IMI2 JU Scientific Committee recommendations regarding rare diseases

Introduction

Rare diseases are often chronic, progressive, degenerative and often life threatening diseases. About 6-8% of the European population are affected by a rare disease. This means around 30 million people in Europe are currently suffering from a rare disease, 75% of which are children. The most common cause (80%) of rare diseases are genetic variations and 98% of rare diseases currently lack effective treatments. There is obviously a high unmet need for innovative drugs for these patients.

It is estimated that there are more than 7.000 rare diseases, which means a very heterogeneous group of diseases. As an example, Orphanet contains information on 6172 unique rare diseases; 71.9% of which are genetic and 69.9% which are exclusively paediatric onset. Of the 5304 diseases defined by point prevalence, 84.5% of those analysed have a point prevalence of <1/1 000 000. However 77.3–80.7% of the population burden of rare diseases is attributable to the 4.2% (n = 149) diseases in the most common prevalence range (1–5 per 10 000).

The context

Common challenges:
Rare diseases have similarities in terms of the challenges that these diseases pose for the patients.

Early diagnosis:
The medium time to get a diagnosis is still about 4 years. A time in which patients with a rare disease don't know the reason of their health issues, and when they might be mismanaged by health professionals.

Gene therapy:
Since most rare diseases have a genetic cause, the way to a real cure has to be a gene therapy. Any developments in improving the speed, costs and sensitivity of genetic testing, as well as improving gene therapy approaches will be beneficiary to a large group of rare diseases.

Access to information:
Patients, caregivers and health professionals need access to validated, up to date information on rare diseases: educational material, clinical guidelines, natural history studies, patient registries and experts as well patient organisations.

Historic neglect:
For the longest time rare diseases have been neglected by researchers. A big change came with the progression of genetic research. The whole genome project revealed the genetic cause of many rare diseases, and allowed for genetic testing.
A lack of incentives made orphan drug development no attractive for the pharmaceutical industry. That only changed in Europe in 2000, with the EU Orphan Regulation entering into force, and the EMA introduced the orphan drug designation. Since then, 169 orphan drugs for 127 rare diseases have been approved by the EMA (https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2019_en.pdf).
In the US, more than 5,000 medicines have been granted an orphan designation and the FDA Office of Orphan Products Development (OOPD) has successfully enabled the development and marketing of over 800 drugs and biologic products for rare diseases since 1983 (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm). Thus, there have been great advances in developing orphan drugs.

The success in developing orphan drugs, however, generated additional challenges. Justification of high prices for technologies in rare diseases is increasingly questioned by many stakeholders. The problem is substantiated by the relatively limited evidence base of new orphan medicines compared to medicines in common diseases. Policymakers have to find answers to fundamental moral and economic questions. If accelerated registration process is granted for orphan drugs to improve patient access, actual access to approved drugs can still be limited because of the delay in decision-making process on pricing and reimbursement mainly due to immature clinical evidence and extremely high prices.

The role of rare disease patients communities

Rare disease patient representatives and rare disease patient communities are an extremely valuable resource for researchers. Their unique experience can help to address patient relevant research questions, to develop patient relevant outcomes and patient reported outcomes and to generate real-world evidence, to design patient friendly and patient centred clinical trials, to recruit for clinical trials and disseminate the results.
Supported by the activities of EURORDIS, rare disease patient organisations could further professionalise, by participating in educational programmes, such as the EURORDIS summer- and winter-school or the EUPATI patient expert training course, rare disease conferences, etc.

Over 280 rare disease patient representatives are involved in the 24 European Reference Networks (ERNs). (http://download2.eurordis.org.s3.amazonaws.com/epag/epag-representatives-list.pdf)
These 24 networks of Europe leading rare disease specialists were set up in 2017 and are an unprecedented infrastructure with the potential to improve care for rare disease patients and boost research. ERNs are open, non competitive networks, that involve patients on all levels.

European rare disease research

The European Joint Programme on Rare Diseases (EJP RD) brings over 130 institutions (including all 24 ERNs) from 35 countries to create a comprehensive, sustainable ecosystem allowing a virtuous circle between research, care and medical innovation. To this end, the EJP RD actions are organised within five major Pillars, Pilar 0 being the central coordination and transversal activities: Fundings and Calls (Pillar 1), Coordinated Access to Data and Services (Pillar), Training and Empowerment (Pillar 3), Accelerated Translation and Clinical Trials (Pillar 4).

The International Rare Diseases Research Consortium (IRDiRC) is a global consortium that involves stakeholders from Africa, Asia, Australia, North America, and Europe. It unites national and international governmental and non-profit funding bodies, companies (including pharmaceutical and biotech enterprises), umbrella patient advocacy organisations, and scientific researchers to promote international collaboration and advance rare diseases research worldwide.

