INTRODUCTION

Rare diseases (RDs), including those of genetic origin, are defined by the European Union as life-threatening or chronically debilitating conditions whose prevalence is so low (less than 5 per 10,000) that special, combined efforts are needed to address them in order to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual’s quality of life or socio-economic potential. This definition first appeared in EU legislation in Regulation (EC) 141/2000 of 16 December 1999, on orphan medicinal products and was extended to the public health field by Commission Communication on RDs: Europe’s challenges of 11 November 2008, and by Council Recommendation on an action in the field of RDs, of 9 June 2009. Around 6000 diseases are described in the Orphanet database, affecting between 6% and 8% of the European population. Due to their severity, diffusion and multi-faceted aspects, RD are an area where collaboration in public health, health care and research provides a major integrated added value. Main areas for policy actions include: the development and implementation of European Reference Networks, as a main strategy for sharing of knowledge, clinical expertise and foster research; integration of high-quality patient registries, biobanks, and bioinformatics support, as key infrastructure tools addressing research and healthcare needs; the implementation of National Plans on RD in EU Member States by sharing experiences, capacity building and linking national efforts through a common strategy at a European level; actions driven by the recommendations for primary prevention of congenital anomalies (the main RD group with multifactorial aetiology); policy provisions to foster research and development of orphan drugs.

POLICIES AND ACTIONS

The Directive 2011/24/EU on the application of patients’ rights in cross-border healthcare clarifies patients’ rights to access safe and good quality treatment across EU. This Directive was the consequence of several decisions of the European Court of Justice related to the free circulation of patients as part of the EU fundamental right of the free circulation of persons. The European Reference Networks (ERNs) are being set up under this 2011 Directive and the European Commission adopted, through legal means the criteria and conditions which the European Reference Networks (ERNs) and the healthcare providers must fulfil. A new era for cooperation in the field of health was unveiled on 9 March 2017 as the first 24 ERNs were launched. Each of the 24 ERNs addresses groups of rare diseases including bone disorders, endocrine conditions, hereditary metabolic disorders, connective tissue and musculoskeletal diseases, immunodeficiency, autoinflammatory and autoimmune diseases; oncological and non-oncological haematological diseases. These networks, each having a co-ordinator, involve more than 900 highly-specialised healthcare units from over 300 hospitals in 26 Member States.

The overarching objective of ERNs is that patients have an improved access to quality diagnosis, care and treatment. This should be achieved by facilitating the mobility of the knowledge: only if absolutely necessary the mobility of patients should be envisaged. Each ERN operates by sharing and generating data and knowledge, clinical guidelines and performing training and e-learning. The...
ERN initiative is mainly driven by EU countries. The Board of Member States is the formal body in charge of the approval and termination of networks and memberships as provided in the Commission’s Implementing Decision [1]. The Board is comprised of representatives of the 28 EU countries and the EEA countries.

In this context, the 4th Conference on European Reference Networks, “ERNs in action” [2] organized by the European Commission took place on 21 and 22 November 2018 in Brussels with the involvement of the main ERNs stakeholders, including ERNs representatives, policy makers, national authorities, scientific communities and patients associations. ERNs are an excellent example of pan-European collaboration, uniting many different stakeholder groups (e.g. patients, Health Care Providers, scientists, policy makers). The ERNs have access to a dedicated Clinical Patient Management System (CPMS) [3] to provide virtual, cross-expert and cross-border consultations for real patients whose cases warrant the pooling of knowledge across the ERN community. The ERNs main challenges for the future are linked to the long-term sustainability and their integration in healthcare systems of the Countries.

The European Commission provides non-competitive funding opportunities and the 2018 Public Health Programme dedicates € 13.8 million to “Multiannual specific grant agreements for European Reference Networks” for the subsequent 3 years. The Networks expect also to receive the outcomes of applications to a Call launched via the Connecting Europe Facility (CEF), to support the ERNs in engaging with and using the CPMS.

Cooperation at EU level makes a real difference to rare diseases patients and their families, as well as the health professionals helping them. No country alone has the knowledge and capacity to treat all types of rare, complex and low-prevalence conditions and diseases, but by cooperating and exchanging life-saving knowledge at European level through ERNs, patients across the EU will have access to the best expertise available.

