasized that the Royal Decree is the appropriate instrument to develop the relevant articles of the Spanish legislation.

FIGURE 6: ELEMENTS OF THE PUBLIC CONSULTATION OF THE ROYAL DECREE ON HEALTH TECHNOLOGY ASSESSMENT



Source: *Ministry of Health (2023)*[39].

Throughout October 2023, during the public consultation period, various key players presented their perspectives on the content of the new Royal Decree. Among these, the allegations made by Farmaindustria stand out, highlighting the importance of processing in parallel and simultaneously both the Royal Decree on health technology assessment and that on drug financing and pricing, the latter also included in the annual regulatory plan. This perspective had previously been shared in public interventions by the Director General of the Common Portfolio of Services of the National Health System and Pharmacy, César Hernández[37].

In summary, European policies related to RDs have undergone significant transformations since 2021. In the Spanish context, several Autonomous Regions converge in the strategic lines outlined to address these pathologies. Likewise, a notable increase has been observed in strategies for the humanization of healthcare between 2021 and 2023. However, some policies aimed at RDs have been faced with legal challenges, such as the annulment of the TPR Consolidation Plan. To fill this regulatory gap, work is underway to regulate Health Technology Assessment. In this dynamic and challenging context, the need to harmonize political and legal objectives emerges to ensure a coherent evolution of policies linked to RDs.



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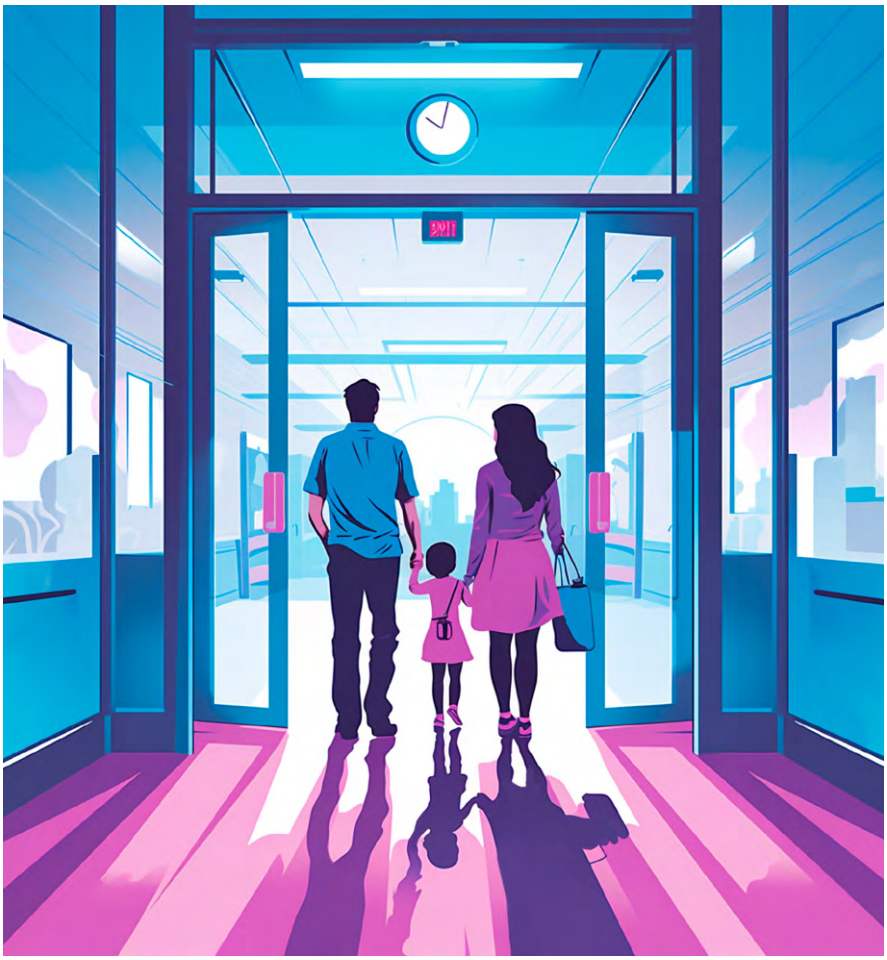
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NAVIGATING IN THE MAZE OF RARE DISEASES: CHALLENGES AND RECOMMENDATIONS FOR EARLY DETECTION AND NEONATAL SCREENING

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Rare diseases (RDs) pose a significant challenge to public health, affecting between 4% and 8% of the world's population[1]. Despite advances in knowledge and technology, the diversity in the manifestation and cause of these more than 5,000 pathologies makes early diagnosis difficult in many cases. Diagnostic delays cause suffering to patients and their families, as well as imposing a high cost on the health system and increasing the risk of complications. In Spain, 57% of people suffering from RDs experience a considerable delay in

their diagnosis, with an average time of more than 6 years[2].

In this context, neonatal screening and early detection play a fundamental role in the impact of RDs, given that approximately 72% of them have a genetic origin and around 70% manifest during childhood[1]. Implementing programs that identify such disorders at early stages is crucial, as they allow for timely interventions and treatments, thus improving the quality of life of affected individuals. In addition, early detection drives the development of specific therapies and advances in clinical research, providing hope to those facing these types of pathologies. Ultimately, newborn screening and early detection not only improve the management of RDs, but also contribute to a brighter future for patients.

This article is structured in three main sections. First, we will address the diagnostic process in RDs, emphasizing the differences between neonatal screening and early diagnosis, as well as the benefits associated with early detection of these conditions. The second section will examine the challenges we face, the scientific advances made to date, and possible solutions proposed to improve early detection of RDs. In the last part, we will focus on the analysis of neonatal screening, assessing the current situation, access and existing barriers in Spain, and presenting the best practices and policy recommendations identified so far. Overall, we will provide an overview of the importance and key aspects of early detection of RDs.

THE RELEVANCE OF EARLY DIAGNOSIS IN RD

Early diagnosis and neonatal screening for RDs are concepts that, although distinct, are interrelated and play a crucial role in the management of rare diseases (Figure 1).

Rare diseases are a public health challenge due to their diversity and diagnostic delays

Early diagnosis focuses on the early detection of the presence of an RD in an individual who already has symptoms or signs indicative of the disease. This identification of the disease can take place at any stage of life (and is therefore not restricted to the neonatal period), and generally requires specific tests, such as blood tests, genetic tests or MRI scans, to confirm the diagnosis in the patient[3].

In general, early diagnosis is a longer process than neonatal screening and begins at the onset of symptoms, which usually leads to an initial medical consultation at a primary care center. This is followed by the period from the first medical consultation to referral to specialized care. Finally, the final period is from referral to a specialist until a definitive diagnosis is made[4,5].

In contrast, neonatal screening is a procedure applied to newborns shortly after birth, usually during the first 24 to 48 hours of life. Its aim is to discover genetic or metabolic diseases in their early stages, even before symptoms become apparent. A simple blood sample taken from the baby's heel is used to look for signs of certain RDs. If the screening results are positive or indicate a possible disease, further diagnostic tests are performed to confirm the diagnosis and provide appropriate treatment in a timely manner[6].

Early detection of RDs presents a number of significant benefits to both patients and the healthcare system as a whole. Some of these benefits include:

FIGURE 1. CHARACTERISTICS OF EARLY DIAGNOSIS AND NEWBORN SCREENING

Early diagnosis

- At any stage of life
- Individual with symptoms
- Specific tests
- Longer process: Symptoms + First consultation + SC -> Definitive diagnosis

Neonatal screening

- Neonatal period
- No symptoms
- Heel prick test
- Faster process: Positive screening + Additional diagnostic tests -> Confirmed diagnosis

Abbreviations: ***SC:*** *Specialized Care*

1. **Treatment in early stages:** Early diagnosis allows initiating the appropriate treatment as soon as possible, significantly improving the patient's quality of life and, sometimes, being vital to avoid deterioration of health and prevent serious complications[7].

2. **Reduced costs:** Early detection of a rare disease can help avoid unnecessary medical procedures and inappropriate treatments, which in turn can lower health care costs for both the patient and the overall health care system[8,9].

3. **Boosting research and treatment development:** Early stage diagnosis allows for a better understanding of RDs, which stimulates scientific research and the development of new treatments to address these conditions more effectively[10].

4. **Emotional and psychosocial support:** Early identification of RDs provides patients and their families with the opportunity to connect with support groups and communities facing similar challenges, often through patient associations[11]. It also allows them to access psychological and social support earlier, which is critical to address emotional distress, increase self-esteem, develop better coping strategies and enhance the psychological well-being of affected families[12].

5. **Family planning:** Early detection of RDs enables better family planning and informed reproductive and hereditary decisions, including future pregnancies, prenatal genetic testing and specialized counseling, among other options[13].

EARLY DETECTION: CHALLENGES, PROGRESS AND PROPOSALS FOR IMPROVEMENT

Challenges in the early detection of RDs

The early and accurate detection of RDs poses major challenges. In this context, the average time to diagnosis of these conditions amounts to 6.18 years in Spain. Approximately 57% of people suffering from these pathologies face a wait of more than one year for a definitive diagnosis. Of this group, 19% suffer a delay of 1 to 3 years, 17% experience periods of 4 to 9 years without clarity about their condition and, particularly alarming, 21% have to wait more than 10 years to get a proper diagnosis[2].

This problem has been studied by the Developing Nations Working Group (DNWG) of the International Undiagnosed Diseases Program (UDNI) in 20 countries, including Spain. The results reveal that limited funding for genetic testing and services, as well as lack of funds for multidisciplinary research, are some of the main factors slowing down the process of detection and diagnosis[14].

In addition, lack of awareness of RDs in both the general population and the medical community represents a significant obstacle, leading to delays in seeking medical care and misdiagnosis. Also, the lack of coordination between health programs and institutions generates inefficiencies in the diagnosis of patients with RD[14].

Neonatal screening and early detection crucial to address the impact of rare diseases

Other factors associated with diagnostic delay have been identified in a study of patients in the Spanish Rare Disease Patient Registry. These include the need to travel to see different specialists, visiting a large number of clinicians, being diagnosed in a region other than the region of residence, and having a nervous system RD[I]. In terms of the time required to consult a specialist, a waiting period of more than 6 months for referral from the first medical visit contributed most to the delay in diagnosis[5,15].

Scientific advances that have improved diagnostic options

These data and challenges highlight the urgent need to improve the processes of detection and diagnosis of RDs. Despite this, it is important to highlight that, in recent years, relevant scientific advances have been made in the field of the detection of RDs,

I *Individuals affected by diseases of the nervous system show a higher risk of experiencing delays, due to the fact that many of these diseases have a high diagnostic complexity and that many of their clinical manifestations overlap, requiring more specific tests to arrive at a specific diagnosis of the disease.*

DELFINA'S STORY[16]

Delfina is a little girl who lived almost a decade without receiving a diagnosis for her disease. Residing in Treinta y Tres, Uruguay, her mother, Soledad Hernández, never gave up and launched the initiative "A diagnosis for Delfi" on Facebook to seek answers.

Thanks to this, Delfina's story came to the attention of Spanish scientists such as José Tubío and Ana Fernández Marmiesse, who worked in the Genomes and Disease laboratory in Spain. Uruguayan physician Nicolás Carbone, who lives in Spain and had contact with these scientists, acted as an intermediary.

In January 2019, the laboratory's genomics research team started working on cases similar to Delfina's, mainly in patients with RDs from Spain and Portugal. When they received Delfina's medical file, they saw that her case fit the type of analysis they were conducting and contacted Soledad to find a solution.

Dr. Fernandez led the investigations of Delfina's case. Thanks to genomic tools specifically designed to diagnose patients according to their clinical phenotype, they achieved a rapid and immediate diagnosis. Although Delfina's disease, mitochondrial DNA depletion syndrome due to mutations in the SLC25A4 gene, is extremely rare and has only a few dozen known cases worldwide, the diagnosis put an end to the odyssey Delfina and her family were living in search of answers.

Although the road to a cure can be long and complex (with no specific treatment available), the diagnosis gave Delfina and her family immense relief and peace of mind. Soledad's perseverance and the collaboration between scientists in different countries opened the door to hope and the search for a better quality of life for Delfina and other people affected by RDs around the world.

which has led to a substantial improvement in the diagnostic options available for people suffering from these conditions.

One of the main strategies that has revolutionized the genetic diagnosis of RDs is exome and genome sequencing. This technique has proven to be highly effective in identifying genetic causes underlying various conditions, such as congenital anomalies and developmental delays or intellectual disability. Thanks to exome sequencing, a diagnostic yield of more than 50% has been achieved in some cases with well-defined clinical presentation. In addition, combined analysis of the patient and his or her parents has increased diagnostic accuracy, allowing more accurate identification of the genetic variants causing the disease[17–19].

In addition to analyzing genes and their sequence, other special techniques called"omics" are also being used to better understand RDs. These approaches include studying how genes are activated and expressed (transcriptomics), how certain chemical modifications affect genes (epigenomics), which proteins are present in the body (proteomics) and which small molecules are involved in metabolic processes (metabolomics). These tools provide additional information that can help solve complicated cases when DNA sequencing has not provided clear answers[17,20,21].

In some studies, the diagnostic yield has been improved by 7.5% to 18% by complementary transcriptome and exome analysis (other "omics" techniques)[21–24]. In addition, the development of new assays and techniques, such as methylome analysis for imprinting disorders[II] and chromatinopathies[III], has opened up new possibilities for the diagnosis of rare diseases[17,27].

Proposed solutions for early and effective diagnostics

Despite remarkable scientific advances, it is imperative to continue to push for the development of solutions that enable early and effective diagnosis of RDs. The following proposals seek to improve the approach in this field[5,14,29,30]:

II *Imprinting disorders: These are rare genetic diseases that occur due to changes in the chemical marks of certain genes. These marks, called "imprints," play an important role in how genes work. When there are unusual changes in these marks, it can cause problems in the body's development and function*[25] .

III *Chromatinopathies: These are medical conditions that occur due to alterations in chromatin structure. Chromatin is the way DNA is organized and packaged in the nucleus of cells. When there are problems in chromatin structure, it can affect how genes are turned on and off, which can lead to various diseases and disorders*[26] .

Unraveling concepts

- **Exome and genome sequencing:** Reading and analysis of genetic information to identify genetic errors and disease-related variants.
- **Combination of patient and parent analysis:** Diagnostic approach that studies the patient and parents to understand whether the disease is inherited or of new origin.
- **Transcriptomics:** Study and analysis of RNA[IV] to understand which genes are active and how they function at a specific time.
- **Epigenomics:** Study of chemical marks and changes in DNA that can influence the regulation of gene activity.
- **Proteomics:** Identification and study of all proteins present in a tissue or organism to understand biological functions.
- **Metabolomics:** Analysis of small molecules and metabolites involved in metabolic processes in the body.
- **Methylome analysis:** Study of DNA methylation patterns[V] to investigate genetic disorders related to epigenetic alterations.

Source: *Pinazo-Durán (2012)*[28].

1. Develop specific public health strategies adapted to the particularities of each country to address the challenges related to the diagnosis of RDs.
2. Ensure adequate funding for genetic testing and diagnostic tools to enable early and accurate detection of RDs.
3. Encourage the exchange of data, clinical research and diagnostic expertise between different countries, which can enrich the understanding and management of these conditions.
4. Establish specialized and multidisciplinary centers of reference for genomic diagnosis, where experts can collaborate and share knowledge to improve early diagnostic processes.
5. Promote the use of artificial intelligence and advanced scientific approaches, such as those mentioned in the previous section (and new techniques that may emerge), to complement diagnostic tools and increase accuracy in the identification of RDs.
6. Perform periodic reanalysis of genomic data to discover new gene-disease associations, which may lead to new diagnostic advances.
7. Improve the efficiency of the health system by addressing waiting times and simplifying referral processes.
8. Increase awareness of RDs among health professionals and patients to improve early detection and appropriate management of these diseases.
9. Empower patients and their families by providing tools and resources that enable them to ask relevant questions during the search for medical solutions.
10. Incorporate the subject of RDs in medical curricula and in the training of health professionals, which will contribute to a greater awareness and capacity to address these pathologies.

NEWBORN SCREENING: CURRENT STATUS, PROGRESS, CHALLENGES AND POLICY RECOMMENDATIONS.

Current situation in Spain and Europe

Neonatal screening is one of the most important programs for the early identification of rare conditions. In Spain, this procedure is regulated by our legislation, being considered both a public health measure, aimed at preserving the welfare of society as a whole, and a health care service of vital importance[31].

In our country, the Neonatal Screening Program (NSP) included in the common portfolio of care services of the National Health System (SNS) covers seven diseases, which are offered to al

IV *RNA (ribonucleic acid) is a molecule that transfers and translates genetic information for protein synthesis.*

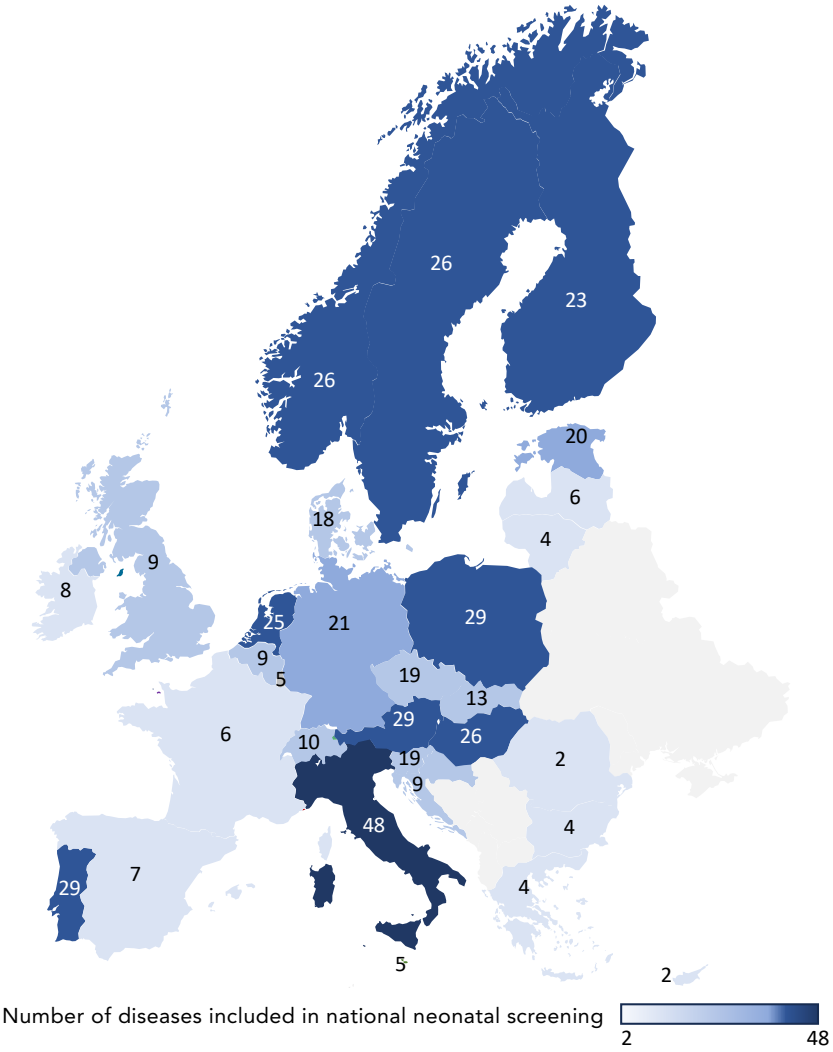
V Methylation is an epigenetic process that involves the addition of methyl groups (-CH3) to certain DNA bases or proteins, affecting gene expression without altering the DNA sequence.

l newborns: congenital hypothyroidism (HC), phenylketonuria (PKU), cystic fibrosis (CF), medium-chain acyl-coenzyme A-dehydrogenase deficiency (MCADD), long-chain 3-hydroxyacyl-coenzyme A-dehydrogenase deficiency (LCHADD), glutaric acidemia type I (GA-I) and sickle cell anemia (FA)32,33 . However, compared to other European countries such as Italy (48), Poland, Austria or Portugal (all with 29), among others, the number of diseases incorporated in the Spanish national NSP is considerably lower, as shown in Figure 2[32].

The inclusion of these seven diseases in the NSP was endorsed by the Interterritorial Council of the NHS in July 201334. In making this decision, essential criteria were considered for each disease, their implementation in programs already established in the autonomous communities, reports on their clinical efficacy, cost-effectiveness analyses (when available), the degree of recommendation based on scientific evidence, and the consensus of the working group and an ethics committee35. Its development and implementation imply the collaboration of the health authorities at national and regional level[31].

In February 2023, the Ministry of Health announced that four endocrine-metabolic pathologies (biotinidase deficiency, maple syrup urine disease, homocystinuria, and congenital adrenal hyperplasia) will be included in the NSP in the future, in addition to incorporating hearing loss screening and prenatal screening programs for chromosomal abnormalities and infectious diseases[36–38].