One of the main obstacles to clinical research and treatment advancements in RDs is the difficulty in conducting clinical trials. Clinical trials in RDs have to deal with the geographic spread of patients but also with the high heterogeneity within the same disease. The approval process of orphan drugs by regulatory agencies may also have to deal with limitations inherent to the small populations.

RD patient registries are powerful instruments that help and facilitate clinical research, planning of clinical trials, patient care as well as healthcare management. A pivotal aspect is the connection of registries with biobanks and clinical bioinformatics for RD research, as developed by the European project RD-Connect [4]. In particular, registries constitute a key support to ERN activities. A rapid proliferation of RD registries has occurred during the last years, either disease-specific or targeting RD groups at national [5], European [6] or international level. The analysis performed within the EPIRARE project (www.epirare.eu) identified three main typologies of registries, on the basis of their main purpose: public health, clinical and genetic research, and treatment registries [7]. Registries should maintain high-quality standards. Recommendations for quality implementation deal with such aspects as governance, Findable, Accessible, Interoperable and Reusable (FAIR) data, documentation, training, and auditing [8].

On these bases, the European Commission has proposed a common platform of RDs registries that will allow improving and increasing integrated uses. The European Commission Joint Research Centre (JRC) develops and maintains this European Platform on Rare Diseases Registration. Currently, the migration of two surveillance networks, the European Surveillance of Congenital Anomalies (EUROCAT) (www.eurocat-network.eu) and the Surveillance of Cerebral Palsy in Europe (SCPE) (www.scpenetwork.eu), has been fully achieved.

One main function of the EU RD Platform is to enable interoperability for the 747 existing RD registries in Europe according to the Orphanet inventory [9]. The second function is to offer a sustainable solution for two large European surveillance networks: European Surveillance of Congenital Anomalies (EUROCAT) and Surveillance of Cerebral Palsy in Europe (SCPE). EUROCAT is European network of population-based registries for the epidemiological surveillance of congenital anomalies. It covers about one third of the European birth population. The Central Database contains about 800 000 cases with congenital anomalies among livebirths, stillbirths and terminations of pregnancy, reported using the same standardised classification and coding. These high quality data enables epidemiological surveillance of congenital anomalies, which includes estimating prevalence, prenatal diagnosis and perinatal mortality rates and the detection of teratogenic exposures among others.

Due to the rarity of the diseases, none of the 28 EU Member States have enough data to conduct epidemiological, clinical or pharmacological studies to advance knowledge in this field. The information that is available is fragmented in these hundreds of registries across Europe, and until now there have been no uniform, accepted standards to govern the collection and organisation of these data. Capitalizing on the earlier set of indicators and common data elements proposed by the project EPIRARE [10], the “Set of Common Data Elements for Rare Diseases Registration” [11] is the first practical instrument released by the EU RD Platform aiming for an increased interoperability of the data registries. It defines the minimum data elements to be registered by all rare diseases registries across Europe, and provides instructions on how and in which format each data element should be registered.

The document describes the 16 data elements considered to be essential to enable further research. They refer to patient’s personal data, diagnosis, disease history and care pathway, as well as information to be provided for research purposes. All existing and new data registries across Europe are recommended to use this standard as the basis for their data collection activities. The standard was produced by a Working Group coordinated by the JRC and composed of experts from EU projects working on common data sets: EUCERD Joint
the critical preparatory phase, the EUROPLAN project (and sometimes second) national plans or strategies. In implementing and evaluating the success of these first national plans or strategies for rare diseases (NP/NS) compared to only 4 in 2008, and countries have adopted a national plan or strategy for rare diseases [13]. Mended that Member States adopt, by the end of 2013, biomarkers, and therapeutics [12].

Genomic research and development will thus be highly relevant for many markets, including genetic testing, high (and unmet) medical needs for most rare diseases. The therapeutics market for rare disease patients via major improvements in diagnostics and therapeutics. The therapeutics market will be the core components of the European RD Registry Data Warehouse constituted by aggregated data and a Reporting data set (RDS) with a Subset of Common Data Set without patient identification. That will create added value for all stakeholders and a selected European RD data publicly access. The general benefits of EDRI ant the created interoperability could be the maximisation of the utility of participating registries, enabling use of data across the registries, to provide accelerated communication, enabling automated data (searching/finding), enabling studies and research, extended use and re-use of existing data for various purposes.

A list of the data elements collected by the registries according to these MDR (Central Metadata Repository) will be the core components of the European RD Registry Data Warehouse constituted by aggregated data and a Reporting data set (RDS) with a Subset of Common Data Set without patient identification. That will create added value for all stakeholders and a selected European RD data publicly access. The general benefits of EDRI ant the created interoperability could be the maximisation of the utility of participating registries, enabling use of data across the registries, to provide accelerated communication, enabling automated data (searching/finding), enabling studies and research, extended use and re-use of existing data for various purposes.

A very useful and promising tool to reinforce and complement the European Platform on Rare Diseases Registration is the European Union Project RD-Connect (https://rd-connect.eu/). Patient registries, biobanks, and bioinformatics support are key infrastructure tools required for genomic research in rare disease; data sharing and linking of patients, samples, and analysis is also essential. The infrastructure developed by RD-Connect supports research in rare disease to find new genes, biomarkers, and therapeutic targets more quickly and efficiently. Its ultimate goal will be to improve outcomes for rare disease patients via major improvements in diagnostics and therapeutics. The therapeutics market in rare disease has strong growth potential due to the high (and unmet) medical needs for most rare diseases. Genomic research and development will thus be highly relevant for many markets, including genetic testing, biomarkers, and therapeutics [12].

The Council Recommendation of June 2009 recommended that Member States adopt, by the end of 2013, a national plan or strategy for rare diseases [13]. 25 countries have adopted a national plan or strategy for rare diseases (NP/NS) compared to only 4 in 2008, and the focus has moved more from “adopting” to actually implementing and evaluating the success of these first (and sometimes second) national plans or strategies. In the critical preparatory phase, the EUROPLAN project [14] has been pivotal in order to share relevant experiences within countries, promote capacity building and link national efforts through a common strategy at a European level. Therefore, EUROPLAN facilitated the implementation of National Plans in almost all EU and several non-EU Countries [15].

At Member State level, there is a great heterogeneity in the state of advancement of national policies, plans or strategies for rare diseases. Significant progress has been made towards this goal: 13 countries have time bound NP/NS which were still apparently active in July 2018: Austria, Croatia, Czech Republic, Estonia, France, Hungary, Ireland, Luxembourg, Netherlands, Portugal, Romania, Slovak Republic and Slovenia. 6 countries adopted time-bound NP/NS which had expired by July of 2018 and appear to have been replaced/renewed: Bulgaria, Finland, Greece, Italy, Latvia and Lithuania. The following countries adopted NP/NS which appear to be “ongoing” (i.e. according to the data received, do not cover specific time periods): Belgium, Cyprus, Denmark, Germany, Spain, United Kingdom. Three EU MS appear not to have adopted a NP/NS: Poland, Malta and Sweden. Switzerland and Norway also now have a RD plan or strategy [16].

It is interesting to mention that in other zones of the World a lot of countries have adopted NP/NS following the European model. This is the case in: Brazil, Colombia, Peru, Argentina, Japan, Singapore, Taiwan, South Korea, India (on discussion), Russia, Ukraine, Kazakhstan and others.

Another very relevant EU action, impossible to implement from a single Member State, is the revision of the International Classification of Diseases (ICD). The EU is cooperating closely with the World Health Organization (WHO) in revising the existing International Classification of Diseases (ICD) to ensure better codification and classification of RDs in the ICD 11th version [17], which should be adequately coded and traceable in all health information systems contributing to their adequate recognition in national health care and reimbursement systems.

Until recently there was no systematic effort to establish an inventory of rare disorders, except in the field of genetic defects where the Online Mendelian Inheritance in Man (OMIM) (www.omim.org) had started to document knowledge on genetic phenotypes as a proxy for genes, then on human genes when identified, as early as 1966 [18]. The compilation of an inventory of rare diseases, beyond genetic diseases, started in a systematic way in 1996, in the context of the rare disease database and knowledge base. Orphanet, established jointly by the French National Institute of Health and Medical Research (INSERM) and the French Ministry of Health [19] before being supported by the EUCERD Joint Action between the Member States of the European Union [20]. As a pilot initiative Orphanet not only collected information on rare diseases published in the scientific literature, but also classified them, from 2007 onwards, with a poly-hierarchy approach, each clinical entity being assigned an Orpha number. This effort was supported by the European Commission which not only co-financed Orphanet from 2001 onwards still today, but also established, in January 2004, a Rare Dise-
eu policiEs and actions for rarE disEasE
Monographic section

In November 2014 a Recommendation on Ways to Improve Codification for Rare Disease in Health Information Systems [22] was adopted by the EU Commission Expert Group on Rare Diseases. The document includes a recommendation to further promote Orpha codes within the development of ICD11 in order to allow a seamless transition of rare disease classification from Orpha codes to ICD11 when the latter is released. The Expert Group recommends that Member States implement the Orpha codes system and that codification of rare diseases be addressed within Member State rare disease national plans.