FIGURE 2. NUMBER OF DISEASES INCLUDED IN EUROPEAN NEWBORN SCREENING PROGRAMMES AT THE NATIONAL LEVEL



Note: *The figure represents the number of diseases included in the NSP at national level, excluding those that may be established by regions and/or autonomous communities, as is the case in Spain.*

Abbreviations: ***NSP:*** *Newborn Screening Programme.*

Source: *own elaboration based on data from Charles River Associates (2021)*[32]

In recent years, an expansion of NSPs has been observed in Europe, increasing the total number of diseases evaluated by screening. This phenomenon is due, in part, to the increasing adoption of technologies that allow neonatal screening, such as the use of tandem mass spectrometry. In addition, the remarkable increase in available treatments, including gene therapies, has expanded the therapeutic options for RDs that previously lacked adequate solutions[32].

Access to screening programs in Spain

In Spain, given the decentralization of health care competencies,

screening programs are not only incorporated at the national level, but also at the regional level. Thus, in addition to the seven diseases included in the NSP of the basic common portfolio of health care services of the NHS, thirteen autonomous communities and the two autonomous cities have officially incorporated other diseases into their NSP, as part of their respective complementary service portfolios. Thus, regions such as Andalusia, Aragon, Catalonia, Galicia, La Rioja, Ceuta or Melilla have implemented tests for more than 30 diseases, while others, such as Cantabria and Asturias, only cover eight[32,39], which in practice implies significant differences in the coverage of diseases in Spain.

In Spain, a total of 40 metabolic diseases are screened for, as shown in Figure 3[39]. Some diseases, such as Severe Combined Immunodeficiency (SCID) and galactosemias are not screened for in practically none of the autonomous communities, which poses a problem when it comes to establishing their early diagnosis[39].

Faced with this situation of inequity in access to NSP, the Spanish Federation for Rare Diseases (FEDER) advocates incorporating into the NHS service portfolio all those diseases that meet the criteria of clinical effectiveness and efficiency, as well as the ethical and legal requirements for the implementation of neonatal screening programsVI . This is based on the experience and success of previously incorporated cases, supported by evidence generated by regional screening programs and collaboration between the different communities[41].

Overcoming barriers, such as lack of funding and lack of awareness, is essential to improve early diagnosis and newborn screening

Barriers, best practices and policy recommendations

In the area of NSP expansion and implementation, national policies play a key driving role. However, in some countries, despite the declaration of intentions by policy makers to improve and expand these programs, there has been a limitation or even lack of significant progress in recent years. Although governmental actions are of great importance, there are several barriers that must be overcome to facilitate the implementation of the different NSPs, including the increased number of RDs to be diagnosed early.

These barriers include the complicated process of proposing the expansion of disease panels to be included, as well as infrastructure requirements that limit the rate of expansion of NSPs and the availability of laboratories and trained personnel. In addition, barriers include variation in program implementation once approved, lack of funding for expansions, and lack of common criteria for demonstrating the value of screening[32].

To overcome these barriers and facilitate the expansion of NSPs, good practices have been identified that could be of great help. Based on this, policy recommendations have been developed, classified according to three key processes identified[32,41]:

Factors affecting disease inclusion proposals:

1. A periodic review process should be applied to the diseases already included in the NSPs to assess whether their benefit-risk profile is still favorable and whether any disease should no longer be part of the program.

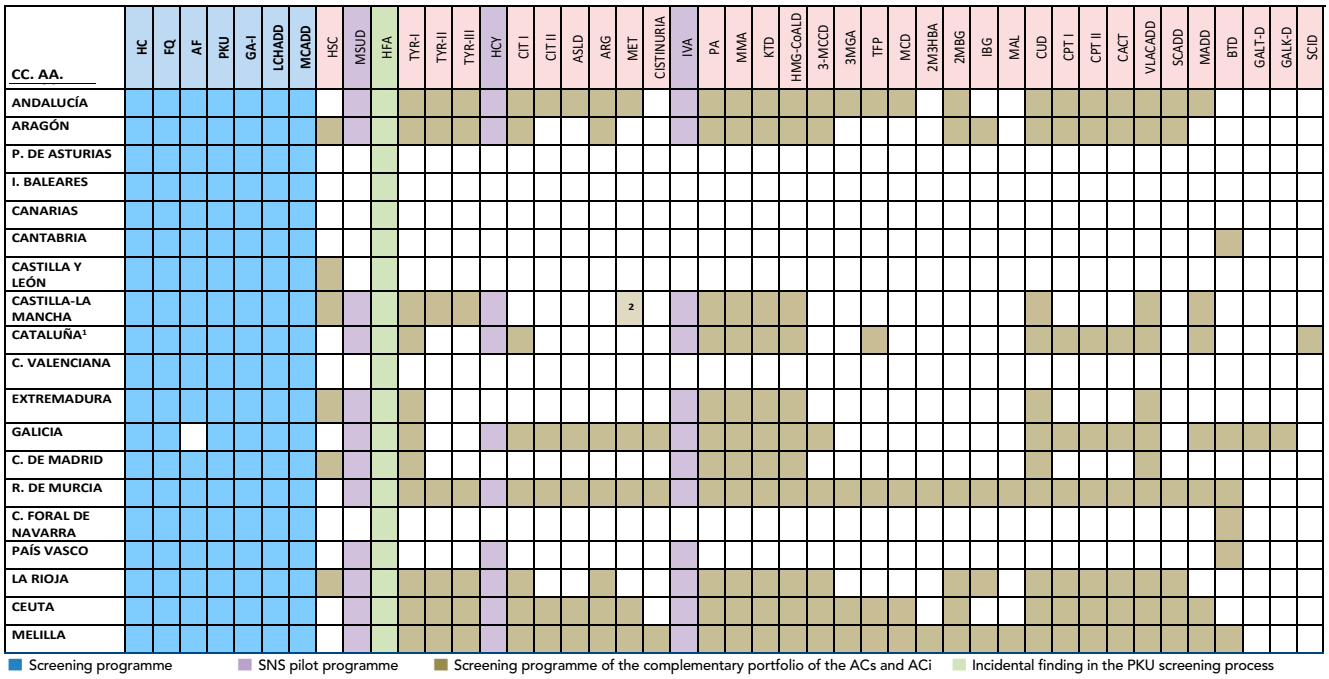
2. Involvement of professional patient representatives (e.g., patient advocacy groups and clinical experts) can leverage political support for the creation of national screening committees and enable the expansion of NSP.

Factors affecting the review and approval of disease inclusion in NSPs:

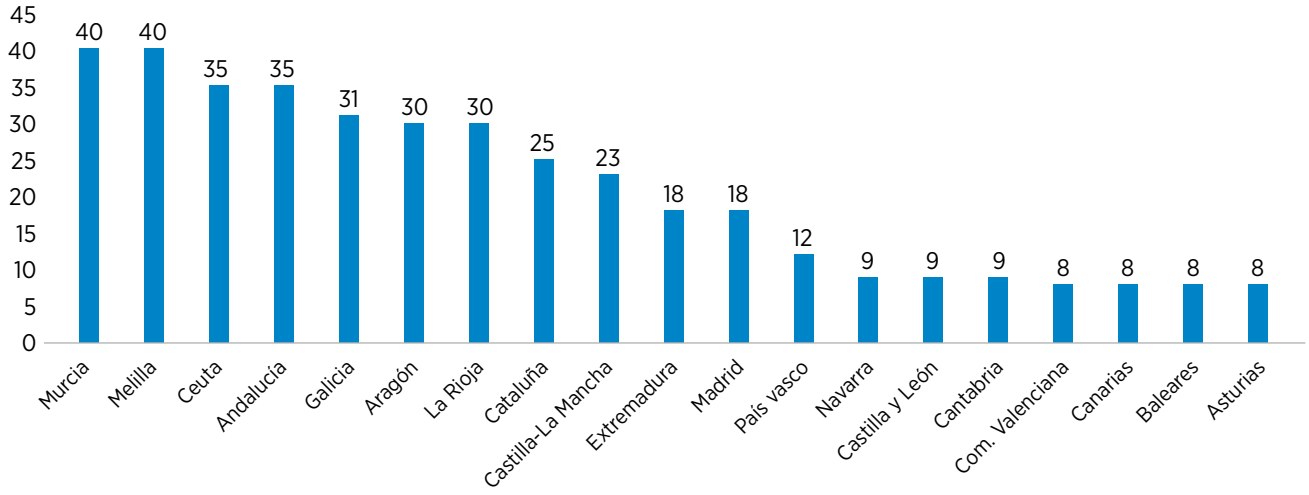
1. Decision-making bodies should be transparent in out-

VI *The criteria that a disease must meet to be included in a neonatal early detection program funded by the Public Health System are: (1) The disease causes severe mental or physical morbidity and/or mortality if it is not diagnosed in the neonatal period. (2) Clinical search by simple physical examination is not effective and does not identify the disease in this period. (3) Effective treatment is available. (4) Early treatment significantly improves prognosis. (5) The disease has a relatively high incidence: > 1 per 10,000-15,000 newborns. (6) A rapid, simple, reliable and low-cost analytical screening test is available*[40].

FIGURE 3. DISEASES INCLUDED IN NEONATAL SCREENING PROGRAMMES BY REGION (2019)



[1]The AC of Catalonia has reported other diseases that are not included in its official complementary service portfolio but have been detected within the programme (incidental finding): chylothorax, transient immunodeficiency, alpha and beta thalassaemia, acquired vitamin B! deficiency and idiopathic lymphocytopenia.
[2]The AC of Castilla-la Mancha has included methonine adenosyltransferase deficiency (MAT I/III)



Abbreviations: ***2M3HBA***: *2-methyl-3-hydrobutyric aciduria;* ***2MBG***: *2-methylbutyrylglycinuria deficiency;* ***3-MCCD***: *3-methylcrotonyl-CoA carboxylase deficiency;* ***3MGA***: *3-methylglutaconic aciduria;* ***AF***: *sickle cell anaemia;* ***ARG***: *argininaemia;* ***ASLD***: *arginosuccinic aciduria;* ***BTD***: *biotinidase deficiency;* ***CACTD***: *carnitine/acylcarnitine translocase deficiency;* ***ACs and AC***: *Autonomous Community;* ***ACi***: *Autonomous City;* ***CIT-I and CIT-II***: *citrullinemia type I and II, respectively;* ***CPT I and CPT II***: *carnitine palmitoyl transferase deficiency type I and II, respectively;* ***CUD***: *primary carnitine deficiency;* ***FQ***: *cystic fibrosis;* ***GA-I***: *glutaric acidemia type I;* ***GALK-D***: *galactosemia due to galactokinase deficiency;* ***GALT-D***: *galactosemia due to galactosin deficiency: galactosemia due to galactose-1-phosphate uridyltransferase deficiency;* ***HC***: *congenital hypothyroidism;* ***HCY***: *homocystinuria;* ***HFA***: *hyperphenylalaninemias/tetrahydropterin cofactor defects;* ***HMG-CoALD***: *3-hydroxy-3-methylglutaric aciduria; HSC: congenital adrenal hyperplasia;* ***IBG***: *isobutyrylglycinuria;* ***IVA***: *isovaleric acidemia;* ***KTD***: *ketothiolase deficiency;* ***LCHADD***: *long-chain 3- hydroxyacyl-CoA dehydrogenase deficiency;* ***MADD***: *multiple acyl-CoA dehydrogenase deficiency;* ***MAL***: *malonic aciduria;* ***MCADD***: *medium-chain acyl-CoA dehydrogenase deficiency;* ***MCD***: *multiple carboxylase deficiency;* ***MET***: *hypermethioninaemia;* ***MMA***: *methylmalonic acidemia;* ***MSUD***: *maple syrup urine disease;* ***PA***: *propionic acidemia;* ***PKU***: *phenylketonuria;* ***SCADD***: *short-chain acyl-CoA dehydrogenase deficiency;* ***SCID***: *severe combined immunodeficiency;* ***SNS***: *National Health System;* ***TFPD***: *trifunctional protein deficiency;* ***TYR-I, TYR-II and TYR-III***: *tyrosinemia types I, II and III, respectively;* ***VLCADD***: *very long-chain acyl-CoA dehydrogenase deficiency;* ***VLCADD***: *very long-chain acyl-CoA dehydrogenase deficiency.*

Source: *Ministry of Health (2019)*[39].

lining their processes, evaluation criteria, and evidentiary requirements to facilitate the submission of proposals for panel expansion.

2. These same agencies should ensure the harmonization of their criteria to promote efficient evaluation processes.

3. Authorities should consult with patient and physician representatives at each stage of the scale-up process to evaluate the inclusion of any additional diseases in the screening panel.

4. Evaluations should consider the availability and clinical benefit of relevant treatments when assessing the potential value of a screening test for a specific disease.

Factors affecting implementation:

1. Mapping exercises of current laboratory locations and capabilities should be conducted to ensure that future NSP updates are implemented in a timely manner.

2. It is necessary to set targets around the timeframe for implementation of approved programs.



In conclusion, RDs represent a significant challenge for public health due to their diversity and difficulties in early diagnosis. Delays in the identification of these pathologies generate suffering for patients and their families, in addition to imposing a high cost on the health system. Therefore, early detection and neonatal screening play a crucial role in the management of these conditions. Early identification allows timely treatment, reduces costs and stimulates the development of targeted therapies and advances in clinical research. The application of strategies such as exome and genome sequencing has significantly improved diagnostic options, and "omics" techniques are providing valuable information to resolve complex cases. To improve early detection of RDs, it is necessary to implement policies that ensure adequate funding, encourage data sharing and clinical research, establish specialized and multidisciplinary centers, and empower patients and their families with resources and support. For its part, neonatal screening is a crucial tool for detecting genetic or metabolic diseases in newborns before symptoms appear. In Spain and the rest of Europe, NSPs have advanced, but there are still disparities in the number of diseases included in the panels. The expansion and improvement of these programs require clear government policies, a transparent and open process for proposing modifications, as well as the participation of interested parties and the adoption of clear criteria to justify the inclusion of a disease in the screening. Implementation of these policy recommendations will pave the way for early and accurate diagnosis of RDs, which will have a positive impact on the quality of life of patients and their families.



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VALUE-BASED HEALTH INITIATIVES IN RDS

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The value-based healthcare model has been proposed by decision-makers as an innovative approach to improve patient experience and health outcomes with the limited resources available in the healthcare setting.

Although this innovative approach is a promising advance, it presents challenges for its implementation, especially in people living with complex, long-term diseases, such as most rare diseases (RDs). These types of conditions pose

difficulties to define its epidemiological impact on the population, to evaluate the associated costs, to define the complete care cycle, as well as to identify the needs of each patient and the appropriate outcome measures to capture the value of the health service received, which is usually multidisciplinary and with different levels of care.

There is a growing tendency to consider value-based healthcare initiatives as a strategic model of healthcare management, since they allow the healthcare and reimbursement process to be adapted and designed with the aim of generating value for the patient while maintaining the economic sustainability of the healthcare system. Reimbursement or value-based payment is particularly relevant for orphan drugs, whose financing can be difficult to justify and sustain from a financial point of view.

In the present article, the general theory of the concept of value-based care is presented, along with the strategic steps needed to implement it, including measuring health outcomes from a patient, cost and process perspective across the entire care continuum, designing the care process to create value for the patient, and incorporating value into the purchase and delivery of care. Throughout the text, some initiatives for measuring, designing and embedding value in purchasing to implement value-based care in RDs are detailed. Finally, possible ways forward for progressing towards a value-based healthcare model for patients with these conditions are reviewed.

GENERAL THEORY OF VALUE-BASED HEALTH CARE CONCEPT

In 2006, Porter and Teisberg introduced the concept of Value-Based Health Care (VBHC) as a framework for restructuring healthcare systems around the world, with the primary objective of delivering value to patients[1]. Following the lead of these authors, other experts have also proposed their own theoretical models based on the underlying idea of value. For example, the "Triple Aim" model of Berwick and co-workers, which focuses on improving the individual experience and health of patients while reducing costs[2] . More recently, the European Commission defined value-based healthcare as an overarching concept based on four pillars[3] (Table 1).

In any case, by focusing on improving the health of patients, value-based healthcare reduces the complexity and progression of the disease, which implies lower spending and reduces the need for ongoing care[4]. Thus, increasing value for patients brings together the interests of all stakeholders in the healthcare system and society, as it benefits healthcare organizations, while increasing the economic sustainability of the healthcare system and improving the health of the population (Figure 1).

Since the introduction of the VBHC concept, there has been a lack of clarity in its definition, which has led to divergent approaches and slow progress in improving outcomes[6] . Some descriptions confuse value-based healthcare with cost reduction, overall process efficiency, quality improvement or patient satisfaction. Although cost containment is importantly, to create value it is essential to improve the health outcomes that matter to patients[4], such as improving their quality of life.

Value-based care models can use a variety of health outcome measures that can be aligned with patient-centered care. Porter and

TABLE 1. PROPOSED DEFINITIONS FOR VALUE-BASED HEALTH CARE

PROPOSAL (YEAR)	DEFINITION OF THE VALUE OF HEALTHCARE
Porter and Teisberg (2006)	Theoretical definition as a ratio where the numerator (outcomes) designates the disease-specific outcomes that matter most to patients, such as functional recovery and quality of life, while the denominator (cost) refers to the total expenditure for the entire care cycle. The value is to achieve the most relevant outcomes for patients at the best possible cost.
Berwick and coworkers (2008)	"Triple aim" of value: **1**) improve the individual experience of care, **2**) improve the health of populations, and **3**) reduce per capita costs of care for populations.
European Commission (2019)	Four pillars of value: **1**) **personal value**: appropriate care to achieve patients' personal goals; **2**) **technical value**: the achievement of the best possible outcomes with the available resources; **3**) **allocative value**: the equitable distribution of resources among all patient groups; **4**) **social value**: the contribution of healthcare to social participation and connectivity.

Source: *own elaboration based on Porter (2006)[1], Berwick (2008)[2], European Commission (2019)[3].*

FIGURE 1. BENEFITS OF IMPLEMENTING VALUE-BASED CARE



Source: *own elaboration based on Barrubés (2019)*[5].

Teisberg's VBHC model defines cost as the cumulative financial cost of all aspects of a patient's care, including hospital visits, rehabilitation, medications and ancillary services. This cost can be estimated from the perspective of the payer, the hospital and the patient himself. In this regard, other experts have proposed incorporating a more holistic view of cost to include not only financial costs, but also direct costs to the patient and the system, opportunity costs and costs arising from harm (including the costs of medication, time, anxiety and clinical harm)[7].

On the other hand, the appropriateness of care is fundamental to value, as it avoids unnecessary treatments that can be performed without complications even though they do not improve the patient's quality of life. For this reason, adherence to evidence-based processes that enable healthcare professionals to effectively treat and manage their patients' conditions should be promoted[8] . In this way, value-based healthcare can draw on the advantages of evidence-based medicine and, at the same time, elevate evidence-based data to a higher level by incorporating the perceptions of patients with a disease into the evaluation of an intervention[9].

Ultimately, the successful implementation of value-based assistance delivery requires assistance integration practices and new payment models to provide the solutions necessary to help improve the experiences and outcomes of the assistance provided and to minimise costs[10].

Implementing the VBHC model requires a lot of time and dedicated funding to ensure its sustainability. This model is suitable for the ongoing management of chronic diseases or conditions such as cancer, diabetes, obesity, high blood pressure, chronic obstructive pulmonary disease and heart disease. However, its application across the whole range of RDs, due to their great diversity, implies a preventive and therapeutic approach based on individuality, and requires alternative ways of empowering and giving voice to patient groups[11].

STEPS TO IMPLEMENT VALUE-BASED HEALTHCARE

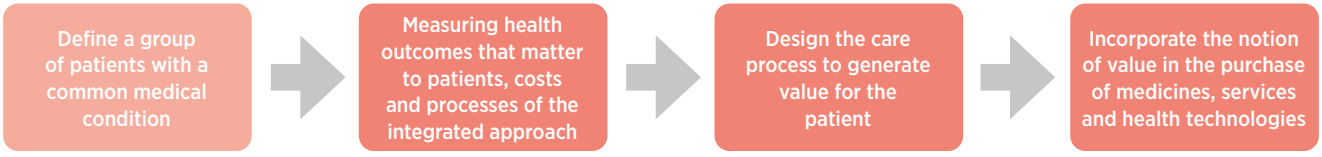
The process for implementing the VBHC model begins by defining a group of patients with a common medical condition, then designing a system for measuring the health outcomes that matter to patients, along with the costs and processes of care required to address the pathology comprehensively, then designing interventions that create value for those patients, and finally incorporating value-based payment models (Figure 2).

Measuring health outcomes, costs and processes

The value of healthcare is derived from measuring the improvement in patient health outcomes against the cost of achieving that improvement, so determining and measuring the health outcomes that matter to patients and the costs is part of the activities required to move to a value-based healthcare delivery system[4].

On the one hand, the measurement of costs and care processes should encompass a holistic view of the patient's care pathway, including not only diagnosis and basic care

FIGURE 2. STEPS TO IMPLEMENT VALUE-BASED HEALTH CARE



Source: *own elaboration based on Barrubés (2019)*[5].

procedures, but also follow-up and recovery of health status[12]. One of the steps to implement a value-based healthcare model is to collect and categorise available patient data from health records and electronic health records. In addition, systems must be created to collect and integrate all information on the care process and the health consumption of citizens throughout the entire continuum of care until they recover or improve their health status[5].

On the other hand, the determination of the relevant set of outcomes to measure for any medical condition should follow principles that allow for the inclusion of the most relevant health circumstances for patients and refer to a period long enough to consider the final results of the care received. To this end, Porter and Teisberg proposed a hierarchy of outcome measures with three levels, which include different outcome dimensions and for each, success is measured using one or more specific metrics, so that the framework is translated and operationalised according to the pathology[13] (Figure 3).

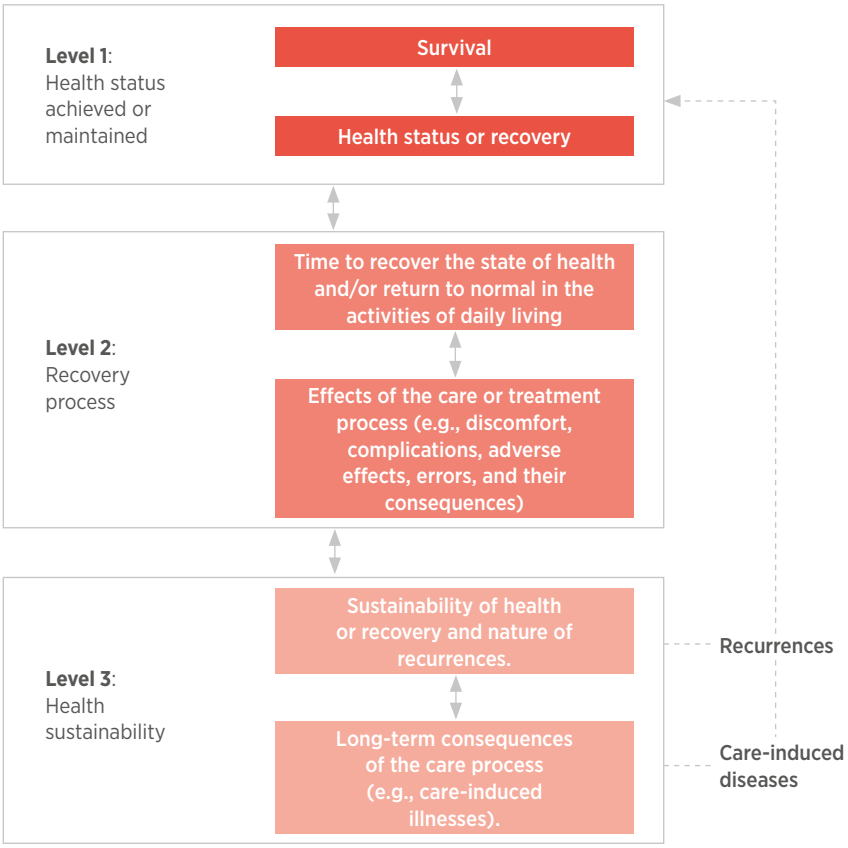
Currently, the indicators most commonly used to assess population health and health system performance tend to focus on the level of care achieved and the prevalence and incidence of disease, but often do not include the health outcomes that patients actually value, such as pain, functionality and quality of life[15]. Implicit in the concept of value in healthcare is the need to measure and quantify the quality of care received from the patient's perspective, so in addition to traditional clinical outcomes or cost-benefit measures, patient-reported outcome measures (PROMs), patient-reported experience measures (PREMs) can and should be taken into account and should also involve the participation of patients and families in the planning and evaluation of value.

Design of the care process

Value-based care process design represents a shift from the traditional health service delivery model that focused on the quantity of services provided, to a focus on value understood as the overall health outcome related to the quality of care and the cost of the whole process. It has been proposed to design the processes as a construction of the healthcare value chain, so that it serves as a descriptive and normative tool for all the care activities to be performed during the patient's pathway, who is responsible for them and how each contributes to achieving the relevant health outcomes for the patient. The main contribution of considering the healthcare value chain in comparison to traditional models is the incorporation of the patient in the design of the care process (Figure 4).

The implementation of VBHC is in its infancy, so identifying best practice is essential for healthcare leaders to start moving in the right direction towards long-term success. A guide for healthcare providers in Europe to address these challenges has

FIGURE 3. HIERARCHY OF PERFORMANCE MEASURE



Source: *Prepared by the authors based on Porter (2010)[14].*

recently been published, including a roadmap for VBHC implementation that has been developed from the experience of leaders representing a variety of roles and types of organizations in the VBHC field[6].

Embedding value in the purchase and provision of health care

Most hospitals and health systems procure medical products on the basis of a short-term, primarily price-based approach without addressing the needs of patients. Since the European Commission, value-based pricing and reimbursement has been defined as a pricing strategy that sets prices primarily, but not exclusively, on the basis of the perceived or estimated value of a product or service to the customer, rather than on the basis of the cost of the product[3].

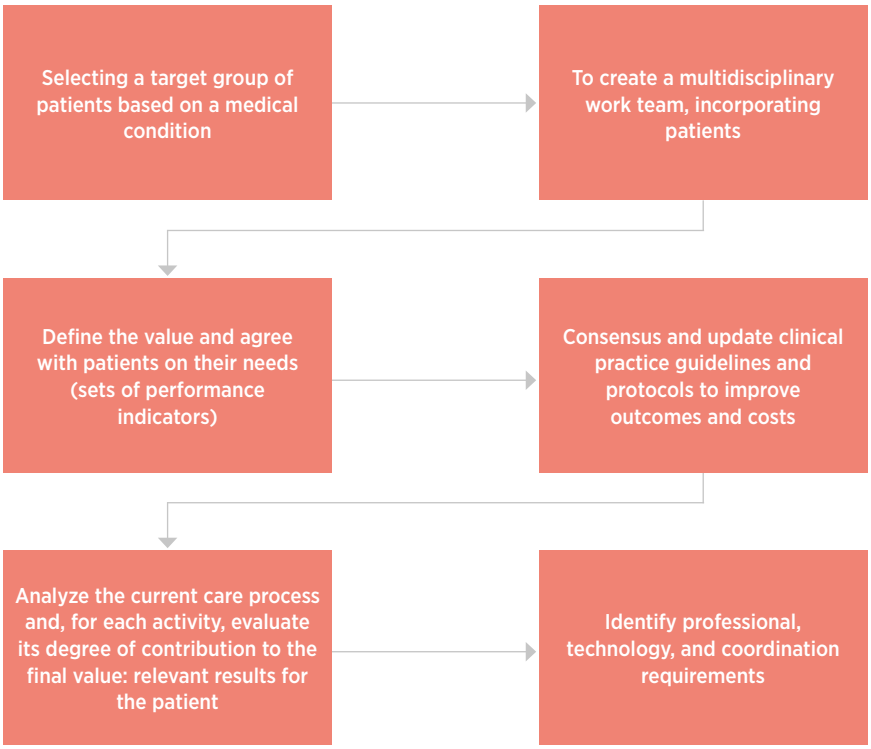
The shift in the public procurement model towards a system that incorporates a more holistic view that takes into account quality, innovation, long-term costs and broader socio-economic considerations in the procurement of medical devices has been encouraged by the adoption by the European Parliament of Directive 2014/24/EU of 26 February 2014 on public procurement and repealing Directive 2004/18/EC[16]which encourages the use of more flexible and collaborative procedures between stakeholders, representing an important step towards value-based healthcare[17].

Purchasing procedures are one of the key tools available to healthcare systems and their organizations for their transformation towards value generation. This means achieving relevant health outcomes for the patient at the lowest possible cost, whether in the procurement and consumption of pharmaceuticals and healthcare products, in the acquisition and renewal of healthcare technology equipment and/or in the provision of external healthcare services (medical transport, home therapies, etc.)[5].

In recent years, new flexible and personalised financing methods have emerged that align the prices of healthcare products, technology and services with the value they bring to the patient. Broadly speaking, there are four models of value-based financing, including fee-for-service, bundled payment, risk-sharing arrangement (RSA), and capitation or full-risk model. These models are organised around the risk of financing for each of the parties involved (healthcare provider or payer) and can generate more or less "value added"[18–20].

On the one hand, fee-for-service payment is limited to maximising the provider's profit, without generating any other value, while bundled payment requires certain quality requirements in healthcare, which leads to increased financial risk[18–20]. On the other hand, in RCAs, both providers and payers jointly bear the financial risk and are often used when healthcare costs are high[18–20]. They can therefore be considered particularly interesting in the field of RDs; in fact, it is an increasingly widespread practice to modulate the price of an orphan drugs according to the clinical outcomes it produces[21,22]. The capitated model, on the other hand, is often a combination of the financing methods described above and entails higher performance in terms of quality,

FIGURE 4. STEPS FOR THE DESIGN OF THE VALUE CHAIN OF A CARE PROCESS



Source: *own elaboration based on Barrubés (2019)*[5].

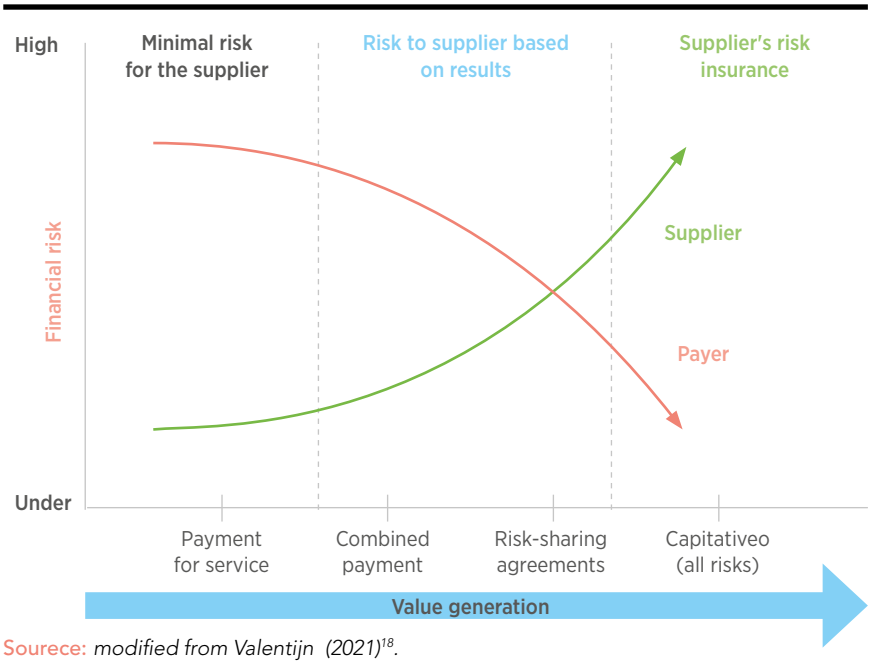
costs, coordination and prevention to achieve the best possible outcomes (implying lower financial risk for payers) (Figure 5)[18–20].

Value-based payment models require identifying the additional benefits of the new medicine, technology, product or service over comparators in order to translate the measure of value into price[23]. Although this model is still under development, value-based purchasing in healthcare has been shown to improve the management and efficiency of processes and the quality of healthcare by reducing costs, improving the overall efficiency of the entire care cycle, and avoiding unnecessary practices or practices that are not sufficiently supported by scientific evidence[5].

An interesting example is Innovative Public Procurement (PPI), which is an administrative action to promote innovation aimed at fostering the development of innovative solutions from the demand side, through the instrument of public procurement. As one of the forms used for value-based healthcare procurement, its main objective is the improvement of public services through the incorporation of innovative goods or services[24–26].

PPI is able to integrate the demands of both society and the payer, redefining the processes when procuring healthcare technologies. One of the first successful PPI projects in the healthcare sector in Spain was formalised in Catalonia, with the replacement of the direct purchase of automatic defibrillator devices by the contracting of a comprehensive service that provides, monitors and maintains the devices regularly and remotely, thus generating a value

FIGURE 5. VALUE-BASED PAYMENT MODELS



Sourece: *modified from Valentijn (2021)*[18].

chain for the patient and the healthcare system[27].

Although these initiatives have not yet been implemented in the field of RDs, they represent a promising development, with an impact on the outcomes of the care process measured in terms of health outcomes and reduced health system costs.

INITIATIVES TO IMPLEMENT VALUE-BASED HEALTH CARE IN RDS

In RDs, the development of a value-based care pathway presents different challenges compared to the usual pathways developed for common diseases. This is due to the characteristics of RDs, such as the large number of disease entities that fall into this category, most of which are chronic and often disabling in nature. In addition, they usually present a heterogeneous manifestation, with multisystemic involvement and are associated with great complexity in diagnosis and treatment. Therefore, these pathways depend to a large extent on multidisciplinary and international cooperation involving all Member States[28].

In Europe, one of the most relevant initiatives to implement the VBHC model in RDs was the creation in 2017 of the *European Reference Networks* (ERNs), which involve healthcare providers from across Europe and aim to address complex and rare diseases that require highly specialised treatment and a concentration of expertise and resources. For the effective implementation of ERNs, it has been proposed to follow the "*RarERN Path*" methodology to create a single organisational reference model for patient care pathways that, when applied in different settings, helps to ensure equitable, cost-effective and patient-centred care for rare and complex diseases[29]. In addition, this model involves and engages patient organizations, thanks to the creation of *European Patient Advocacy Groups* (ePAGs)[30].

In recent years, a major effort has been made in Spain to create national strategies and documents to support patients with RDs. Of particular note is a document published in 2004 jointly created by the Institute for Rare Diseases Research (IIER) and the Carlos III Institute of Health (ISCIII), which summarises and classifies the main RDs and gives a brief introduction on orphan drugs, social services and other aspects of interest[31]. In addition, since 2008 the collaboration between National Alliances and EURORDIS has been key to adopt legislation on RD and orphan drugs in Europe and implement National Plans and Strategies through joint actions to integrate policy measures[32]. In the field of research, in 2011 the ISCIII and the Consortium for Biomedical Research on Rare Diseases Network (CIBERER) created a national registry of patients with Rare Diseases (CIBERER)[33] and also highlight collaborations between research centers and hospitals to concentrate efforts on specific diseases and provide comprehensive management of the pathology[34].

The following details initiatives that have been undertaken for each of the basic steps required to implement the VBHC model in RD, starting with initiatives for measuring outcomes, interventions designed to generate value, and finally cases where the concept of value has been incorporated into the purchase and provision of healthcare.

Measuring health outcomes, costs and care processes in RDs

For the whole range of RDs, it is particularly important to document the progression of health status and associated quality of life, as well as to assess other health outcomes that matter to patients, the processes of care throughout the care cycle and associated costs, such as medical costs, the financial impact on carers and the impact on patients' employability[11].

In RD, initiatives to implement value-based healthcare pose some differential challenges compared to those developed for common illnesses

In recent years, initiatives have been undertaken to contribute to the development, standardisation and implementation of a new generation of metrics of the healthcare received that matter most to patients with RD and to establish the measures to be considered in future research. On the one hand, the Organisation for Economic Co-operation and Development (OECD) launched the *Patient-Reported Indicator Surveys* (PaRIS) initiative in 2017, with the aim of benchmarking the outcomes that matter most to patients[35]. It highlights the PaRIS initiative to collect the experiences and outcomes reported by patients with chronic diseases, from which patients with RDs could also benefit[36].

On the other hand, the International Consortium for Health Outcomes Measurement (ICHOM) is an organisation founded in 2012 with the aim of unlocking the potential of value-based healthcare, by defining global sets of outcome measures that matter to patients and driving the adoption and reporting of these measures globally, generating value for all stakeholders[37]. Although studies published to date have focused on the fields of orthopaedic surgery, general medicine, bariatric surgery, obstetrics and cancer, a number of different EERs are also being included[8] and cancer, a variety of RDEs, such as congenital anomalies, are also being included.

In general, the ICHOM represents the set of core measures of the agreed outcomes by means of a circle detailing the measures and the domains into which they fall. As an example, the set of the 9 agreed core measures for autism spectrum disorder, which fall into 4 domains, are represented (Figure 6).

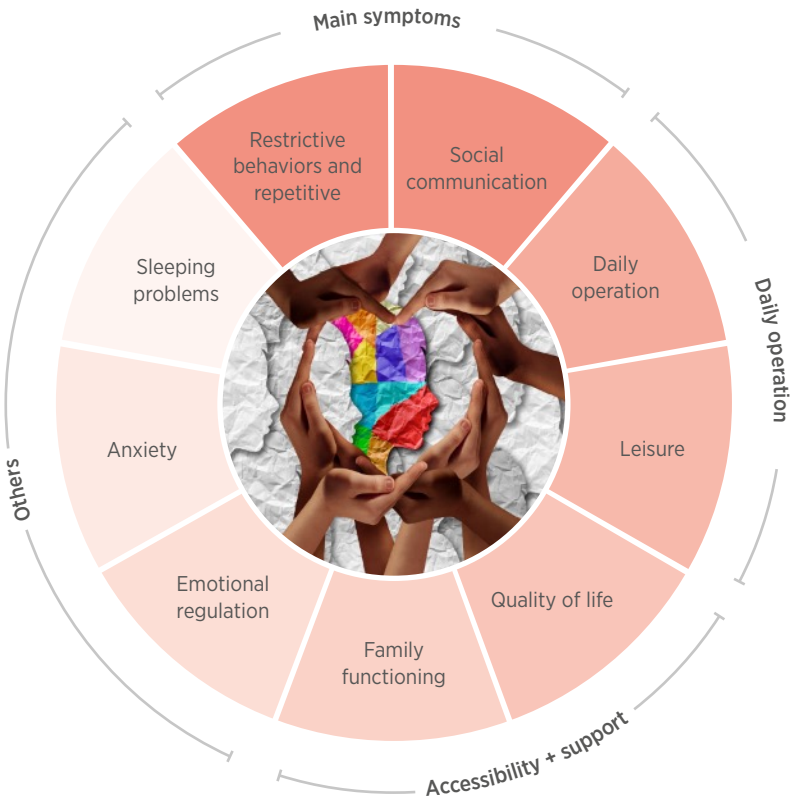
Standardised sets of outcome measures agreed by patients and healthcare professionals are particularly important for different RDs where there are no validated guidelines on which outcome domains and measurement tools best assess the quality of care provided. These sets are developed using a Delphi technique to actively transform individual opinions into group consensus after intensive preparation, discussion and collaboration between multidisciplinary clinicians, academics, administrators and patients from around the world. Broadly, this process involves defining the patient population, outcome domains, associated measurement tools and time points for their measurement, as well as relevant case set adjustment variables to aid stratification and comparison of patients (Table 2).

Designing the care process for RD patients

The design of the care process to create value for patients with RD is characterised by its complexity and multidimensionality. In many cases, patients require follow-up by multiple health and social care professionals, requiring a high level of integrated care and coordination of services between hospital, community, social and primary care services[49]. To achieve this, it is necessary to design actions at micro, meso and macro management levels that focus on fostering outcomes that make a difference for patients with a disease or condition, while driving cost-effectiveness of health services[12].

A study has recently been carried out in Spain, in collaboration with the Spanish Federation for Rare Diseases (FEDER), to assess the experience of RD patients and their caregivers in order to identify targets for optimal patient care[50]. In the analysis, they applied a modified version of the IEXPAC instrument adapted to the context of rare diseases[51] adapted to the context of RD. This tool includes a series of items to explore the characteristics and content of interactions between patients and professionals. Each item was rated by patients/caregivers and responses were transformed into a scale of 0 to 10, with 0 being the worst experience and 10 the best, to allow comparison with other Spanish studies of patients with chronic diseases and their caregivers[50]. According to the results, caregivers of paediatric patients obtained higher scores, i.e. better experiences, except for the coordination of social and health services

FIGURE 6. SET OF OUTCOME MEASURES FOR AUTISM SPECTRUM DISORDER



Source: *Own elaboration based on ICHOM (2022)[38].*

. In addition, the results reflect that the experience of patients with a rare disease is much lower rated (3.5 out of 10) than for other chronic diseases[50].

In the study by Soto et al (2022), a multidisciplinary group of experts agreed on a total of 15 proposals to improve the management of haemophilia A in the Spanish National Health System (NHS) and performed a social return on investment analysis to estimate the impact of implementing this set of proposals in the NHS within one year, in relation to the investment required. The proposed measures are related to the assistance of multidisciplinary teams with all the professionals involved, including measures for the integration of these teams, the creation of national registers and the training of patients and professionals[52].