An assessment of the number of rare clinical entities having a specific code in ICD 10 can be derived from the effort carried out by Orphanet to cross-reference Orpha codes with ICD 10 codes, starting from the Orphanet list of rare clinical entities defined as a clinically unique, distinct entity, whatever the number and nature of the causes, and following the European definition for rarity, i.e. a prevalence equal of no more than 1 in 2000 in the general population of Europe (Figure 1). The cross-referencing is based on the 2010 online version of the ICD-10, but takes into account the official WHO updates endorsed in 2011 and 2012. In January 2015, among the over 6954 clinical entities listed by Orphanet, 355 of them only have a unique specific code in ICD 10. Each entry in the health information systems (group, disorder, subtype) is given a unique and stable ORPHA number (the Orpha codes). Each entry is given a preferred term and as many synonyms as necessary. In fact the situation is complex as one ICD code sometimes corresponds to one Orpha code, but also one ICD code can correspond to a group of rare entities or to a group of both rare and non-rare entities.

To increase rare disease representation in ICD-11, the objective is to expand the number of specific codes. The Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) (www.snomed.org) is run by the International Health Terminology Standards Development Organisation and is available in over 50 countries. It has been adopted as the standard terminology for the National Health Service in the UK and includes not only disease classification but also other medical terminology areas. Nearly 3000 rare diseases have a specific SNOMED CT code. The lack of data about rare diseases, due to the absence of codes for most rare diseases, deserves a special effort in epidemiology to make rare diseases more visible in the healthcare systems, in parallel with the ongoing process to incorporate codes for rare diseases in ICD and SNOMED-CT, as this process will not provide full results before several years [22].

The implementation of ORPHA codes [23] in national health information systems is ongoing. In addition to the progression of this implementation in Germany and France, pilot experiences are being conducted in Hungary, Latvia and Norway. ORPHA codes are currently being used in centres of expertise in the Netherlands and Slovenia. ORPHA codes are also being implemented in patient registries in Portugal, UK and Spain. In Switzerland, the Hôpitaux Universitaires de Genève and CHUV implement ORPHA codes in digital patient records since 2015. The use of ORPHA codes as a complement to already existing coding systems is being explored in most EU Member States [24], as recommended by the European Commission Expert Group on Rare Diseases.

In the meantime, the European Commission supports the Orphanet approach to improve quality and traceability of RDs in health information systems by using “Orphacodes” on a voluntary basis at a national

Figure 1
Overview of Rare Diseases coding terminologies in Europe.
level. These Orphacodes refers to the Orphanet classification of diseases and it is a stable and evidence-based nomenclature based on published expert classifications.

The European Joint Programme – Rare Diseases (EJP-RD) [25] is an instrument from the European Commission allowing high-level strategic organization and performance of research activities in an organized and transversal manner. It is operated by Programme Owners (typically ministries) and Programme Managers (Research Funding and Research Performing Organizations) in conjunction with other relevant stakeholders (e.g. patients’ organisations, regulatory bodies and the private sector). The 2018 Work Programme of the EU Horizon 2020 Programme included a very important call, to establish an EJP in the field of rare disease research with an EC budget of € 55 million for 5 years (2019-2023). In preparation for this call, an expert drafting committee was assembled in late 2016, to outline the contents of an EJP for RD. The basic goal was to support translational research in the rare disease arena, from bench to bedside and back again: in other words, to develop a sustainable ecosystem allowing a virtuous circle between rare disease care, research and medical innovation. The proposal was further developed during the course of 2017 and 2018, and the drafting group expanded to a vast consortium of 85 partners, led by the French INSERM. The proposal was submitted in April 2018 and approved in July, with an anticipated start date of January 2019. The total budget of the entire EJP is expected to exceed € 110 million (€ 55 million directly from the EC, supplemented with substantial national and in-kind contributions). 33 countries will participate in total, from 25 EU Members States, 8 Associated Countries, and one Third Country (Canada). The main goals of the EJP RD are: to improve the integration, the efficacy, the production and the social impact of research on RD through the development, demonstration and promotion of Europe/worldwide sharing of research and clinical data, materials, processes, knowledge and know-how; to implement and further develop an efficient model of financial support for all types of research on RD (fundamental, clinical, epidemiological, social, economic, health service) coupled with accelerated exploitation of research results for benefit of patients. EJP-RD is an inclusive effort, building on existing resources, experiences and networks including eRare, Orphanet, RD-Connect, EURORDIS, ERNs, and research infrastructures like ELIXIR (www.elixir-europe.org), BBMRI (www.bbmreric.eu), EATRIS (https://eatris.eu/), ECRIN (www.ecrin.org), INFRAFRONTIER (www.infrafortier.eu), amongst many others.