On the other hand, the study by Fuch et. al (2021), using the example of a number of Swiss referral hospitals, has analysed how the VBHC model can be integrated and refined in the care of sarcoma patients, demonstrating the importance of active collaboration at national and international level to achieve this. The multidisciplinary sarcoma organisation in Switzerland is articulated in integrated practice units (IPU) and is characterised by the integration of the country's relevant sarcoma institutions, the Swiss Sarcoma Network (SSN), to evaluate and share transdisciplinary

TABLE 2. SET OF AGREED-UPON OUTCOME MEASURES FOR RDS

Disease	Set of agreed outcome measures	Reference
Autism Spectrum Disorder	**9** consensual baseline measures in 4 domains (core symptoms, daily functioning, accessibility+support and other), accompanied by measurement tools and case set adjustment variables.	ICHOM (2022)[38].
Congenital anomalies of the upper limbs	**6** agreed baseline measures in 2 domains (health status and patient care burden), accompanied by measurement tools and case set adjustment variables.	ICHOM (2018)[39].
Cleft lip and/or cleft palate	**9** consensual baseline measures in 2 domains (health status and burden of treatment and complications), accompanied by measurement tools and case set adjustment variables.	ICHOM (2018)[40].
Craniofacial microsomia	**8** consensus baseline measures in 4 domains (treatment burden, functioning, appearance, psychosocial), accompanied by measurement tools and case set adjustment variables.	ICHOM (2017)[41].
Pulmonary sarcoidosis	**15** agreed baseline measures in 5 domains (physiological/clinical, treatment, resource use, quality of life and death).	Harman (2022)[42].
Paediatric chronic intestinal failure	**10** consensus baseline measures from 98 measures assessed from the systematic review.	Demirok (2022)[43].
Inherited metabolic diseases	**9** consensus baseline measures for PKU from 97 assessed measures from the systematic review, **8** measures for MCAD deficiency from 83 assessed measures, accompanied by measurement tools.	Vanderhout (2021)[44].
Osteogenesis imperfecta	**24** consensus baseline measures in adults, **28** in children from 402 assessed measures from systematic review.	Nijhuis (2021)[45].
Congenital heart disease	**15** consensus baseline measures incorporating physical, mental, social and general health outcomes from 80 measures assessed from the systematic review, accompanied by measurement tools and case set adjustment variables.	Hummel (2021)[46].
Autosomal dominant polycystic kidney disease (ADPKD)	**4** consensus baseline measures (renal function, mortality, cardiovascular disease and pain) from 41 measures assessed from the systematic review, accompanied by measurement tools.	Cho (2021)[47].
Paediatric facial paralysis	**23** consensus baseline measures from 83 assessed measures from the systematic review, accompanied by measurement tools and case set adjustment variables.	Butler (2019)[48].

Abbreviations: *MCAD: medium-chain acyl-CoA dehydrogenase; PKU: phenylketonuria.*

Source: *Prepared by the authors based on references included in the table.*

sarcoma data within a prospective real-world data platform (RWD prospective Sarcoma Registry of Quality). In addition, on an international level, the SSN belongs to SELNET, a European and Latin American sarcoma network supported by the EU Horizon 2020 framework programme, and is thus integrated into the largest existing sarcoma network of multidisciplinary sarcoma experts with the aim to bring value to patients by improving sarcoma diagnosis and clinical care[53].

The Netherlands is an example to follow in the application of VBHC in RDs, with Leiden University Hospital pioneering a research-led approach to bring added value to patients with these pathologies[54]. In particular, the study by Wind et. al (2021) was based on an experience at this centre with patients with systemic lupus erythematosus and/or antiphospholipid syndrome in pregnancy complications. They have found that patient management within a multidisciplinary clinical pathway has led to clinically relevant outcomes, with a focus on the value provided to patients. This contrasts with most clinical pathway evaluation studies that focus on outcomes such as cost issues or reduced length of hospital stay[55].

Studies have also been conducted to assess the quality of care of a value-based intervention compared to standard care, the needs of these patient groups, and the costs associated with different RDs, both for clinical service pro-

viders and for patients and caregivers[56,57].

The most relevant results of the above-mentioned studies, which aim to promote value-based healthcare in different RDs, are summarised below (Table 3).

Embedding value in the purchase and provision of health care

Examples and publications on incorporating value into health care procurement in RD are scarce and are mainly limited to quantifying the economic impact of incorporating new orphan drugs into health systems. However, over the last few years, new initiatives have emerged that consider a broader approach to establishing the value of orphan drugs as a whole, including their social perspective, and without strictly economic criteria.

One of the first such initiatives was proposed by Paulden et al. in 2015[58] by recognising a number of value arguments in published academic articles related to orphan drugs reimbursement and linkages between them to build a coherent decision framework. In this regard, they identified a set of factors that help guide value-based reimbursement decisions for orphan drugs, without considering only the cost-effectiveness of orphan drugs. Some of these factors are value drivers per se and relate to the disease itself (especially rarity), the treatment, the population to be treated and socio-economic aspects; but there are also others (such as feasibility of diagnosis and/or treatment) that may condition the funding of the medicine, as they do not generate the expected value (Figure 7).

They also identified three possible sources of preferences: those of patients, physicians and society, and a series of proposals on how values should be incorporated into the decision-making process[58]:

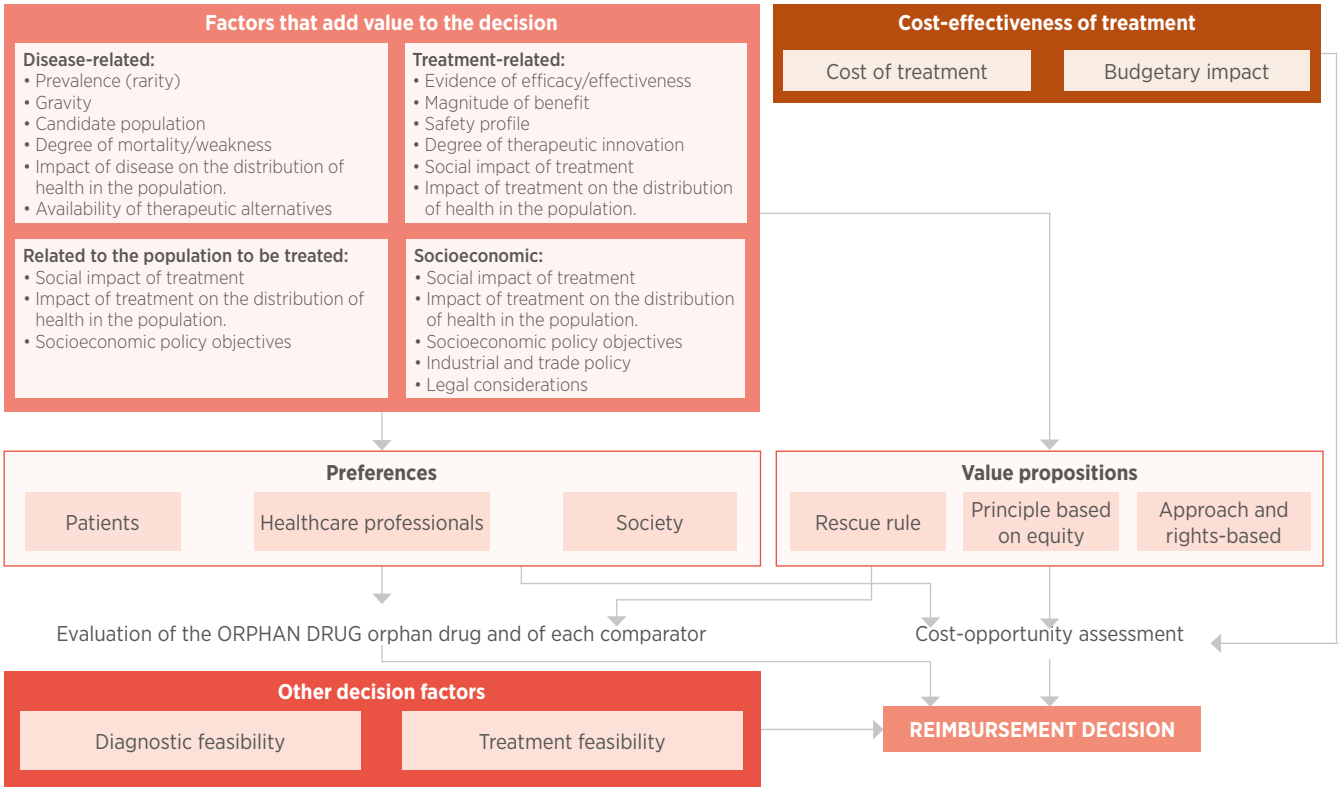
- The 'rescue rule', which supports the non-abandonment, regardless of pharmacological cost, of identifiable patients with life-threatening disease if effective treatment is available.
- The 'equity principle', which argues against special consideration for patients with RDs.
- The 'rights-based approach', which proposes that people have the right to a dignified

TABLE 3. RESULTS OF INITIATIVES TO GENERATE VALUE IN RD

DISEASE	COUNTRY	RESULTS OF THE VALUE CREATION INITIATIVE	REFERENCE
Haemophilia A	Spain	The implementation of the full set of 15 proposals would require a total investment of 2.34 million euros and would have a total impact of 14.60 million euros, i.e. each euro invested would produce a social return of 6.23 euros (3.37 euros in the worst case scenario and 9.69 euros in the best case scenario) in tangible and intangible costs.	Soto (2022)[52].
Sarcoma	Switzerland	They have identified a number of key steps to implement the VBHC model: (1) Structuring IPU around a medical condition; (2) Measuring outcomes with value (multidimensional and that matter to patients); (3) Aligning reimbursement with value; (4) Clinically integrated care delivery systems; (5) Geographic expansion; (6) Integrated technology platform.	Fuchs (2021)[53].
Systemic lupus rythematosus and/or tiphospholipid syndrome	The Netherlands	The application of a multidisciplinary clinical care pathway, including pre-pregnancy counselling, significantly reduced disease-related flares during pregnancy. Maternal and foetal complications of pregnancy did not differ between patients who were managed with this multidisciplinary clinical pathway and those who were not.	Wind (2021)[55].
Pulmonary hypertension	France	Involvement of clinical pharmacists in collaborative care resulted in more problem solving than in the usual care group (86.5% vs. 66.7%; p = 0.01) and reduced the costs of drug-related hospitalisations. Time to clinical deterioration, adherence, satisfaction or quality of life was not statistically different between groups.	Roustit (2020)[57].
Alstrom Syndrome	United Kingdom	The clinical cost assessment for multidisciplinary care was less than £700/patient/year compared to standard care of £960/patient/year. However, the real savings were in terms of quality of life for patients, who were very satisfied with the care they received. In addition, there was a significant reduction in the frequency of clinic visits and test ordering since the establishment of the national service.	Van Groenendael (2015)[56].

UPI: Unidad de práctica integrada; **VBHC**: Atención sanitaria basada en el valor (*Value-Based Health Care*).
Fuente: *elaboración propia a partir de referencias incluidas en la tabla.*

FIGURE 7. FRAMEWORK FOR VALUE-BASED REIMBURSEMENT DECISIONS BY ORPHAN DRUG



Source: *adapted from Paulden et al. (2015)*[58].

minimum standard of medical care, implying that treatments for RDs should be available if the respective patients have no other therapeutic alternatives.

However, while this approach would allow payers to arrive at a value-based coverage decision by identifying which value factors they consider relevant, whose preferences they wish to consider, and which value propositions underpin their decisions, the reality is that it is not yet (even partially) replicated in standard practice.

On the other hand, several authors consider the need for a common framework for action at the reimbursement level for orphan drugs, involving all stakeholders, homogenising evaluation criteria and collecting real-world data to support innovative financing schemes that allow patients' equitable access to these therapies[59–61]. This would allow reimbursement conditions to be defined not only on the basis of economic factors, but also on the basis of the burden of disease, the cost without optimal treatment, the availability of alternative treatments, the degree of therapeutic innovation, the direct and indirect medical costs avoided by the use of the medicine, and the expected change in patients' survival and quality of life[61].

In Spain, it is interesting to note that in 2019 the first orphan drugs was financed for the first time in the NHS under an innovative financing model at national level, based on payment by clinical outcomes, which facilitated access despite high clinical uncertainty. By 2022, there were already 7 orphan drugs financed under this model, which are being monitored through VALTERMED[62]. Likewise, the Autonomous Communities (ACs) and hospitals themselves already have experiences based on payment by results for different orphan drugs, previously establishing a series of clinical variables that allow the efficacy of the treatment to be oriented[63,64]. (Note: the September 2002 issue of newsRARE expands on this information and includes a list of orphan drugs included in VALTERMED and financed in Spain through risk-sharing agreements (RSAs)).

Although much remains to be done in this area, such can guide future orphan drug reimbursement policies, with value arguments to meet the needs of both decision-makers and society, and with clear examples of the values on which they are based and how these have been implemented in funding decisions.

CHALLENGES AND PROPOSED MEASURES TO IMPROVE VALUE-BASED CARE IN RDS

There are specific challenges to establishing a value-based model of care in RDs, as these patients often experience significant difficulties in obtaining a diagnosis and accessing appropriate and coordinated services, care and treatment. Indeed, lack of care coordination, inefficient use of resources and fragmentation of services has been reported to be a major barrier to accessing timely interventions and has a major impact on the health and wellbeing of those affected by RDs[49].

The COVID-19 pandemic has further highlighted the health challenges for people with RDs and the need to strengthen health systems. One of the most significant challenges we face in Europe is that there is a lack of defined care pathways and standards of care for the whole of the RD population, with health professionals reporting a lack of access to educational opportunities on RD and advocating for the need to meet the unmet needs of this patient group[49]. Overall, it can be concluded that the lack of evidence and knowledge of this group of pathologies delays the development of treatments and hinders both diagnoses and access to evidence-based, coordinated and comprehensive medical care (Table 4).

TABLE 4. CHALLENGES TO IMPLEMENTING THE VALUE-BASED CARE MODEL IN RDS

The scope and capacity of most registries and databases are limited to the purely medical and clinical domains.
Insufficient knowledge of most RDs.
Longitudinal data collections are scarce.
The results of treatment and care are diverse and difficult to quantify.
Diagnoses are difficult and often delayed, there is limited capacity to recognise RDs at the entry level of the care pathway.
The development of therapies and treatments is not homogeneous and is often slow.
Specialised and coordinated medical care is scarce and expensive due to its complexity and multidimensionality, lack of defined care pathways and standards for RDs.
Standards of care for treatment and rehabilitation are not evidence-based because health research is necessarily done on a small scale.
Lack of financial support and incentives.

Source: *Prepared by the authors based on Fantini (2019)[11] and Ward (2022)[49].*

One of the most significant challenges we face in Europe is that there is a lack of defined care pathways and standards of care for the whole of the RD population

As we have seen above, the European Commission has proposed a series of general recommendations for implementing the VBHC model to support the pillars on which the concept of value is based. These measures aim to promote both personal value, by achieving appropriate care to meet patients' personal goals; technical value, as the objective is to achieve the best possible outcomes with the available resources; allocative value, with the equitable distribution of resources among all patient groups; and finally, social value, through the contribution of healthcare to social participation and connectivity[3].

These guidelines are to be adapted with specific measures to benefit RDs[3]. First, there is a need to create a long-term strategy to include the value-based care model in the RDs, driving the adoption of the necessary policies and helping to coordinate care[65]. Furthermore, it is essential to support research and encourage the appropriateness of interventions to avoid inequity, reallocating resources if necessary through the possibility of personalising prevention, care and health promotion. In short, in RD, the new paradigm of value-based health care must promote the three "Es" (Effectiveness, Efficiency and Equity)[11] and a five "Ps" plan, promoting personalised, preventive, predictive, participatory and population-based medicine11 with the aim of tailoring diagnosis and therapeutic or preventive measures in a more individualised way[66].



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THE ROLE OF STAKEHOLDER INVOLVEMENT IN THE EVOLVING EU HTA PROCESS: INSIGHTS GENERATED THROUGH THE EUROPEAN ACCESS ACADEMY'S MULTI-STAKEHOLDER PRECONVENTION QUESTIONNAIRE

Van Haesendonck L, Ruof J, Desmet T, Van Dyck W, Simoens S, Huys I, et al. The role of stakeholder involvement in the evolving EU HTA process: Insights generated through the European Access Academy's multi-stakeholder pre-convention questionnaire. J Mark Access Health Policy. 2023 Jun 4;11(1):2217543. https://doi.org/10.1080/20016689.2023.2217543

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SUMMARY

Van Haesendonck's article analyzes the role of the main actors in the drug evaluation process in the wake of the new European regulation on Health Technology Assessment (HTA). A regulation adopted in December 2021, and which aims to harmonize HTA with joint assessments between European bodies, as well as to make the process more transparent with the participation of third parties (such as patients and professionals) and the creation of a network to support the Coordination Group.

In this context, the article first analyzes the current and expected participation of the different stakeholders in the HTA process based on data collected from a survey launched for this purpose; then the barriers that are being encountered; and finally, the efficient practices that have been identified and that can be carried out to develop this work.

The survey was answered by patient representatives, clinicians, regulators, and health technology developers. In general, each of the groups rated their own involvement lower than others felt

There is a significant discrepancy between how different actors perceive their own involvement in the HTA process and how they are perceived by others



they had, suggesting a feeling of subpar involvement. For example, patient representatives self-rated themselves with a mean score of 2.0, whereas the external rating ranged from 2.67 (by representatives of HTA bodies) to 3.0 (by payers and policy makers). On the other hand, clinicians self-assessed themselves with a mean score of 2.5, with external ratings of 3.0 (by HTA bodies), 4.20 (by payers) and 4.33 (by policy makers). Whereas, in the case of regulators, the self-assessment was 2.0, with an external assessment of 2.86 (by HTA bodies), 4.0 (by payers) and 4.33 (by policy makers).

There is a significant discrepancy between how different actors perceive their own involvement in the HTA process and how they are perceived by others.

The study concludes that a coordinated effort and a specific research agenda are needed to ensure the effective participation of all stakeholders. This includes establishing clear processes and pathways to ensure that input from patients, clinicians and health technology developers is effectively utilized and not just collected to meet regulatory requirements. Further research is still needed to optimize the participation of all stakeholders, define their roles and address the specific challenges faced by each of them. Challenges include HTA training to ensure that the technically and ethically complex procedures are based on a broad societal consensus in the EU member states.

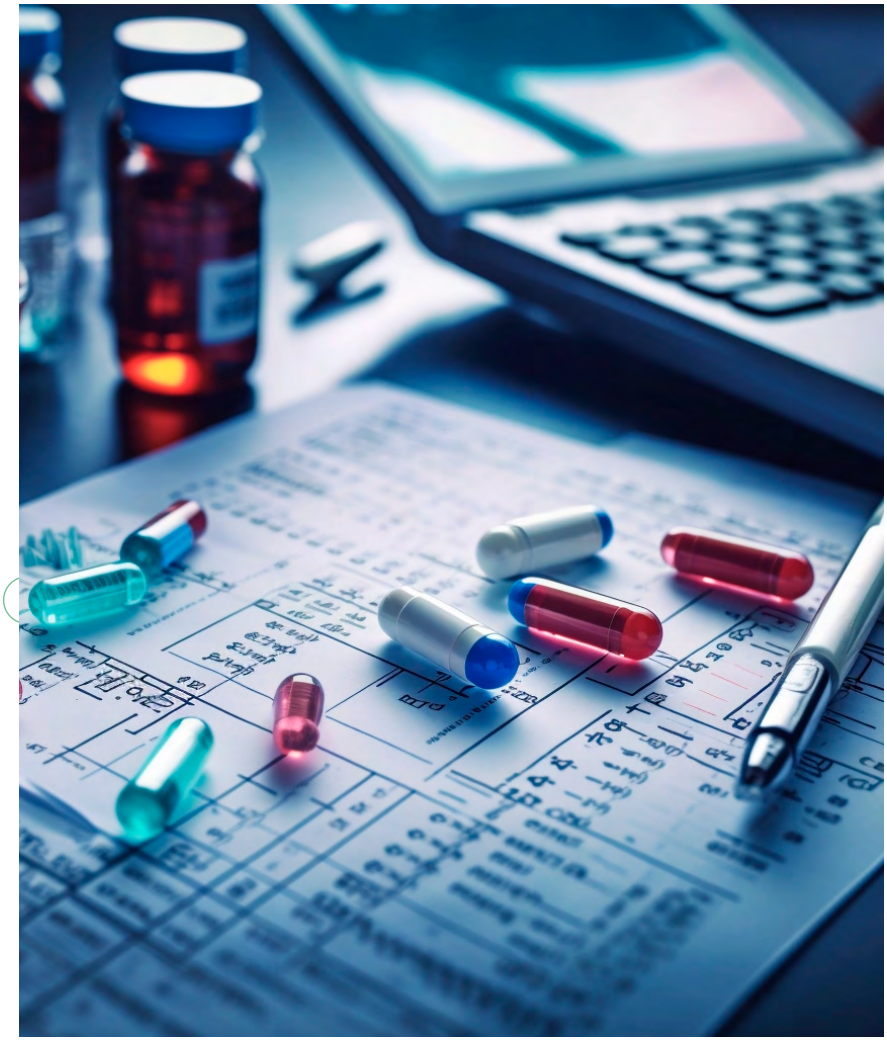
As I see it, this study illustrates the need to improve communication between stakeholders and policy makers in the EU.