Primary prevention and health promotion are also relevant to RD policies. At least 20% of RD have a multifactorial basis. In particular, congenital anomalies (CA) are the paradigm example of RD liable to primary prevention actions, since most of them have a multifactorial (gene-environment) etiology. However, the insufficient attention to an integrated preventive strategy has led to the prevalence of CA remaining relatively stable in recent decades. On 2012 two European projects, EUROCAT and EUROPLAN, have joined efforts to provide the first science-based and comprehensive set of recommendations for the primary prevention of CA in the European Union. The resulting EUROCAT-EUROPLAN “Recommendations on Policies to Be Considered for the Primary Prevention of Congenital Anomalies in National Plans and Strategies on Rare Diseases” [26] were endorsed by European Union in 2013. The recommendations exploit interdisciplinary expertise encompassing drugs, diet, lifestyles, maternal health status, and the environment; evidence-based actions are pointed out aimed at reducing risk factors and at increasing protective factors and behaviors at both individual and population level. The recommendations therefore provide a comprehensive tool to implement primary prevention into national policies on RD in Europe and elsewhere [27, 28].

Recognising that the rare diseases constitutes a world problem for which the transatlantic cooperation was an obvious necessity the International Rare Diseases Research Consortium (IRDiRC) (www.irdirc.org) was created in 2014 as a platform for cooperation between the European Union, USA and Canada. IRDiRC announced a new vision and goals for 2017-2027. IRDiRC was conceived with two main goals: to contribute to the development of 200 new therapies and the means to diagnose most rare diseases by the year 2020. The goal to deliver 200 new therapies was achieved in early 2017, while the goal for diagnostics is considered to be reachable as well. IRDiRC goals are to ‘enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention’. The last six years have seen considerable progress on these goals: the goal to deliver 200 new therapies was achieved in early 2017 – three years earlier than expected – and the goal for diagnostics is within reach. These accomplishments were celebrated at the 3rd IRDiRC Conference in Paris in February 2017 [29].

From the IRDiRC perspective, an accurate molecular diagnosis [30] is essential for informed patient management and family counselling, as well as for rare disease research including natural history studies, biomarker identification and clinical trials. There are ~7000 rare diseases and the relevant gene is known (as of 2016) for approximately half of these, thus around 3500 are still without a defined molecular pathogenesis. In addition, a significant fraction of rare disease patients are without a molecular diagnosis due to a lack of universal accessibility of diagnostic testing. For diagnostic testing to be available for the majority of rare diseases by the year 2020, IRDiRC must focus on the discovery of the genes for the 3500 phenotypes that are currently without an associated disease gene [31]. Another challenge faced is diagnostics beyond the exome, and approaches to overcome these barriers to gene discovery are limited; the development of innovative approaches for discovery is required to solve these unsolved conditions, and IRDiRC aims to gather key researchers and review strategies to address this challenge [32]. International efforts to establish guidelines for the clinical reporting of genomic sequencing in a clinical setting, including the approach to report incidental findings, will expedite...
the delivery of high-throughput and cost-effective testing to the rare diseases patient community as a whole, e.g., guidelines for diagnostic next-generation sequencing developed by EuroGentest and the European Society of Human Genetics [33]. In addition, the necessary bi-directional flow between the clinic and research will be enabled by the IRDiRC Policies and Guidelines [34].