COMMENT

The study by Van Haesendonck et al. provides an overview of the role played by the different key players in the HTA process. This research is particularly relevant given that HTA is decisive in healthcare decisions and resource allocation in healthcare systems.

The survey conducted highlights a very relevant point: there is a significant discrepancy between how the different agents perceive their own participation in the HTA process and how they are perceived by others. This gap in perception could have implications for the usefulness of HTA if the parties that should be involved feel disadvantaged because their participation is being limited; which could result, in my opinion, in disenchantment with HTA outcomes if they do not fully reflect their needs and concerns. Therefore, the study highlights the importance of the transparency and collaboration that the new European regulations are intended to bring about. It is important that

As I see it, this study illustrates the need to improve communication between stakeholders and policy makers in the EU



effective participation is achieved so that decisions integrate this variety of viewpoints; this would undoubtedly help to achieve subsequent acceptance of the conclusions. However, although this is desirable, the findings suggest that there is still a lot of work to be done if we really want to make the parties feel included.

As I see it, this study illustrates the need to improve communication between stakeholders and policy makers in the EU. Among many other measures, improvements could be made with clear instructions on stakeholder expectations, formulating more precise consultations and providing feedback on what has, or has not, been taken into account, along with a justification as to why.

It is essential that participation not be instrumentalized and that it not be limited to a mere formality, but translate into a tangible influence on HTA decisions. This requires not only greater transparency in the process, but also an active commitment to incorporate the contributions of all stakeholders when these meet the criteria expected of them. We understand that representation should be based on dialogue, but also on evidence. We must make an extra effort to justify that what we share accurately reflects the significant sentiment of the population or subpopulations we represent and want to protect and benefit.

Finally, this study opens the way for other research that could further explore how to improve the participation of third parties in HTA processes. It would be interesting to better investigate the actual expectations of what each of the groups expects with respect to the others to help us know how to reduce the gap between them. Likewise, we still need specific strategies aimed at increasing effective participation and to know how these strategies could be adapted to different national contexts within the EU. Not forgetting how important it would be to measure the long-term impact of participation in terms of quality of inputs and acceptability of HTA findings.

In summary, the article by Van Haesendonck et al. is an important reminder that to achieve an HTA that is truly representative and fair, we need not only to encourage participation but to test its value and the parties' sense of inclusion.

OWARDS BETTER PHARMACEUTICAL PROVISION IN EUROPE-WHO DECIDES THE FUTURE?

Horgan D, Spanic T, Apostolidis K, Curigliano G, Chorostowska-Wynimko J, Dauben HP, et al. Towards Better Pharmaceutical Provision in Europe-Who Decides the Future? Healthcare (Basel). 2022 Aug 22;10(8):1594. https://doi.org/10.3390/healthcare10081594



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SUMMARY

In recent years in the EU, a number of significant advances have been made in the context of human health. New drugs, vaccines and treatments have been developed to address some of the major causes of diseases, many of them life-threatening. It is clear that investment in research, development and innovation (R&D&I) of innovative medicines and treatments is essential to advance disease prevention and treatment.

In view of the legislative processes around the pharmaceutical sector, which should start by the end of 2022, discussions and debate should focus on how Europe can and should best promote the enormous potential benefits of the new science and technology perspective. To this end, the challenges for European healthcare, which were detailed by different panelists at the round table organized by the European Alliance for Personalized Medicine (EAPM), must be taken into account.

The results of the panelists' discussions have been summarized and reorganized in this paper under six dimensions:

1. Innovation
2. Unmet medical needs
3. Access
4. Security of supply
5. Adaptation to progress
6. Efficiency

Algunas de las conclusiones que surgieron del panel son un llamamiento a una mejor solución holística y una correcta visión del futuro de la industria farmacéutica, así como de la salud en Europa, además de un esfuerzo colaborativo entre todas las partes interesadas, que ven la prestación farmacéutica como parte de un panorama más amplio de la atención sanitaria.

COMMENT

The authors have based this document on a systematic review of the literature with the aim of contextualizing the challenges and opportunities related to the expected revision of the pharmaceutical sector legislation. The methodological description is adequate and concise and is in line with the objective pursued. The panel of experts consulted is varied and highly qualified, both technically and politically, so we can affirm that the conclusions and recommendations reflected in this article deserve a careful and reflective reading. Among the main suggestions distilled from the text is the proposal to achieve an optimal and more useful approach, based on replacing the current silo thinking with a vision based on consensus that pivots on the common interest,



and on constantly improving and adapting services and products to the European Union as a whole, knowing and demonstrating that health is wealth, and vice versa.

In order to achieve this new purpose, the authors recommend focusing on six dimensions: innovation, unmet medical needs, access, security of supply, adaptation to progress and efficiency. I am sure that all readers of this commentary will agree with me that the proposal they make is more than accurate. With regard to the innovation dimension, they focus on the improvements needed to make the European environment attractive to private investment (regulatory incentives, agile assessments, data protection and market exclusivity), but they ignore the fact that a chapter on own investments to promote open innovation would also be desirable. As far as unmet clinical needs are concerned, the proposal is somewhat diffuse, although it is true that they stress the priority of achieving an organizational model focused on defining and finding health solutions for people. With regard to access, the diagnosis of the situation once again puts the finger on the sore point, since Europe is slow in this dimension. In fact, this is one of the key aspects when it comes to reforming the legislative aspects and, of course, avoiding the tremendous inequalities that exist between the countries of the European Union. The summary comment on security of supply converges in something known and suffered by all Europeans, the dependence on third countries suffered in the COVID pandemic; and it is not enough to improve communication and coordination, but a practical and budgeted policy is needed to promote autonomy in the production of medicines and essential health products. Adaptation to progress is something we all understand as a basic premise, but this document does not adequately explore synergies with other socioeconomic and technological sectors and focuses exclusively on the latest advances in oncology. Finally, under the umbrella of efficiency, is where the concept of "digitalization" is framed as well as that of acceleration in the development of clinical trials, ignoring something as important as a review and application of health technology assessment methodologies, apart from the well-known disparity in the application of the concept of "value-based health".

ASSESSING THE VALUE OF ORPHAN DRUGS USING CONVENTIONAL COST-EFECTIVENESS ANALYSIS: IS IT FIT FOR PURPOSE?

Postma, M.J., Noone, D., Rozenbaum, M.H. John A. Carter, Marc F. Botteman, Elisabeth Fenwick & Louis P. Garrison. Orphanet J Rare Dis 17, 157 (2022). doi.org/10.1186/s13023-022-02283-z



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SUMMARY

The overall purpose of this article is to evaluate whether the "conventional" Cost Effectiveness Analysis (CEA) method is appropriate for Orphan Drugs. For this purpose, the article is divided into three parts, where the authors:

1. They show the limitations of "conventional" CEA for orphan drugs.
2. They evaluate alternative and supplementary approaches.
3. They offer ideas on possible steps forward.

Context: the conventional CEA

As an introduction to the article, the authors briefly summarize the current situation of some aspects related to orphan drugs, highlighting in this summary, it is worth highlighting the increase in the number of countries with policies that offer aid to R&D in orphan drugs. Thus, while in the early 2000s, around 10% of the countries offered guaranteed market exclusivity, tax credits and accelerated authorization, among others, by 2020 it is already 50%.

In this introduction, they also note that a frequently used method to measure the economic value of a drug in a country, determine its availability, and its appropriate level of reimbursement, is the "conventional" CEA. Thus, the key metric would be the Incremental Cost Effectiveness Ratio (ICER), and where effectiveness is measured by Quality Adjusted Life Years

(QALYs). In order to make the decision, this additional cost per QALY is would be compared to a threshold, either predefined or reflecting the revealed willingness to pay. But as the authors argue, this method was developed for drugs for more prevalent diseases, so assessing orphan drugs with this traditional approach is not appropriate (we will comment on this and the implications of how to measure "value" later). These limitations are detailed in the next section; however, before that, it is important to note that the authors end the Introduction with a note of clarification about the relationship between rare diseases and their severity. Thus, it is stated that not all rare diseases are "serious", but that they tend to be associated more frequently with shorter life expectancy and moderate-severe symptoms, compared to non-rare diseases, so the authors refer to rare and serious diseases when the term "rare" is used, unless otherwise stated.

Practical and theoretical limitations of the conventional CEAACE for orphan drugs

The authors organize the limitations into three categories:

(1) Conflict of basic principles: the nature and characteristics of orphan drugs conflict with the basic motivation of conventional CEA principles applied to new drugs.

This limitation is framed in the intersection between ethics and economics, where the authors describe three possible conflicts. The first concerns horizontal equity versus vertical equity. Horizontal equity emphasizes equal treatment of equals (i.e., a utilitarian approach) for example, applying the same cost per QALY threshold for all diseases. Vertical equity emphasizes unequal (but equitable) treatment for unequals and would describe a system that considers disease rarity in its appraisal of new drugs.

The second conflict is between "uti-litarianism" versus "non-neglect", or in other words and as used in the context of health economics specifically, maximized good for all versus favoritism toward those in dire need.

Finally, there is the conflict between "welfareism", or welfarism (the idea that the individual knows best what is best for his or her own welfare, which is broader than simply health, interest) versus "extra-welfarism", or extra-welfarism (the idea that democratically agreed principles can place limits on individual freedom in pursuit of other objectives such as equity). Thus, under welfareism, the emphasis is on individuals maximizing their welfare. Under extra-welfareism, social welfare involves taking into account considerations of equity of access, health outcomes, and well-being.

(2) The complex nature and limited scope of QALY metrics: highlighting problems in measuring health outcomes based on QALYs for orphan drugs.

The discussion about the validity and usefulness of QALYs is far from new, and it is a well-documented topic. The authors offer three aspects that dominate criticisms of this health outcome measure, given its current use in conventional CEA. First, QALY, particularly when measured with generic instruments, may not fully capture the benefits and harms of a treatment, health condition, etc., because the domains covered by the measure may not adequately capture the context of the disease or the impact of the treatment. Second, there is a "disability paradox" whereby an affected population judges their health more positively than the general population. Third, conventional CEA assumes that all QALYs are the same (giving rise to the famous phrase 'a QALY is a QALY is a QALY', implying that the value of 1 QALY is the same regardless of the patient's baseline situation or the severity of the disease), which can be problematic for orphan drugs for severe disease.

(3) High uncertainty: how the valuation of orphan drugs exacerbates uncertainty within the CEA convention framework.

There is uncertainty about the efficacy and safety of orphan drugs when they are launched on the market. The reasons are various but include a limited number of patients in clinical trials, lack of randomization or comparator, the need to use surrogate measures of efficacy, or uncertainty about the durability of long-term benefits.

Having outlined these limitations, the authors review possible alternatives to the conventional CEA for orphan drugs.

Alternatives to conventional CEA

Before introducing the options, the authors comment that there are countries that are already using alternatives to conventional CEA for orphan drugs, which demonstrates and reinforces the practical challenges faced by health systems when they are incorporating them into their portfolio. It is also true that some of these alternatives are still on 'paper', in the sense that they have not been introduced in practice. Thus, the authors list the possible options to the conventional CEA, one of the objectives of which is to increase the scope of what is considered relevant to the benefit/risk profile of a treatment - but avoiding double-counting.

As I will discuss later, how and what criteria or attributes we should take into account to measure the value of a measure in general, and of HMMs more specifically, is a complex issue. From my point of view, and although the authors do not do so, in this debate we can separate between two concepts when thinking about alternatives. First, we would have the variables or attributes of value that we want to include in the evaluation of a drug, whether orphan or not. Secondly, the process used to make the decision (and once the criteria to be used in the evaluation have been agreed upon).

In the discussion part below, I concentrate on the first debate, i.e. on the attributes to be taken into account, and what the authors call an 'augmented' CEA, and partly reflected in the ISPOR value flower which I discuss later.

Regarding the second debate (processes), the concept of Multi-Criteria Decision Analysis (MCDA) has been proposed for years as an alternative to determine drug prices and financing. In addition, other options discussed include the concept of "fair-innings" (which benefits people with rare diseases by prioritizing treatments to extend the quantity and quality of life of younger patients, who otherwise will not survive to a lifespan considered acceptable), the generalized risk-adjusted cost-effectiveness (GRACE) approach or increasing cost-effectiveness thresholds.

Possible steps forward

For the authors, MCDA and "augmented" CEA (discussed in more detail in the next section) are the most sensible and objective alternatives to conventional CEA. In fact, there are already countries that have adjusted their approaches to address the limitations described above, including having a variable ICER threshold that takes into account the severity of the disease.

Having summarized the article, I will now comment on some aspects that I believe may be of more interest to the reader.

COMMENTS

We are at a key moment in Europe for the future of the orphan drug for several reasons. First of all, a few years ago the European Commission published an impact assessment of the European legislation for rare diseases and orphan drugs (introduced in the early 2000s), with the aim of subsequently revising it. This is not the place to talk about it, but it is worth saying that these incentives have been very important to be where we are today, in the sense of having (many, but not all we need) orphan drugs in the market. The new regulation is about to be published.

The European Pharmaceutical Strategy and the European Health Technology Assessment Regulation will significantly influence the way orphan drugs are evaluated and regulated

Second, less recently the EU published the European Pharmaceutical Strategy, where rare diseases and orphan drugs play a key role. This strategy will also influence the development of legislation on orphan drugs in Europe.

And, thirdly, the so-called European Health Technology Assessment Regulation (HTA Regulation) on Joint Clinical Assessments, i.e., on clinical assessment. It is important to clarify that this Regulation is not about "economic assessment", which will remain the competence of the Member States. However, the idea is that this clinical assessment at the European level can then be the basis for the economic assessment at the country level.

But assessing the value of a new drug, including orphan drugs, is a national competence of the Member States. And it is here that I would like to comment, at a general level, on how the criteria to be used in this evaluation have evolved. The idea is to provide a more graphic overview to facilitate reading. In

addition, I have had the pleasure of participating in some of the references used by the authors.

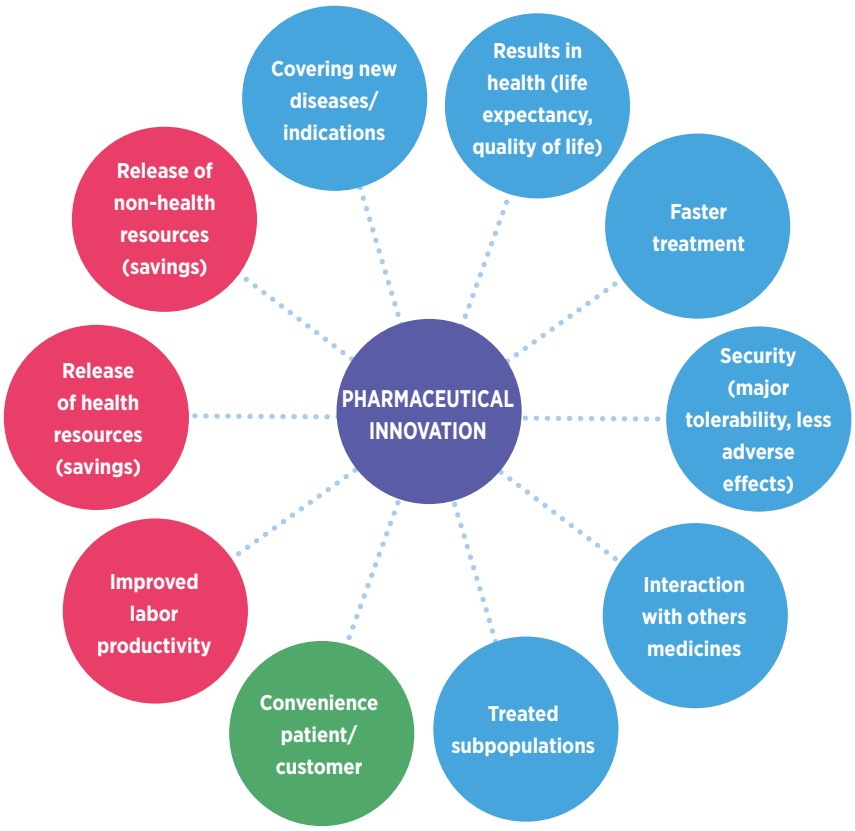
Defining "value" and "innovation"

Semantics in pharmaceutical policy is very important, and one aspect to note is the terminology used. In 2005, at the Office of Health Economics, my workplace at the time, we prepared a report on the many facets of innovation: The Many Faces of Innovation (OHE, 2005). And yes, I said innovation, not value, but the concepts are similar. However, almost 20 years ago, there was more talk of "innovation" than of "value". In addition, as Postma and colleagues point out in their article, back then we had drugs that were different from the new drugs that are now available we have been seeing over the last 15 years, including orphan drugs. Thus, we had launches of new molecules, for diseases of primary care setting, with high volume and "low" price per patient; for example, statins, H2 antagonists, or proton pump inhibitors. And at that time, the debate was about the concept of "incremental innovation", as it was common to encounter for certain diseases, many of them. The new drugs were often referred to as "me-too" by critics of these strategies on the part of the pharmaceutical companies, and often in a pejorative manner. Critics of these strategies on the part of pharmaceutical companies used to refer to these new drugs as "me-too", often in a pejorative way. In part, and from my point of view, this also drives the development, use and popularity of the conventional ACE (as mentioned above) as a way of trying to seek more efficient drug spending.

Moreover, at the time, innovation was often classified in a relatively "simple" and sometimes almost binary way: radical/disruptive ("breakthough") versus incremental innovation, or even as a dichotomous "yes it is innovation" or "no it is not innovation". And in part, the aim of our OHE report on the multiple facets of innovation was to argue that the innovation of a drug should be measured in terms of several attributes, beyond the conventional CEA approach, and cost per QALY, and that the choice of having pharmacological alternatives for the treatment of diseases can generate socioeconomic benefits beyond the treated patient. It should be remembered that the conventional CEA approach focuses on the effects of the treatment (or the technology to be used) on the patient using it. In 2012, we published an update of our Report, with some modifications on the criteria to be included to determine the degree of innovation of a new drug (Mestre-Ferrandiz et al., 2012). In these two reports, we graphically presented these potential attributes of pharmaceutical innovations, which we replicated in Figure 1. Perhaps with this figure we offered a first "value flower" - although we called it internally "the bubble diagram" at the time.

The semantics used in the debate on the evaluation of medicines, and

FIGURE 1. ELEMENTS OF PHARMACEUTICAL INNOVATION



Source: *OHE (2005), Mestre-Ferrandiz et al. (2012), and adapted in Spanish in Zozaya et al. (2017).*

of health systems more generally, were already changing at that time, in the sense that the word "value" was beginning to appear in the debate; for example, value-based pricing. Without going off topic, in parallel there were already quite a number of initiatives that we were trying to analyze the attributes that should, or could, be taken into account to measure the value of new drugs. In addition, we were beginning to have new drugs that were different from existing ones: for example, orphan drugs for much smaller populations, and with greater clinical and economic uncertainty. And as Postma and colleagues rightly argue, the traditional CEA approach falls 'short' for evaluating these types of drugs.

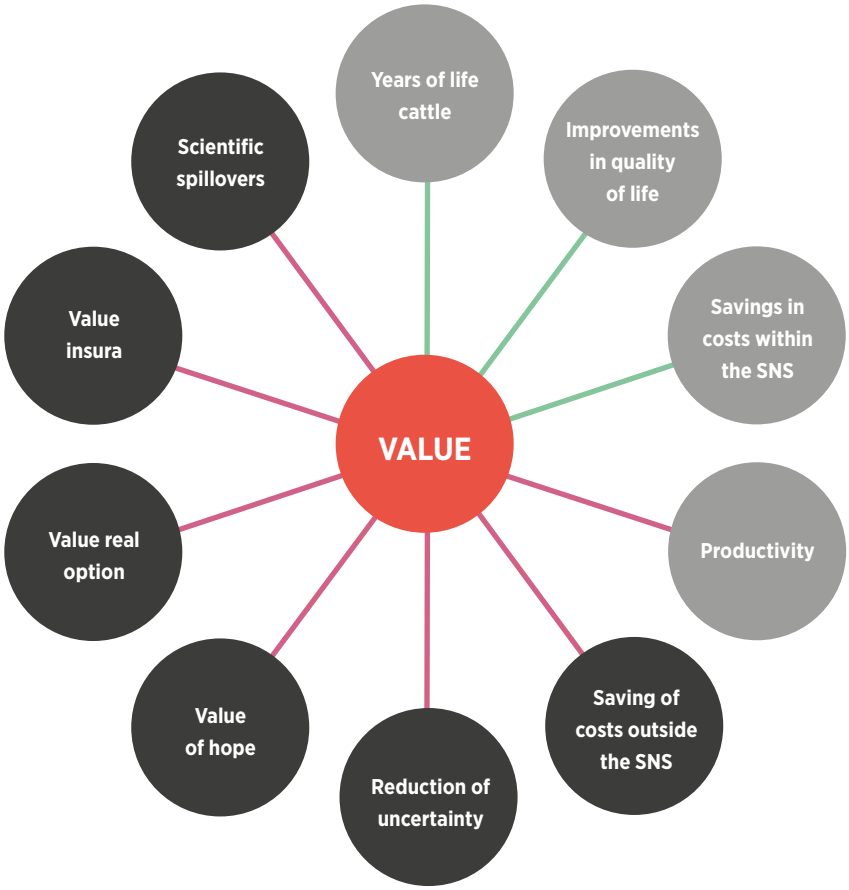
And here we would like to refer to two papers (one mentioned by Postma et al) that have been highly referenced in the debate on how to value new drugs in general, and with implications for orphan drugs. The first, in which I also participated with the OHE, assessed the value attributes (and yes, we had already changed the terminology to value) of diagnostic tests (not drugs). The second came from ISPOR, which gave rise to the so-called 'ISPOR value flower', and where one of the co-authors who led the initiative had also been involved in the diagnostics work. In addition, these two reports evaluate the use of these attributes in drug evaluation processes (core elements, common but inconsistently used elements, and new elements), as well as their perspective (payer/national health system perspective vs. societal perspective).