IRDiRC is focused on accelerating progress in the field of rare disease research through international cooperation and collaboration [30], with the ultimate goals of enabling the means to provide a diagnosis for all rare diseases patients, and to contribute to the development of new therapies for rare diseases. In order to increase the joint impact of rare diseases investment by funding agencies, industry, researchers, regulators, and rare diseases patient advocates, harmonization of efforts that address common roadblocks is needed. To assist in this task, IRDiRC developed a set of Policies and Guidelines [35], which are the principles that IRDiRC members agree to adhere to, focused on data sharing and standards, ontologies, diagnostics, biomarkers, patient registries, biobanks, natural history, therapeutics, models, publication and intellectual property, and communications about the Consortium. The IRDiRC Policies and Guidelines are the detailed and worldwide agreements of major public and private funding organizations to govern rare disease research, with the Consortium representing over 2 billion US dollar of investments. While it is too early to fully gauge the depth and magnitude of impact on rare disease research and patient benefit, the IRDiRC Policies and Guidelines have already significantly contributed in improving transparency and collaboration in this field. IRDiRC is now making steps towards addressing gaps and barriers in rare disease research; Task Forces are established to specifically address some of these gaps through policy recommendations and/or technical solutions. Rare disease research has made considerable progress in the last decade, and the IRDiRC Policies and Guidelines will further push the discovery progress of rare disease diagnosis and treatment, thereby advancing this important field of research.

According to the European legislation, a medicinal product can qualify for orphan designation under certain conditions. Today there are 221 orphan designations from which 164 initial orphan marketing authorisations and 22 extension of indication granted to date [36]. The medicine is assessed by the Committee of Orphan Medicinal Products (COMP) in the EMA (European Medicines Agency). The EMA will now publish an orphan maintenance assessment report for every orphan-designated medicine as part of a medicine’s European Public Assessment Report (EPAR) after the European Commission has adopted its marketing authorisation decision.

The European medicines regulatory system is based on a network of around 50 regulatory authorities from the 31 EEA countries (28 EU Member States plus Iceland, Liechtenstein and Norway), the European Commission and EMA. This network is what makes the EU regulatory system unique.

Results from a recent study [37] confirm that the number of medicines for rare diseases has increased since after 2010 and that the number of medicines in use and the resources spent vary widely among European countries. Despite these differences, some medicines are available in all countries and are mostly indicated for treating rare cancers and immune diseases. Similarly, the European Organisation for Rare Diseases (EURORDIS) study in 2010 showed that oncology medicines for rare diseases were the most widely available in nine European countries analysed [38]. Furthermore, our mean time to first continuous use seems to be comparable with the findings from the 2007 EURORDIS study that included 17 European countries [39]. The study reports the mean European time to first use of orphan medicines as 341 days (0.93 y) after marketing authorization. In the study, the average time to first continuous use assessed for orphan medicines was 1.6 years, which seems longer, but it represents uninterrupted use and includes the times of slower European markets. The study demonstrated that times to first use for orphan and non-orphan medicines did not differ in the biggest markets, whereas some smaller markets needed more time to introduce orphan medicines compared with non-orphan medicines, which could be due to higher prices. In Europe, half of the medicines for rare diseases introduced (orphan or not) are in use within 1 year after marketing authorization. The most successful countries in providing numerous medicines to the market in the quickest time are Germany, Norway, Finland, Sweden, and France, as observed previously. These countries also have specific mechanisms to improve patient access to these medicines and to grant full or substantial reimbursement from public resources. Italy and Spain have introduced several medicines for rare diseases, but it takes them longer than 1 year until the medicines are first used. In addition, Italy enables full reimbursement of orphan medicines, whereas Spain covers medicines with therapeutic advantage. Austria and The Netherlands also provide many medicines in a short time and substantially cover orphan drugs. Similarly, Ireland is fast in enabling first use, but reimbursement depends on community and national schemes that may not cover the medicine. Also, the number of medicines reported is quite low and does not represent total product availability.

Smaller markets, such as the Bulgarian, Croatian, Czech, Greek, Hungary, Polish, Romanian, Slovenian, and Slovakian markets, offer between one-third and one-half of the medicines analyzed, which is a significant number of medicines for rare diseases. However, the time to first use is much longer and more variable in these markets than in the larger European markets.

The fight against inequalities and inequities for the access to orphan drugs for all the patients of rare diseases around the EU constitutes a very relevant objective for the coming years even if the prices of such medications are a serious handicap for a single approach in all the European Union. The growth of pharmaceutical expenditures due to new high-cost innovative medicines, under the current institutional framework, creates financial challenges to health systems. The recognition
that the current path of growth cannot be continued indefinitely leads to the search of new ways to ensure that innovation “that matters” is produced, that patients have access to innovation and that health systems are financially sustainable. This context leads to the discussion of innovative payment models for new medicines (including orphan medicinal products) that improves the way the three above-mentioned objectives are met. It is unlikely that a single payment model will be optimal for all situations. Some broad principles should be observed when defining specific payment models for innovative medicines and deciding on rewarding R&D in pharmaceutical products [40].

In 2017, the PRIority MEdicines (PRIME) scheme was launched by the EMA (European Medicines Agency). This initiative was launched in March 2016 to provide early and enhanced support to medicines that can potentially address patients’ unmet medical needs, came into its second year of application. The EMA adopted a total of 81 eligibility recommendations in 2017, 20% more than in 2016. The success rate for acceptance into PRIME remained low, with only one out of five applications being successful, to ensure the Agency focuses on the most promising medicines.

A last example of European Union cooperation in fields having an influence in the rare diseases policy is the Health technology assessment (HTA). HTA is a research-based tool to support decision-making in healthcare. HTA assesses the added value of new or existing health technologies — medicines, medical devices and diagnostic tools, surgical procedures, as well as measures for disease prevention, diagnosis or treatment — compared with other health technologies. The HTA process is performed by currently about 50 European HTA agencies. Fragmented approaches from HTA agencies may have a negative impact on R&D investment in Europe. The Commission adopted its legislative initiative on 31 January 2018 [41]. The proposed regulation on HTA aims to strengthen EU-level cooperation among Member States for assessing health technologies. According to the Commission, it would not only make innovative health tools reach patients faster, but also boost innovation and improve competitiveness of the European healthcare sector, which accounts for 10% of the EU’s GDP. Building on existing EU cooperation on HTA, including the HTA Network and the EUnetHTA Joint Action (www.eunethta.eu), the proposal would provide the basis for a permanent, sustainable cooperation.

The proposal covers new medicines and certain new medical devices. It focuses the future cooperation (the “joint work”) on assessing clinical aspects of HTA, namely: the description of the health problem addressed by the health technology and the current use of other health technologies addressing that health problem; the description and technical characterisation of the health technology; the relative clinical effectiveness and the relative safety of the health technology. Member States would continue to be responsible for assessing non-clinical (e.g. economic, social, ethical, organisational) aspects of HTA, as well as for making decisions on pricing and reimbursement.

The proposal provides for joint work in four areas: i) joint clinical assessments focusing on the most innovative health technologies with the most potential impact for patients; ii) joint scientific consultations, whereby health technology developers (i.e. the pharmaceutical industry and medical-device manufacturers) can seek advice from HTA authorities; iii) identification of emerging health technologies (“horizon scanning”), with a view to identifying promising health technologies at an early stage; and iv) continuing voluntary cooperation on other aspects of HTA.

The cooperation would be Member State-driven, with the Commission hosting a secretariat to provide administrative, scientific and IT support. Participation in the joint clinical assessments and use of the joint clinical assessment reports at Member State-level would become mandatory after six years: following the regulation’s entry into force, the Commission proposes a three-year period for adopting tertiary legislation, and another three-year (transitional) period to allow Member States to fully adapt to the new system. Parliament’s Committee on the Environment, Public Health and Food Safety adopted the rapporteur’s draft report on 13 September 2018. The committee report was endorsed in plenary on 3 October 2018 with 200 amendments to the Commission proposal.

All these European achievements after years of action, are envisaged to be instrumental in guiding policy and research in the field of rare diseases in the forthcoming years looking for a fruitful and beneficial future for rare disease patients and stakeholders.

Funding
This work was supported by the Health Programme of European Union, in the framework of the Joint Action for Rare Diseases, Project n. 677024 “Promoting Implementation of Recommendations on Policy, Information and Data for Rare Diseases - RD-ACTION”.

Conflict of interest statement
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Submitted on invitation.
Accepted on 24 April 2019.

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