Figure 2 and Figure 3 replicate the relevant graphs. Thus, while the analysis for the diagnostics includes 10 elements, the ISPOR "value flower" includes up to 12 attributes. (Note: in some ISPOR figures the element "factors to improve adherence" does not appear, and "family spillovers" does).

Perhaps one of the weaknesses of the article by Postma and colleagues is that it does not compare more graphically how the debate has evolved around the attributes to be included in the concept of

Almost 20 years ago, we talked more about 'innovation' than 'value', but today, the focus has shifted to value assessment

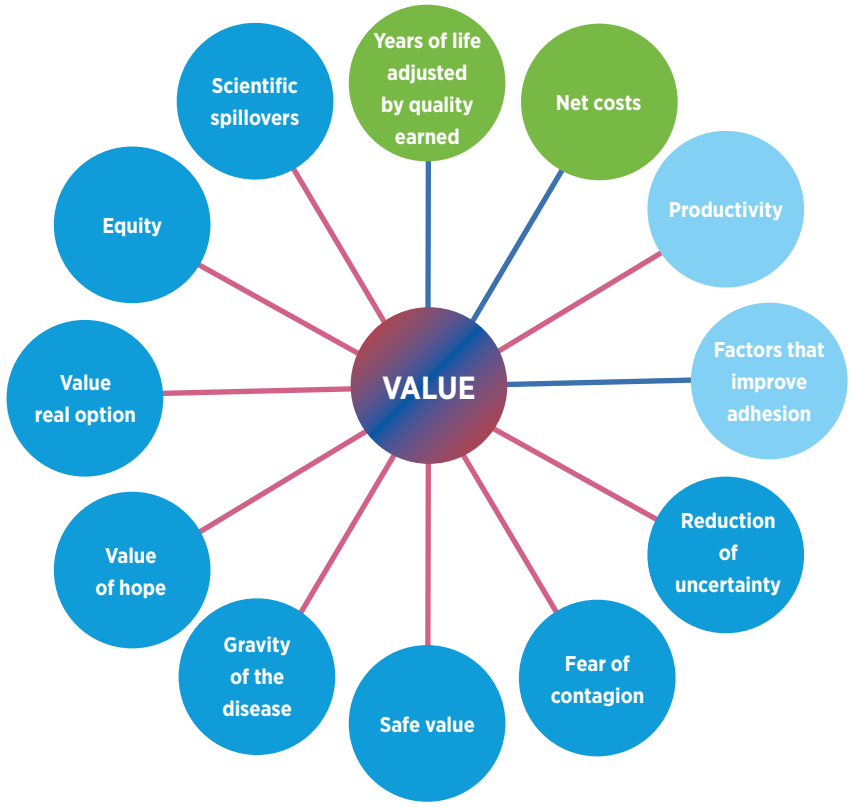
FIGURE 2. ELEMENTS OF VALUE FOR DIAGNOSTIC TESTS



- Light gray circle: element used in conventional ETS/ACE
- Strong gray circle: extended value frame, but not traditionally used/measured in ETS/ACE
- Payer perspective/national health system Included in
- Societal perspective

Source: *Garrison et al., 2016.*

FIGURE 3. ISPOR VALUE FLOWER



- Element used in conventional ETS/ACE
- Common element but inconsistently used in ETS/ACE New value element
- Payer perspective/national health system Included in societal perspective

Source: *Lakdawalla et al., 2018.*

Not all rare diseases are "serious" but tend to be associated more frequently with shorter life expectancy and moderate-severe symptoms

value, or innovation. Therefore, in the Table 1 I have attempted to summarize this information for the three reports.

And finally, then, what is and how can we measure the value of new drugs and, in particular, of orphan drugs? The "easy" answer: it depends on the color of the glass you look through. And here we have many, and potentially different 'colors': patients, clinicians, pharmacists, payers, evaluators, decision-makers, industry... However, it is necessary to agree and bring together all these agents involved in the evaluation of HHMs, and to try to ensure that the color of the glass used to measure value is, at least, of similar tones.



TABLE 1. ELEMENTS OF VALUE: SUMMARY TABLE

ELEMENT OF VALUE/INNOVATION	OHE (2005, 2012)	DIAGNOSTICS (Garrison et al. 2016)	ISPOR VALUE FLOWER (Lakdawalla et al., 2018
Covering new diseases	x		
Health outcomes (quantity and quality)	x	x	x
Faster treatment	x		
Security	x		
Interaction with other drugs	x		
Treated subpopulations	x		
Patient/caregiver convenience	x		
Factors that improve adherence			x
Family spillovers			(x)
Improved labor productivity	x	x	x
Release of health resources	x	x	
Release of non-health resources	x	x	
Net costs			x
Uncertainty reduction / Value of knowledge			
Value of knowing		x	x
Fear of contagion and disease			x
Value of insurance (financial / health)			
Insurance value (Financial & health)		x	x
Severity of the disease			x
Value of hope Value of hope		x	x
Actual value of the option			
Real option value		x	x
Equity			x
Spillover effects			
(Scientific spillovers)		x	x

Core value elements Common but inconsistently used value elements Potentially new value elements

Source: *author, based on OHE, 2005; Mestre-Ferrandiz et al., 2012; Garrison et al., 2016; Lakdawalla et al., 2018.*



Garrison, L, Mestre-Ferrandiz, J., Zamora B. 2016. The Value of Knowing and Knowing the Value: Improving the Health Technology Assessment of Complementary Diagnostics. White Paper. Office of Health Economics and EPEMED.

Office of Health Economics, 2005. The Many Faces of Innovation. Report for the European Federation of Pharmaceutical Industries and Associations.

Lakdawalla DN, Doshi JA, Garrison LP Jr, Phelps CE, Basu A, Danzon PM. 2018. Defining elements of value in health care—a health economics approach: an ISPOR Special Task Force Report [3]. Value Health, 21:131–9.

Mestre-Ferrandiz, J., Mordoh, A. and Sussex, J. 2012. The Many Faces of Innovation. London: Association of the British Pharmaceutical Industry.

Zozaya, N., Martínez, L., Alcalá, B., Hidalgo-Vega, A. 2017. Evaluación, financiación y regulación de los medicamentos innovadores en los países desarrollados. España, Madrid: Fundación Weber.

TOWARDS VALUE-BASED HEALTHCARE FOR INHERITED METABOLIC DISORDERS: AN OVERVIEW OF CURRENT PRACTICES FOR PERSONS WITH LIVER GLYCOGEN STORAGE DISEASE AND FATTY ACIDOXIDATION DISORDERS



Venema A, Peeks F,Rossi A, Jager EA, Derks TGJ. Towards values-based healthcare for inherited metabolic disorders:An overview of current practices for persons withliver glycogen storage disease and fatty acidoxidation disorders.J Inherit Metab Dis. 2022;45(6):1018-1027. doi:10.1002/jimd.12555

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SUMMARY

In recent years, value-based healthcare (VBHC) delivery models have become increasingly important in healthcare systems, which have evolved from traditional (evidence-based) medicine to the current model based on the value provided to the patient. These improvements are often reflected in improvements in the quality of care received by patients and in the efficiency of the healthcare system by reducing costs. The article by Venema and coauthors (2022) analyzes the difficulties in implementing these models in rare diseases, focusing on patients with congenital or genetically inherited metabolic disorders. For this, they choose two types of pathology: patients with liver glycogen storage disease (GSD) and those with fatty acid oxidation disorder (FAOD).

Today, value-based medicine is applied in prevalent and well-known diseases, such as diabetes, and also in primary care, but the very definition of value-based medicine is not only applied in the field of diabetes, but also in primary care of rare diseases (those diseases that affect at least 5 people out of every 10,000) hinder their adoption and are related to the lack of information, knowledge and dissemination



of rare diseases in society, the scarcity of data beyond those related to clinical histories, the difficulty in diagnosis or the complexity in quantifying the impact of treatments on these patients and the lack of coordination between professionals. Venema and coauthors briefly summarize these difficulties in Table 1 of the article. The main difficulty lies in the concept of how to measure health improvement. Fantini and Vaccaro (2019) suggest broadening this concept to include indicators that measure overcoming the disease and include others related to the well-being of the patient in aspects related to his or her life. This is an important consideration as it includes not only the patient's well-being but also the patient's and also to their families or caregivers, and transcend other political, economic and social spheres.

To advance the adoption of value-based models in patients with rare diseases, Venema and coauthors identify three key pillars. First, in the area of value-based research practices, the authors suggest fostering the involvement of patients and their families in the activities of biomedical research and define their role well. For example, in those cases where patients with liver glycogen storage disorders (GSD) were involved in the prioritization of the research questions to be asked, it helped to better define clear priorities for these patients, their families and health care professionals and to identify the main problems related to the evolution of the disease and possible complications. Secondly, the authors stress the desirability of publishing guidelines with disease-related treatments, including the opinions of patients, for example. This, together with the adoption and use of digital health technologies (telemedicine), proves to be fundamental in helping them to manage their disease with continuous monitoring from home thanks to the inclusion of biomedical, physiological and dietary parameters in the tools, the authors also suggest the need to introduce value-based practices into the curricular models of clinical practice training programs. Thirdly, the authors suggest the need to introduce value-based practices in the curricular models of clinical practice training programs. This point is really important because of the high level of specialization required in the treatment of rare diseases. However, it is not straightforward and can generate the desired effects. Unwanted side effects. To avoid them, some initiatives have focused on fostering this knowledge in primary care, the inclusion of digital health tools or providing students in clinical practice programs with the necessary skills to better interact with patients.

In summary, the low number of patients and the high complexity of these rare diseases make it difficult to apply these value-based models to the management of these diseases. In addition, and despite significant advances in the diagnosis and treatment of patients with congenital metabolism disorders,



access to diagnosis is still an odyssey for many families. In the pathologies analyzed by the authors, it is important to transcend the academic sphere and place the patient at the center of the whole process by encouraging his or her participation in the development of new therapies, facilitating greater use of digital health tools by patients and families or to encourage greater international consensus on the results to be measured. However, there is still much to be done and it will be necessary to encourage greater coordination between the different actors, to be able to measure the results for each patient, to increase the quality of services at a geographical level, to facilitate the adoption of digital health technologies and the infrastructure they entail, or to propose provider reimbursement models for specialized services among other options.

COMMENT

Approximately 300 million people in the world (4% of the total population) suffer from some type of rare disease[1,2]. In the European Union, this figure stands at around 30 million people (approximately 6% of the respective population). In Spain, there are around 3 million people with rare diseases. To visualize the situation, the day of rare diseases (February 28) has been established at the national level and progress has been made in the cataloguing of rare diseases (around 6000 different pathologies) and the differentiation between those whose cause is genetic (80%) or autoimmune (10%), oncological (4%) toxicological (3%) or other causes (3%)[3].

For the adoption of value-based models, Venema and co-authors identify the main challenges to be addressed: 1) facilitating the establishment of virtual networks that function as integrated practice units; 2) improving the measurement of health outcomes; 3) creating information technology platforms to overcome the ethical, legal, social and technological challenges resulting from research into therapies for these diseases and ensuring the protection of patient data in the practices; To these challenges, it is worth adding those related to reimbursement of healthcare providers and other actions to advance the implementation of these value models in rare diseases.

At the international level, the generation of value is usually linked to a series of results that are clearly aimed at increasing the quality of care and safety of the patient. In the United Kingdom there is a program aimed at improving the value of patients requiring Prescribed Specialised Services (PSS) in the area of Commissioning for Quality and Innovation (Commissioning for Quality and Innovation, CQUIN). Specialized services within this program (PSS CQUIN) are provided by a few hospitals that are highly specialized and are utilized in the promotion of innovation and quality for patients with rare or complex diseases[4]. In addition to the need to assess the economic impact of research programs, the appropriateness of provider reimbursement mechanisms should also be analyzed. Feng and coauthors (2019) analyze the strengths and weaknesses of introducing Pay for Performance (P4P) reimbursement mechanisms for these specialized services in England[5]. To do so, they analyze 26 incentive schemes in various programs to find out whether the incentive was designed to incentivize structure (facilities or staff qualifications), processes (what and how care is delivered) or outcomes (health outcomes or other objectives such as efficiency or productivity). As a main conclusion, Feng and co-authors suggest that given the complexity in the design of the schemes within the CQUIN HSP, it is advisable to evaluate the processes and incentivize the suppliers for the best ones obtained over time.

Under these premises, in order to implement value-based models for

rare diseases, a number of actions have been carried out at the European level[6]. The most important include the establishment of a European Reference Network (ERN), the registration of a platform for rare diseases, the establishment of a coding system that allows to know and classify existing pathologies or support for research in rare diseases. In 2017 it formed the European Reference Network (ERN) comprising 24 institutions and around 300 hospitals in the 26 Member States, one of them being MetabERN which interconects institutions in inherited metabolic disorders. One of the main problems encountered is the scarce evaluation of policies in this field. In order to find out what exists and improve on what has been done, the European Commission launched in December 2022 a project to evaluate these ERNs with the aim of finding out the state of the art in this field.

The current focus is on coordination and governance, clinical practice, quality and patient safety, patient-centered care, contributions to research, training, networking and dissemination of activities[7]. In Spain, much remains to be done and efforts are focused on improving the care network and promoting research into rare diseases. Although initiatives have come more via the Spanish Federation of Rare Diseases (FEDER), both institutional support and evaluation of the actions carried out are essential to ensure equity in access to diagnosis and treatment.

To ensure access to these treatments, efforts should focus on fostering greater integration among healthcare providers and evaluating the economic impact of research activities and remuneration mechanisms for these highly specialized services. In the first of these aspects, the provision of treatment through integration among service providers is essential to ensure a greater coordination and dissemination of knowledge among professionals and researchers, optimizing resources, or increasing the quality of life of both patients and their relatives or caregivers[8] (integration) are necessary actions such as the establishment of reference networks at European and national level or greater interaction between different institutions in various fields (research, service provision and patients). To this end, progress must be made along the lines that are being proposed at European and national level. With regard to the evaluation of the actions carried out, these should be carried out with appropriate methodologies to identify causal effects that allow us to decide whether or not the impact is the intended one.

In Spain, much remains to be done and the efforts are focused on improving the care network and to promote research on rare diseases



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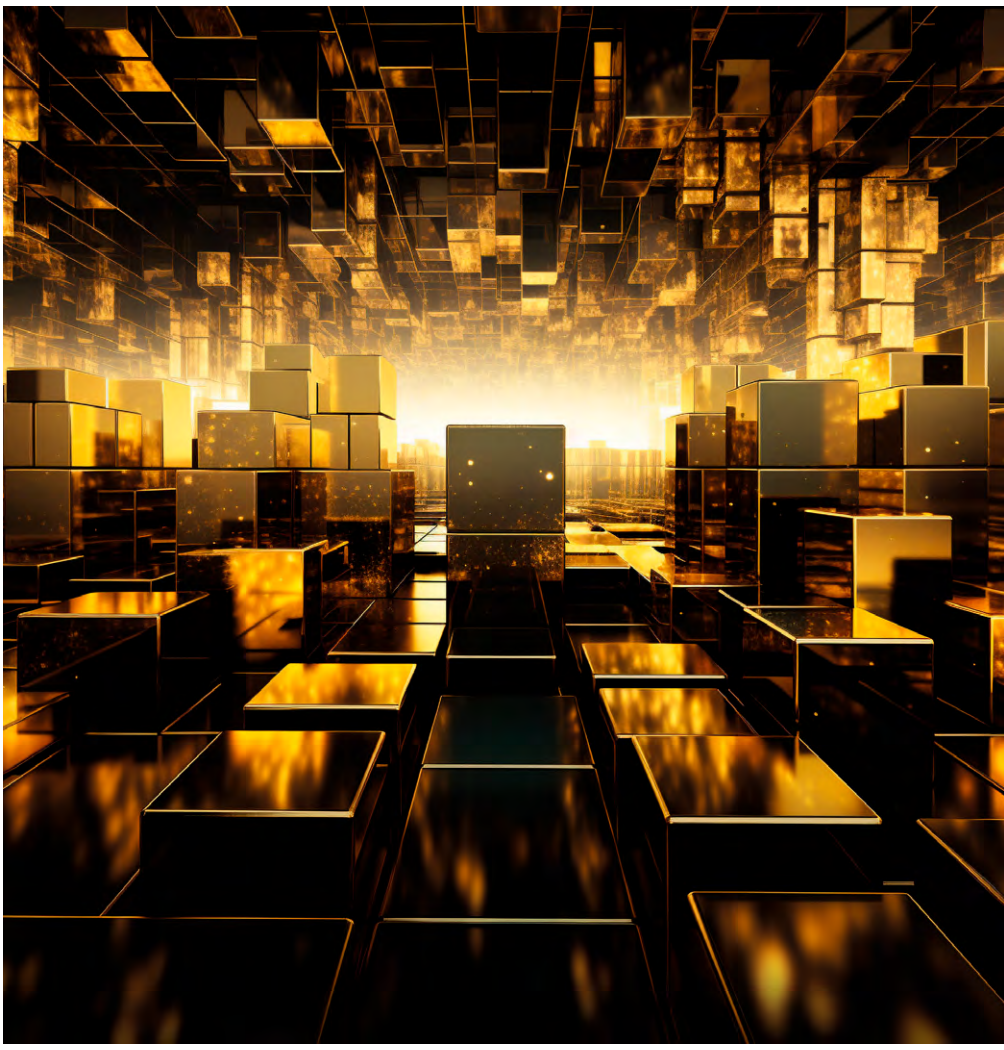
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NEEDS AND OPPORTUNITIES IN 20 COUNTRIES PARTICIPATING IN THE UNDIAGNOSED DISEASES NETWORK INTERNATIONAL

Taruscio D, Salvatore M, Lumaka A, Carta C, Cellai LL, Ferrari G, et al. Front Public Health. 2023 Mar 2;11:1079601. doi: 10.3389/fpubh.2023.1079601



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SUMMARY

This article summarizes the results of a survey on the needs and opportunities for patients with rare undiagnosed diseases, in which experts and national representatives from 20 countries participated. In October 2020, the Developing Nations Working Group of the Undiagnosed Diseases Network International (DNWG-UDNI) prepared a series of open-ended questions on 8 domains, which were answered by all group members (100%).

This international UDNI network, established in 2014, seeks to overcome the difficulties experienced by many patients with rare diseases in which a correct diagnosis is not achieved, especially in ultra-rare diseases. It also seeks to facilitate the translation of research into clinical practice and patient involvement in a framework of international collaboration among the 41 participating countries. The working group, called Developing Nations, is made up of representatives from 20 countries from 5 continents, both developed countries and those considered to be low or middle income. Its aim is international cooperation to improve diagnosis and care for people with rare diseases.

The survey was developed within the DNWG-UDNI working group and was organized into 8 domains on: Unmet patient needs, Health organizations, Insurance systems and regulations, Resources, Centers of expertise for genomic diagnostics, Regulatory aspects, Translational research activities at national and international level and other important issues representing barriers or impediments. The results are represented in figures and tables that collect the responses of the representatives of the 20 participating countries (Australia, Brazil, DR Congo, Ecuador, Spain, USA, Philippines, Georgia, Ghana, Hungary, India, Italy, Mali, Mexico, Pakistan, Singapore, Sri Lanka, Sweden, Thailand and Turkey).

The results of the survey show the great heterogeneity and variability between the different participating countries in terms of socioeconomic level, type of health organization, insurance system, available resources, access to specialized centers, financing of genetic testing, institutional support and coordination programs. The majority of the countries (80%) indicate that there are limitations in resources, in access to services and genetic testing, as well as in the financial coverage of these studies. The inequity and difficulties suffered by people with this type of rare diseases without diagnosis stand out.

Although most of the country representatives point out that they have centers of expertise, specific resources for rare diseases and regulations to facilitate the exchange of data and samples at the international level, the survey reflects doubts about the real access of patients to these resources and the lack of equity. The results indicate



that, although medical and scientific centers are making important efforts to meet the needs of these patients, there are still many difficulties in getting a correct diagnosis in many people suffering from such complex rare diseases. There is a lack of strategies and resources on the part of governments, in addition to increasing social awareness, improving the training and knowledge of physicians, increasing access to genetic studies and their financing, promoting international cooperation, facilitating interdisciplinary care teams with more human resources and achieving greater equity.

The study identifies numerous barriers, including funding problems, shortage of resources and expertise in genomic analysis, insufficient healthcare structures and high costs. These barriers give rise to serious problems of inequity and lack of access in all countries, contributing to the continuing needs of patients suffering from undiagnosed rare diseases.

COMMENT

This article reports the results of an international survey that analyzes interesting issues related

to the needs and opportunities of patients suffering from complex rare diseases, who suffer from the lack of an accurate diagnosis and the impossibility of accessing specific treatment.

Unfortunately, undiagnosed rare diseases still represent a significant proportion of the total number of rare diseases in all countries of the world. The suffering of patients and families is increased by the uncertainty generated by the lack of diagnosis, the lack of knowledge and understanding conveyed by health professionals, as well as the impossibility of access to any curative therapy, beyond the symptomatic relief that can be achieved only in some patients.

At the present time of enormous technological development, of great advances in access to information and artificial intelligence, most patients and families do not understand that medicine is not capable of solving the enigmas of many diseases. Many professionals who care for these people also suffer with them, because of the failure that the inability to establish an accurate diagnosis to provide adequate and curative treatment for these people represents. Patients, families and professionals suffer numerous frustrations in the difficult odyssey to establish a diagnosis. This issue of undiagnosed diseases generates little scientific interest and there are few articles of international cooperation.

This study shows very relevant results because it gathers the assessments of national representatives from 20 countries with different economic resources. The 8 domains raised in the survey are important for assessing the needs of people with undiagnosed diseases, offering a global and international vision due to the participation of countries with very different resources. However, the results are quite general and depend on the opinion of the representative of each of the countries. No objective or quantitative data are established to compare the needs and opportunities of patients in each country.

In the comparative table on unmet needs for people with undiagnosed rare diseases, 2 countries stand out in which only one of the 10 domains is missing: Spain due to inequity in access to services and Sweden due to the lack of coordination between the programs and institutions involved in clinical care. Other countries in our European environment, such as Austria and Italy, and with a high level of development such as the United States, report a lack of social awareness, problems with funding and coverage for genetic testing, a lack of resources and limited funds for interdisciplinary care and research. Some low-income countries, such as Pakistan, the Philippines, Thailand, Georgia and India, report a lack of resources and multiple difficulties in the care of these patients.

The performance of international studies and the global vision of the needs of these patients is very interesting, but it seems important to me to expand this type of cooperation initiatives to collect more specific data. Many countries report having strategies and coordination programs for interdisciplinary care, registries, resources for genetic studies, biobanks, regulations for sending samples to other countries and insurance coverage. However, I feel it is necessary to specify these data. In some countries, such as Spain, we officially have most of these resources, but we should assess what the diagnostic odyssey is like for these patients, how many have complete genetic studies, how long it takes for them to be referred to specialized centers, what participation in registries and the inclusion of samples in the available biobanks is like, what the real knowledge of the healthcare teams is, and whether access to this specialized care is the same in rural and urban areas, in small towns and in large cities.

In today's age of technological advances, access to information and the use of artificial intelligence, many patients and families do not understand why medicine does not solve the riddles of some diseases

For all these reasons, it seems important to me to continue to make progress in the knowledge of unmet needs through a more direct participation of patients, their families and the professionals directly involved in their care, in order to gather more concrete information that will help to identify the main problems and seek more concrete and adapted solutions in each of the countries.

NEWBORN SCREENING BY GENOMIC SEQUENCING: OPPORTUNITIES AND CHALLENGES

Bick, D.; Ahmed, A.; Deen, D.; Ferlini, A.; Garnier, N.; Kasperaviciute, D.; Leblond, M.; Pichini, A.; Rendon, A.; Satija, A.; et al. Int. J. Neonatal Screen. 2022 Jul 15;8(3):40. https://doi.org/10.3390/ijns8030040



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SUMMARY

Undoubtedly, neonatal screening programs for the early detection of diseases, which require and for which rapid intervention is possible, are key in public health strategies. To a large extent, these programs have demonstrated their effectiveness in preventing damage associated with a significant number of congenital disorders, thanks to the implementation of measures such as dietary changes and elimination of toxic metabolites, among others. The importance of these programs has increased substantially in recent years, due to the growing number of disorders for which different agencies have demonstrated the benefit of early detection in the newborn. Today, at least in developed countries, their application is universal. However, much remains to be done. Mainly in developing countries, and in some European countries, including our own, achieving uniformity between screening panels in different regions remains a challenge.

The work published by David Bick and collaborators[1] evaluates the use of next generation sequencing (NGS), or massive sequencing, in the detection of diseases of genetic origin in newborns. This method, as we will see below,



makes it possible to analyze, in a relatively simple way and with a small amount of sample, a multitude of genes involved in the development of diseases. In addition, this method is increasingly less expensive thanks to the significant technological advances achieved in recent years in sequencing and bioinformatics analysis capacity. While there are obvious advantages to a method that can examine all disease-causing genes in a single assay, the implementation of genomic sequencing for neonatal screening presents numerous challenges that have been carefully evaluated in this work. Some of these are intrinsic to the detection of rare diseases and others are specifically related to the technique. On the other hand, Bick et al. also evaluate the ethical, communication, data management, legal and social implications of genomic screening programs.

COMMENT

Currently, in newborn screening, most of the tests used are based on biochemical analyses performed on a small blood sample obtained from the newborn, the commonly known heel prick test. These tests detect specific metabolites that are produced in the patient as a result of the absence or malfunction of a protein associated in many cases with mutations in the gene coding for these proteins. The number of metabolites, and therefore of diseases that are analyzed, varies depending on the country. In our country, we also find very important differences depending on the region, an aspect that should be resolved as it is a source of important health inequalities.

The first disease to be introduced into neonatal screening programs was phenylketonuria, and in the early 1990s, with the introduction of tandem mass spectrometry in laboratories, a major revolution in the field took place. This technique allows the simultaneous quantification of more than 50 metabolites, thus screening more than 40 inborn errors of metabolism, among which we find aminoacidopathies, organic acidurias and deficits of ß-mitochondrial oxidation. At this time, with the possibilities offered by the technique, it was necessary to establish criteria to determine which diseases should be included in screening programs. Thus, in 1968, the World Health Organization



published the Wilson and Jungner principles[2], the aim of which is to guarantee that the main objective of neonatal screening programs is achieved: "maximum benefit at minimum cost". Bick et al. evaluate these principles in the context of NGS screening. Whereas screening by biochemical analysis has inherent limitations of the technique (such as the amount of sample available, the need for assay set-up and increased cost) NGS analysis offers virtually unlimited possibilities. The scalability of NGS offers an unprecedented opportunity to address a major global health problem: the diagnosis and management of rare diseases.

A large number of studies are currently underway worldwide to determine whether and how to use genomics in neonatal screening3-9. There are different techniques that differ mainly in the number of genes analyzed and the cost, starting with gene panels, which analyze a limited number of genes; whole exome sequencing (WES), which analyzes coding sequences; and whole genome sequencing (WGS), which analyzes the whole genome. The main problem with these powerful techniques is the interpretation of the data, and the implications for the individual and their relatives. These techniques use short-read sequencing, i.e., they can only determine small fragments of the gene. This information is then analyzed using computer programs designed for the correct interpretation of the data. Once the data from the computer analysis has been obtained,

Evaluation of the Wilson and Jungner criteria in the context of neonatal screening using NGS

the most important part of the process is to determine the biological significance of the variants found.

The criteria established by Wilson and Jungner are as follows: the condition sought must be a major health problem, the natural history of the disease must be known, which must have a recognizable latent or early symptomatic stage, and an appropriate test or examination must be acceptable to the population. On the other hand, there must be an agreed policy on who to treat as patients and there

must be an accepted treatment for patients with recognized disease. Although it may seem obvious, among the criteria to be met we find that facilities for diagnosis and treatment must be available. An additional criterion, of great importance, is that the cost of diagnosis and treatment must be economically balanced in relation to the potential expenditure on medical care as a whole. Finally, case ascertainment must be an ongoing process.

According to current screening practice, a newborn sequencing program may choose genes associated with treatable disorders that appear in infancy and where there will be significant morbidity and mortality if left untreated. This criterion is not at odds with the severity (acute or chronic) of rare diseases in general. However, it is important to keep in mind that the concept of what constitutes a significant health problem differs according to individual and family perceptions, and considering the great potential of genetic analysis, it should be carefully analyzed.

Although detection by genome sequencing can solve the problem associated with the cost of neonatal screening, due to its progressive cheapness and the large amount of data it generates, it has a major limitation derived from understanding the biological significance of mutations. The need to carefully select variants with high specificity is offset by the adverse impact it will have on sensitivity. For example, for genes associated with cystic fibrosis (CFTR) and spinal muscular atrophy (SMN1), where a large fraction of the causative variants are known, NGS has high sensitivity and therefore very few false positives. However, this is not the situation for the vast majority of genetic diseases, with a large number of uncertain variants leading to a significant number of false positives.

It is also important to note that, in some cases, the use of NGS may allow the identification of untreated or late-onset diseases. The identification of untreated diseases is, in many cases, important for individuals and families who need to identify the cause of the disease and name it. This is a factor that must be taken into account and that clinicians are confronted with on a recurrent basis in their practices. On the other hand, there are diseases that are going to debut at an older age but whose knowledge can condition the habits of that person and reduce the severity of the pathology. This could be the case of Wilson's disease, which could be attenuated by a diet low in Cu or treatment with Zn salts; or familial hypercholesterolemia, which would benefit from dietary management and early treatment with statins. However, families would have to face the waiting period, a time in which one lives with the anguish of what is going to happen and when. On the other hand, while this may help parents, it will not directly benefit the child's health and conflicts with the child's autonomy to decide whether to learn about adult-onset conditions.

Another problem with newborn screening based on genetic techniques is the time required to obtain the result and to be able to communicate it. In some cases, such as diseases associated with urea cycle enzyme deficiency, newborns may suffer hyperammonemia before they have received the result. It is important to take this into account and to try to speed up the analysis as much as possible.

On the cost side, because NGS testing involves hundreds of conditions, the development of economic models is highly complex. When all conditions are considered together, genomic testing will identify many more infants with treatable conditions compared to current screening. In this regard, the Screen4Care consortium5, using and validating different genetic testing strategies, aims to demonstrate that the scalability of neonatal genetic screening for rare diseases will significantly reduce the cost of screening per disease and per patient compared to the current strategy.

To build a sustainable NSW newborn screening program, ongoing evaluation is needed that assesses health outcomes, psychosocial outcomes, costs, cost-effectiveness, and implementation. This will require long-term contact with families who have been screened. In addition, it will be important to generate data on conditions that could be included in screening in the future. Because whole genome sequencing data have the potential to detect so many disorders, creating the right consent and governance of the research is critical.

This will result in a better understanding of the natural history, better screening approaches and optimal monitoring of treatment outcomes. Another important aspect of newborn genetic testing is that it can provide information on parental susceptibility to some diseases; this should be well explained to families. Therefore, the training of the medical professional and patient education are going to be factors of extraordinary impor-

tance for the implementation of these new techniques.

Given the potential for revisiting genomic data in the future, for example, with improved screening algorithms or as new treatments become available, clear expectations should be set for families on recontact after the initial screening result. Programs should consider whether additional consent will be required before rescreening a genome and at what age the infant, now a young person, would need to be involved in the decision to rescreen his or her genome.

An NGS screening program must balance the rights and needs of the child with those of the family and government agencies. Parents may choose to know what disorder the child has, but it is only going to manifest itself once the child reaches adulthood. This is knowledge that the child, upon reaching adulthood, would not want to know. The complexity of the information and the uncertainty about the results of a newborn NGS may lead parents to opt out of the current newborn screening.

Despite the great potential and flexibility of sequence-based testing, it is unlikely to replace current neonatal screening. There are a significant number of diseases, such as congenital hypothyroidism, for which there is no identifiable molecular basis. In addition, metabolite analysis by mass spectroscopy has a higher sensitivity and specificity for currently tested disorders than genomic testing. However, the two techniques are not mutually exclusive and provide valuable information on patient management that requires early intervention, preventive action or follow-up to best determine the debut of the disease.

Despite the great potential and flexibility of sequence-based tests, they are unlikely to replace current neo-natal screening



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UNVEILING OPPORTUNITIES: LESSONS IN INNOVATION AND PERSISTENCE FROM EVERY CURE

DAVID FAJGENBAUM

MD, MBA, MSc, Assistant Professor, University of Pennsylvania and Co-Founder of Every Cure

What was your motivation to start researching rare diseases, specifically Castleman's disease?

DF: I first became motivated to study rare diseases when I became a rare disease patient myself. I was a third-year medical student when, out of nowhere, I became critically ill with idiopathic multicentric Castleman disease. I spent months in the ICU and required numerous treatments to achieve remission. Being a patient inspired me to study this disease. My research on Castleman disease uncovered many issues across rare diseases, fueling my passion for unlocking more treatments for these conditions.

What is the origin of Every Cure and its role in promoting research and treatment of rare diseases, including Castleman's disease?

DF: Ever since I discovered that sirolimus could be a life-saving treatment for me and repurposed it to save my life, I have dreamed, along with my co-founder of Every Cure, Grant Mitchell, and our other co-founder, Tracy Sikora, of a future where all FDA-approved drugs are used for all the diseases they can potentially treat. This experience of having my life saved by a drug not originally intended for my disease, combined with working with colleagues who have tremendous expertise in artificial intelligence and clinical trial design, inspired us to leverage all the amazing data and drugs available to help as many people as possible.

What specific activities does Every Cure undertake to drive progress in the field of medicine and improve the quality of life for patients affected by these uncommon conditions?

DF: Every Cure leverages the world's biomedical knowledge, everything known about every drug, disease, gene, and protein and uses that information as a foundation. We apply artificial intelligence algorithms to generate scores for the likelihood of each of the 3,000 drugs to treat any of the 22,000 diseases, resulting in 66 million scores computed in just a few days.

We use these scores to identify the most promising drug-disease matches, focusing on those that could help the most people most quickly. We then



conduct further clinical studies on these opportunities and advance them into patient treatments.

What challenges does the organization anticipate facing in promoting research and treatment of rare diseases?

DF: One of the primary challenges in advancing research and treatment for rare diseases is their rarity, which makes it difficult to find patients for clinical trials and secure funding. Fortunately, we plan to collaborate closely with existing rare disease groups that are already dedicated to this important work. Another challenge is the economic aspect—convincing drug companies to invest in rare diseases, especially when the treatment is expensive. Drug companies often prioritize rare diseases if they can set prices accordingly.

At Every Cure, our focus is on FDA-approved drugs that have already been established. While the economics may not always align perfectly, we are enthusiastic about partnering with pharmaceutical companies to identify older drugs that are no longer in use but could be repurposed to benefit patients with rare diseases.

What lessons have been learned along this journey that could be valuable to others in the fields of medicine and medical research?

DF: I believe there are a few crucial lessons to share. Firstly, when Grant and I began envisioning this organization about ten years ago, we initially assumed there must already be an entity fulfilling our intended role of ensuring drugs are fully utilized. However, upon deeper investigation, we discovered there was actually a significant gap in the system. This taught us not to assume that someone else is addressing what needs to be done; sometimes, there's a critical role waiting to be filled.

Persistence and determination are key: solving complex problems is never easy, but moving forward in spite of the obstacles is essential

Secondly, persistence and determination are key. Solving complex problems, especially those of significant magnitude, is never straightforward. Despite encountering numerous obstacles and rejections along the way, we persevered and continued pushing forward.

Lastly, having an exceptional team is essential. Starting with a small group of individuals, we have since expanded, but our success has always been rooted in the strength of our team. None of the accomplishments achieved by myself or my co-founders would have been possible without the dedication and expertise of our remarkable team. These three points—recognizing gaps, persistence in the face of challenges, and building a strong team—are fundamental to our journey and success.



ADVANCING RARE DISEASE TREATMENT: INSIGHTS FROM EFPIA ON INNOVATION, COLLABORATION, AND POLICY

TINA TAUBE

Director, Market Access & OMP Policy Lead EFPIA

What is the vision and mission of EFPIA?

TT: EFPIA stands for the European Federation of Pharmaceutical Industries and Associations and represents the biopharmaceutical industry operating in Europe. Through our membership of 37 national associations, 40 leading pharmaceutical companies, and a growing number of small and medium-sized enterprises, EFPIA's mission is to create a collaborative environment that enables our members to innovate, discover, develop, and deliver new therapies and vaccines for people across Europe, as well as contribute to the European economy.

In your opinion, what are the main achievements and challenges in the field of rare diseases and orphan drugs?

TT: Reflecting on the positive impact of the Orphan Medicinal Product (OMP) regulation, this policy makes a difference. Before the regulation was introduced in 2000, there were only 8 medicines for rare diseases. The introduction of the regulation, along with new incentives, resulted in more than 2800 new orphan designations, leading to over 244 authorized new treatments for around 90 rare diseases. This is a true European success story. However, it is also evident that more needs to be done in this field, as a significant number of medical needs remain unmet. Less than 5% of rare diseases have an approved treatment, and many diseases with approved treatments still significantly impair patients' life expectancy, quality of life, or daily functioning. It is imperative that clinical progress continues. Considering rare diseases, there are inherent scientific, regulatory, and economic challenges to research and development. Now is the time, as the European Union is currently reviewing the OMP regulation. EU policymakers have the power to build a revised legislative framework that will support a world-class ecosystem for developing innovative medicines. Therefore, it is crucial to strengthen the existing framework in the European Union and restore and maintain a leading position in global drug development.

From EFPIA, what recommendations or initiatives are proposed to help address the challenges in the field of rare diseases?

TT: When discussing how to effectively address rare diseases there are essentially three areas to consider. First, with the current legislative review, we propose concrete revisions for the OMP regulation to strengthen the legislative framework and enhance support for orphan medicinal products. We need to consider how to encourage innovation, particularly through incentives like market exclusivity.

Robust and reliable incentives are essential if we are to research new treatments to meet needs of patients suffering from rare diseases. Current incentives should be strengthened to encourage further investment in underserved areas where research and development is particularly challenging.

The second area, which falls outside the legislative framework, is ensuring we continue to make advances is science. EFPIA is one of eight partners collaborating in the Rare Disease Moonshot initiative, a joint effort within the rare disease community.

Lastly, we have proposed a number of solutions to help address the issue of unequal access to medicines, which continues to be an issue across Europe. EFPIA would like to see the implementation of a high level stakeholder forum in order to find solutions that work for all partners.

What role do you think the European Reference Networks can play regarding research, clinical and access to innovation levels? Will EFPIA be involved in them in any way?

TT: The European Reference Networks (ERNs) are a unique, permanent infrastructure of European excellence. With their introduction, every rare disease now has a home, regardless of the country.

The ERNs have immense potential that is yet to be fully unlocked, particularly in terms of pooling fragmented medical expertise, providing diagnoses, collecting and leveraging data, creating registries, conducting clinical trials, and offering comprehensive coverage across the European Union. However, from our perspective, what is missing is collaboration between public institutions and industry. This partnership is crucial, and a framework for such collaboration is vital, but it is currently fragmented. To create the right conditions for advancement in research and care, collaboration is essential.

EFPIA has joined an initiative called "Together for Rare Diseases," a multi-stakeholder collaboration that includes European Reference Networks, coordinators, researchers, clinicians, patient advocates, and industry representatives.

With the introduction of ERNs, every rare disease now has a home, regardless of the country

Can EFPIA elaborate on its role in advocating for policies that prioritize research and development for rare diseases, as well as ensuring equitable access to treatments across European countries?

TT: In 2022, together with seven partners from across the rare disease community, we launched the Rare Disease Moonshot. The aim is to enhance the translational research ecosystem, optimize clinical trials and regulatory pathways, and develop an infrastructure to accelerate the journey to diagnosis and treatment.

This multisectoral collaboration aims to discuss and outline challenges in these areas for public-private partnerships, and to make recommendations to address them.

The goal is to pool efforts and implement changes that no single stakeholder can achieve on its own.

The Rare Disease Moonshot is a commitment to collaboration among players in the translational and clinical research ecosystem, aimed at boosting the effectiveness of public-private partnerships.

How does EFPIA collaborate with stakeholders to address disparities and delays in access to treatments for rare diseases, particularly in the context of evolving treatment paradigms like gene and cell therapies?

TT: At EFPIA, we advocate for a high-level forum at European level to discuss the access challenges and how best to overcome them, with the expertise of relevant stakeholders.

In order to improve access to rare disease treatments, we have engaged in a structured dialogue with EURORDIS, the European patient organization representing people living with rare diseases, and in 2022,



we published a joint statement on patient access to medicines for rare diseases.

One of our clear commitments at EFPIA is to propose that our members file for pricing and reimbursement applications in all European countries no later than two years after marketing authorization has been granted for a medicines, if a Member State allows it.

We have created a European access portal where authorization holders can provide information regarding pricing and reimbursement applications in the 27 European countries. This portal includes reasons for any delays in pricing and reimbursement decisions or why the marketing authorization holder has not filed in a particular market, aiming to increase transparency about access challenges, which vary from country to country. Understanding these challenges is crucial to addressing them.

Less than 5 % of rare diseases have an approved treatment, and many diseases with approved treatments still significantly impair patients' life expectancy, quality of life, or daily functioning

Our industry is also proposing a system for Europe where the countries who can afford to pay less for medicines, pay less – a concept called equity based tier pricing. This type of agreement would require solidarity among Member States to embed these 'fair principles' and prevent them from being undermined, for example, through international reference pricing or through supply diversion, where a medicine sold more cheaply in one country is immediately exported to a country with higher prices.

In addition, at the European level, the implementation of the EU Health Technology Assessment (HTA) regulation, which will become effective at the beginning of 2025, and is an important legislative measure to address some of the access challenges we see in the European Union.



EMPOWERING THE CDG COMMUNITY: COLLABORATIVE EFFORTS, RESEARCH, AND ADVOCACY FOR A BRIGHTER FUTURE

VANESSA FERREIRA

President and Founder of the Portuguese Association for CDG and Other Rare Metabolic Disorders (APCDG-DMR)

What motivated you to found the APCDG-DMR and what has been the journey since its creation?

VF: The biggest motivation is the fact that my sister was born with congenital disorders of glycosylation (CDG), and she is the main inspiration behind all our work in the field of advocacy. This motivation extends not only to my sister but also to all the other children, teenagers, and adults living with CDG. From early on, I had a strong desire to connect with other families for more support and awareness about CDG. We realized that the community was quite dispersed and there was an enormous lack of information and support for families dealing with CDG. We identified many needs, and it became clear that a patient group like APCDG could help overcome these challenges. I must say that the journey since the early days of the creation of the Portuguese Association for CDG has been full of challenges. Initially, it was not easy to gain recognition or establish a solid organization, as a nonprofit association requires many resources, time, and dedication. These were significant challenges for us.

What kind of support and guidance does the APCDG-DMR offer to families facing a diagnosis of Congenital Disorder of Glycosylation (CDG)?

VF: We offer various forms of support and guidance through several major activities we have initiated with many other partners. One of the most important activities is the World Conference for CDG. This conference provides indirect support and guidance for families as it is community-driven, using different methodologies to listen to the needs of the community. When I refer to the community, I mean families, researchers, medical doctors, and a few companies interested in the field. This conference is one of the major platforms for families to access up-to-date information on CDG, including current care and management options. It also connects families with medical experts and specialists in CDG and facilitates connections between different patient groups representing the CDG patient voice worldwide. This platform allows for the exchange

of information and peer-to-peer support. In addition to the conference, we provide extensive information in lay language to help families better understand their diagnosis, access reliable information, and ideally, feel empowered to participate in discussions and decisions with their medical doctors.

Could you share a success story or an inspiring case of families or patients who have been supported by the association?

VF: In our case, what we do is for the community as a whole, benefiting all families. Since 2016, the Portuguese Association for CDG has focused on research. We started a collaboration with a glycoimmunologist from the NOVA School of Science and Technology (NOVA FCT) a Portuguese faculty of the NOVA University Lisbon and co-founded CDG and Allies, an international community centric research networkand community center. This network conducts research based on the priorities identified by the community, aiming to help as many families as possible. I would consider this a success story. Our collaborative research efforts with families, healthcare providers, and researchers have led to more accurate diagnoses and improved care and management. Our research also focuses on areas such as patient-reported outcomes and the impact of the disease on family life, which is crucial knowledge during and after clinical development.

Additionally, through the World Conference for CDG and the World Awareness Day for CDG, we combat the isolation many families feel. These initiatives have helped families connect, speak with one another, and reduce their sense of isolation. Our established research model can be easily adopted by other communities, further extending its impact.

Could you tell us about some of the initiatives and events that you have organized to raise awareness about CDG and other rare metabolic diseases?

VF: One of our most significant initiatives to raise awareness is the World CDG Awareness Day on May 16th. We've been organizing this event for many years. Initially, our outreach was limited, but over time, we've achieved substantial outreach metrics. During the World CDG Awareness Day, we disseminate a lot of information about CDG, which helps raise awareness significantly.

Conferences are another vital way we raise awareness for CDG. We not only host the World Conference for CDG but also strive to participate in as many conferences as possible in the fields of rare diseases specially, rare metabolic diseases. We present our unique community-centric research through posters and presentations at these events.

Additionally, we raise awareness through fundraising events, social media, and media appearances, although the latter can be challenging. We also take advantage of educational programs, seizing opportunities to educate schools and communities about CDG and rare metabolic diseases. For us, it's crucial to increase understanding and awareness about CDG and related conditions.

The key to our success with this CDG and allies research network is that our research is driven by the needs of the community

How does the association promote research in the field of CDG and other rare metabolic diseases? Are there collaborations with academic or research institutions?

VF: Our strategy was quite straightforward. In 2015, we identified that CDG research was not incorporating the patient voice. To promote a community-centric we established a collaboration with researchers, medical doctors and citizen patient groupsallies, forming an unique international community center and research network in 2016. Funded primarily by donations, this network has since published over 30 peer-reviewed articles, significantly increasing knowledge about CDG across various levels, including immunology, quality of life, and the impact of the disease on families. We are now also focusing on mental health and well-being in CDG, along with many other research lines we have developed.

The key to our success with this CDG and allies research network is that our research is driven by the needs of the community. By focusing on what the community identifies as important, we conduct research that better serves their needs.



Additionally, we have partnered with key academic institutions and top research centers worldwide. This collaborative spirit has allowed us to advance research in areas that were previously neglected within the context of an orphan disease like CDG.

What are your expectations and goals for the future of the APCDG-DMR and the impact you wish to have on the rare disease community in Portugal and internationally?

VF: Our activities at the Portuguese Association for CDG and the CDG Allies Research Network are conducted on an international level, and I have many expectations. One of them is to continue expanding the reach and influence of different patient groups, dedicating efforts to CDG both locally and globally. In 2021, we established an informal World CDG Organization to reach as many families as possible, leveraging the power of patient groups at various levels and across different countries.

Another expectation is to increase awareness and understanding of CDG and related rare metabolic diseases. We also hope to secure more funding for CDG research. The current low budget for basic and translational research, not just for rare diseases but in general, is a significant concern. We hope to see increased spending because CDG can serve as a model for more common diseases. Funding CDG research will likely have a broader impact on many other conditions.

Additionally, we aim to continue advocating for better care and management of the disease, positively impacting our families. We also strive to build a strong, connected community of patients, families, healthcare providers, and researchers to drive significant positive changes in the lives of affected families.

Lastly, I hope to see data collected more systematically to demonstrate the power of numbers. This will lead to better-designed clinical trials and, ultimately, treatments for our children, teenagers, and adults. This is the greatest expectation of any family member, and I believe that through collaborative efforts and the unity of our community, these treatments will arrive soon.



ADVANCING NEWBORN SCREENING: INSIGHTS AND SUCCESS STORIES FROM SMA ADVOCATES

KACPER RUCIŃSKI

Steering Committee, European Alliance for Newborn Screening in Spinal Muscular Atrophy

Could you explain what SMA Europe is and the role it plays in the context of newborn screening for spinal muscular atrophy?

KR: SMA Europe is a collective organization uniting 29 national organizations dedicated to spinal muscular atrophy. We bring together patient advocacy and research-focused organizations to lead advancements in treatment development, elevate care standards, and enhance the quality of life for individuals with SMA. One of our key initiatives at SMA Europe has been the Newborn Screening Alliance.

Spinal muscular atrophy is a rare genetic disorder that manifests as a progressive loss of muscle function. It can affect people of any age, although initial symptoms typically appear within the first few months of life: children get weaker and weaker until they are unable to move, swallow, or breathe. Before new treatments became available in the last decade, most children were dying within two years. These treatments completely stop the disease progress, and thus the sooner the child is treated, the better the outcomes. Initiating treatment before symptoms appear can prevent SMA altogether, enabling children to live a symptom-free life.

Given these factors, newborn screening stands as the most effective method to detect SMA early in the population – adding a test for SMA to routine newborn screening tests is pivotal for optimal SMA diagnostics and management. The Alliance underscores our commitment to the vision of a world where a diagnosis of SMA brings a promise of health, not of suffering and death.

What methods are currently used in newborn screening to detect spinal muscular atrophy, and how effective are they?

KR: Spinal muscular atrophy is a genetic disorder caused by a mutation in a single gene, which makes it relatively simple to diagnose using genetic testing. A quick, low-cost test detects genetic mutations responsible for SMA and provides reliable results in approximately three hours.

How can increased awareness and cooperation among European countries contribute to the success of the newborn screening initiative for SMA?

KR: This is such a concise question, and yet the answer feels so elusive! The fundamental challenge is linked to the disparities between countries not only as regards screening for SMA but, essentially, as regards newborn screening in general. As mentioned, there are countries in Europe that screen newborn babies for only one or two disorders, and there are countries that screen newborns for nearly 50 disorders. How is such a disparity possible? Historically, national screening programs developed independently over decades. Unlike in the United States where there's a federal screening panel in place, to-date little has been done in Europe to ensure even minimal alignment between a multitude of screening programs, some of which are run on a province level. Currently, we face the reality of some children in Europe going undiagnosed and developing life-limiting diseases while other children, properly tested at birth, receive timely medical care and live symptom-free – only because they were born a few kilometers down the road.

Such health inequalities in the 21st-century Europe are shocking. We aim to raise awareness among decision-makers not only within the EU institutions but also across the European continent. Robust neonatal diagnostic to prevent severe disorders is not simply a matter of healthcare. Being often a difference between life and disability or death, I believe it is a matter of equality and basic human rights.

What are the expected challenges in implementing universal newborn screening for spinal muscular atrophy across all European countries by 2025?

KR: When referring to European countries, it helps to distinguish between states members of the European Union and those outside of it. Primarily, European Union is built on the idea of harmonization. People are expected to enjoy the same rights as EU member states are encouraged to align their policies with each other. Even though healthcare has been explicitly left out of the EU treaties, political goodwill can go a long way, as we have seen with the EU health strategy and its various components, such as the European Medicines Agency, European Reference Networks, or EU pharmaceutical legislation. Besides, EU is still a relatively wealthy region. All this encourages us to focus our efforts on EU institutions, in search of a shared solution to what ultimately is a burning public health problem.

In contrast, countries outside the EU are either less well-off or – perhaps with the notable exception of Norway – often reluctant to align with anyone. UK or Switzerland, for instance, have been traditionally unwilling to incorporate foreign expertise and thus have the most rudimentary newborn screening programs in the developed world. Then, lower-middle income countries often give priority to other healthcare needs, while smaller countries frequently do not have sufficient expertise or capacity to embark on mass genetic testing.

In the EU, the Alliance asks the European Commission to take a leadership role in driving the policy and helping member states to align their national newborn screening programs. Outside the EU, we support national organizations that advocate for SMA newborn screening with their respective governments. Whether we'll get there in 2025, it remains to be seen; we are on a good track, but as long as even a single child is left behind untested, our efforts will continue.

Can you share any success stories or case studies where early diagnosis through newborn screening has significantly impacted the lives of children with SMA?

KR: Today, seven in ten babies born in Europe are tested for SMA at birth, which means that hundreds of children every year will develop in full health, never experiencing symptoms of this terrible disease. Each child is a success story – a success for the screening lab, for treating clinicians, for the society, and of course for the child.

Can you imagine the difference between living with a severe lifelong disability, never being able to stand and walk, and living a life in full health? This is precisely the miracle of newborn screening in SMA.

Let me add that introducing newborn screening in a country is not as complex as some say. We have observed countries implement it swiftly, where it took barely a few months between decision and implementation: Austria, Czechia, Denmark, Norway, Poland, Switzerland. Ukraine expanded its national newborn screening program, by adding SMA and 16 other disorders, in late 2022, in the midst of war. Geographical challenges did not prevent Russia and Turkey from implementing nationwide screening for SMA incredibly quickly. Russia actually now screens more babies and for more disorders than any other country, second only to the United States, the global leader. There is abundant knowledge and wealth of experience across the world, there are rapid screening tests available on the market, there are successful models that can be replicated.

The European Alliance for Newborn Screening in SMA works to promote this knowledge and to convince health authorities that preventing this terrible disease is doable, is simple, is cost effective, and indeed is an absolute necessity.

WEBER FOUNDATION AND SHARE4RARE LAUNCHES "RARE HORIZONS", A NEW PODCAST FOCUSED ON RARE DISEASE RESEARCH

We have launched a monthly podcast, in collaboration with Share4Rare, which aims to explore diverse topics relevant to rare disease research and innovation.

Named Rare Horizons, the podcast will delve into critical issues such as the diagnostic process, the importance of biobanks and registries in the investigation of rare disorders, advancements in animal models, and the latest breakthroughs in gene therapy. Each episode will offer insights drawn from the experiences of patients, caregivers, and experts spanning different research fields, highlighting the ongoing progress in rare disease research and its potential implications for enhancing the quality of life within this 300-million-person community.

In our podcast's debut episode, Obtaining a diagnosis, a key issue for rare disease patients, we're diving into the critical importance of getting an early and accurate diagnosis. This issue is not just crucial for patients and families, but also for healthcare professionals. Yolanda Scott will be sharing her daughter's journey, who was diagnosed with a congenital disorder of glycosylation at just eight months old. We chat with Dr. David Fajgenbaum, a medical doctor and Associate Professor at the University of Pennsylvania, who battles Castleman disease himself. With his dual perspective as a patient and an expert, Dr. Fajgenbaum will recount his own experience with a disease that nearly took his life. And let's not forget Dr. Antonio Martínez Monseny, a Paediatric Geneticist at Sant Joan de Déu Barcelona Children's Hospital, who will shed light on the diagnostic process and discuss different initiatives aimed at enhancing it.

The second episode of our podcast draws attention to this big community of patients who are forced to learn to navigate uncertainty. We spoke to Lisa Beaton, a mother of an undiagnosed young girl and a member



of the Patient Participation Panel at Genomics England and SWAN UK, and Karen Duncan, who is in her sixties and has never received an accurate diagnosis for her multisystemic syndrome. Michelle de Silva, Associate Genetic Counsellor at Murdoch Children's Research Institute and program manager at Rare Diseases Now explains how this initiative delivers genomic diagnoses and personalised care to children in The Royal Children's Hospital in Melbourne (Australia). Maya Pinn, a mother of a child with a rare genetic syndrome shares her experience and highlights SWAN Australia's supporting role. Finally, Share4Rare coordinator Begonya Nafria elucidates how the platform can play a role in facilitating connections between undiagnosed patients and their families.

More information: https://weber.org.es/weber-foundation-launches-rare-horizons-a-new-podcast-focused-on-rare-disease-research/

EUROPEAN PARTNERSHIP OPENS A NEW ERA IN RARE DISEASE RESEARCH

The European Rare Diseases Research Alliance (ERDERA) officially launched in September 2024 with the aim to improve the lives of 30 million people affected by rare diseases in Europe and beyond. The initiative is spearheaded by France's National Institute of Health and Medical Research (INSERM) and backed by the European Union (EU) through its Horizon Europe program, with the EU contributing €150 million and the remainder of the funding coming from member states, associated countries, and private sector contributions.

ERDERA brings together over 170 organizations from both public and private sectors, including leading research institutes, patient organizations, pharmaceutical companies, and healthcare authorities. It aims to consolidate the progress made by previous EU-funded initiatives such as SOLVE-RD, ERICA, and the European Joint Programme for Rare Diseases (EJP RD), which has operated for the last five years. The alliance will focus on advancing research in prevention, diagnosis, and treatment of rare diseases, many of which still lack effective therapeutic options. Today, there are around 7,000 rare diseases, affecting over 300 million people worldwide, and many patients face delays of up to four years to receive a diagnosis, with 50 % of them never obtaining a definitive molecular diagnosis.

ERDERA aims to address these issues through a tripartite mission: (1) integrating high-value resources, services, and cross-disciplinary expertise under one roof; (2) boosting clinical research to ensure every patient with a rare disease can be found and included in suitable clinical studies; and (3) driving innovation and EU competitiveness through collaboration across national, regional, and international levels. The alliance will help shape the European Research Area on rare diseases, advancing the use of health data, artificial intelligence (AI), and digital technologies to accelerate the translation of research into solutions for patients.

The partnership will operate across four key pillars:

1. Funding – ERDERA will support international research collaborations, clinical trials, and networking initiatives.

2. Clinical Research Network – This will include all in-house research activities, enhancing diagnostic tools, trial readiness, and the development of advanced therapies.

3. Support Services – These include hubs for global data integration, expertise in translational and clinical research, and partnerships with industry to advance promising research.

4. International Alignment – ERDERA will ensure national and international research strategies are aligned, supporting countries that are lagging in rare disease research plans.

The alliance will host a launch event on October 28, 2024, where it will present its roadmap for the next decade, highlighting how it intends to transform rare disease research and significantly improve patient care. ERDERA's work is expected to boost Europe's position as a global leader in rare disease research and innovation, enhancing EU competitiveness, creating jobs, and ultimately offering better diagnostic and treatment options for millions of patients.

More information: *https://erdera.org/news/european-partnership-opens-a-new-era-in-rare-disease-research/*

WHY 2024 IS ALREADY AN ENCOURAGING YEAR FOR THE RARE DISEASE COMMUNITY



Recent headlines in research and advocacy show promising news for the treatment of rare diseases.

We're approaching the end of 2024's first quarter, and we're thrilled to be able to say the year is off to a great start for the future of rare diseases. In various areas, from new drug approvals to research on emerging treatments to healthcare advocacy, there are several areas of progress that have caught Know Rare's attention.

Some of the year's early highlights in rare disease news:

NEW DRUG APPROVALS. The FDA has already approved 15 new drugs that affect rare diseases, including some that are intended to treat rare cancers. One of these drugs, Dupixent (dupilimab) was approved to treat eosinophilic esophagitis, illustrating how some drugs that are previously approved to treat a common disease can have additional impact for people with unrelated rare diseases.

ORPHAN DRUG RESEARCH. In the EU, the European Medicines Agency granted orphan drug designation to 22 drugs affecting 25 different rare diseases. Orphan drug designation encourages pharmaceutical companies to conduct molecular research that has the potential to lead to benefits for specific patient groups. (In 2023, almost half of all new medications approved by the FDA were classified as orphan drugs.)

STATE HEALTHCARE REPORT CARDS. The National Organization for Rare Disorders (NORD) recently released their annual state report card, which assesses the performance of states across the US in the areas of access, affordability, and overall effectiveness with relation to health coverage. Key assessment areas included findings on state-regulated insurance, the costs of out-of-pocket prescription drugs, access to medicaid, access to telehealth services, and the impact of rare disease advisory councils. you can find out how your state performed on NORD's website.

More information: *https://www.knowrare.com/blog-v2/q1-2024-rare-disease-news*

Observatory

ORPHAN DRUGS

CROSS-COUNTRY COMPARISON OF AVAILABILITY OF OD, BY YEAR OF APPROVAL

22

2024 1

CROSS-COUNTRY COMPARISON OF ACCESS TO OD, BY AVAILABILITY RATES

35%

2024 2

CROSS-COUNTRY COMPARISON OF AVAILABILITY OF NON-ONCOLOGICAL OD, BY YEAR OF APPROVAL

15

2024 3

CROSS-COUNTRY COMPARISON OF ACCESS TO NON-ONCOLOGICAL OD, BY AVAILABILITY RATES

32%

2024 4

TIMELINE

CROSS-COUNTRY COMPARISON OF AVERAGE TIME BETWEEN EUROPEAN MARKETING AUTHORISATION AND NATIONAL APPROVAL OF OD (DAYS)

488

2024 5

CROSS-COUNTRY COMPARISON OF AVERAGE TIME BETWEEN EUROPEAN MARKETING AUTHORISATION AND NATIONAL APPROVAL OF NON-ONCOLOGICAL OD (DAYS)

487

2024 6

This observatory compiles some of the main relevant indicators in the field of rare diseases, grouped in six areas.

By clicking on the ⊕ symbol you can observe the evolution over time of some of them.

The symbol allows you to access the source of data origin.

Abbreviations:
RDs: Rare Diseases
OMPs: Orphan Medicinal Products
EMA: European Medicines Agency

SOURCE OF DATA ORIGIN

1 2 3 4 5 6
IQVIA

newsRARE

Scientific dissemination magazine on Rare Diseases

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