In this context, the Innovative Medicines Initiative (IMI) as a public-private partnership could contribute and complement existing initiatives by further:

- Setting up or scaling up European rare disease patient registries, biobanks,.. ;
- Conducting natural history studies, developing outcomes measures;
- Developing methodology for rare and ultra-rare samples (adaptive designs,..);
- Developing emerging technologies with a rapid return for patients and companies.

Public private partnership (PPP) as key to success for orphan drug development

The key factors for rare disease research to be successful is a strong collaboration of patient organisations, dedicated academia, pharmaceutical companies as well as health authorities working on innovative projects. Significant funding, shared risk and building a research infrastructure in a pre-competitive space can accelerate sustainable orphan drug development. This environment can be provided through PPPs such as IMI2 because IMI has evolved to create multistakeholder platforms that facilitate the interactions by providing a neutral basis avoiding conflict of interest of the project partners.

In contrast to many other areas of research in IMI2, the trigger for such a project might initially come from public partners who identified an area with specific clinical need or, ideally, a specific solution to this need. Both the solution and the clinical need might not be as evident to pharmaceutical companies. The PPP context can thus be instrumental in raising awareness, leveraging the risk considerations and thereby driving innovation in fields that may not have been obvious targets for industrial partners.

Recommendations

In this perspective, we identified several topics that are fully relevant:

1. Digital solutions

Integrating the patients voice through digital solutions

Digital solutions can offer an effective approach of integrating patients' voice that would serve two purposes:improving the quality of care by empowering the patients and supporting the work of researchers and health professionals by empowering researchers.

Empowering patients: The EMPATHIE project[1] concluded, that an empowered patient needs to be educated, involved in shared decision making and able to self manage their own disease. This can be provided through a digital Platform, that educates patients about:

- Their own disease;
- Finding the closest specialist;
- Finding the closest patient organisation;
- Diagnostic criteria, clinical guidelines, recommendations, treatment options;
- Qualification of the burden encountered by patients and families;
- Research (recruiting for clinical trials, socio-economic survey, lay summaries of finished studies, ..).

Moreover a digital platform can be a tool to conduct patient surveys and improve communication with the patients and various actors of the health care system, in particular health care professionals and drug developers, so that patients' opinion can be integrated in every aspect of health care and drug development.

Empowering researchers: Generating real world evidence directly from the patients provides an unfiltered look at the reality of rare disease patients. This information is vital for researchers, health professionals as well as authorities in order to:

- Improve therapies;
- Set patient relevant priorities;
- Collect information during clinical trials (patient reported outcomes);

- Evaluate the economic burden of the disease;
- Assess the impact of new drugs on patients.

Computational models for rare diseases

With the advancement of computational approaches and abundance of biomedical data, it will be possible to develop rare diseases models. A broad range of technical approaches has been proposed. Linear and nonlinear mixed models, self-modelling regression, differential equation models, and event-based models have been applied to provide a better understanding of disease progression patterns and biomarker trajectories. Useful statistical techniques include Kaplan-Meier estimates, cluster analysis, regression techniques, binary decisions trees, word clouds, and geographic mapping. Artificial intelligence (AI) has the potential to overcome deficiencies encountered by these models, which in turn can improve our understanding of rare diseases. Taking advantage of high performance computer capabilities, AI algorithms can now achieve reasonable success in predicting risk in certain cancers and cardiovascular disease from available multidimensional clinical and biological data. In contrast, less progress has been made with the rare diseases so far.

These approaches are promising tools to:

- Model the natural history of the diseases;
- Identify and model clinical outcomes;
- Identify new potential targets for rare diseases - through bioinformatics, AI, modelling analysis;
- Identify drug repurposing opportunities for rare diseases - through bioinformatics, AI, modelling analysis;
- Develop virtual cohorts to evaluate drug efficacy.

2. Innovative technologies

Innovative technologies are also key:

- To accelerate preclinical development through experimental models, run drug screenings using Induced pluripotent stem cells (iPS) models;
- Unlock most of the rare diseases with genetic origin. The dramatically reduced costs of DNA sequencing allow for more targeted approaches and large scale newborn screening;
- Gene therapies for rare diseases have been envisioned some decades ago and come now to reality. However this new opportunity requires more investment and broader use.

3. More explicit value framework for orphan medicines

All stakeholders, including regulatory agencies, health technology assessment bodies, payers, innovators, health care professionals and patient groups would benefit from more transparent international policy guidance on what contributes to the value judgement of new technologies in rare diseases, and how uncertainty in the evidence should be managed in the value assessment process.

On behalf of the Scientific Committee

Isabelle Bekeredjian-Ding, Chair

References

- Brasil S, Pascoal C, Francisco R, Dos Reis Ferreira V, Videira PA, Valadão AG. Artificial Intelligence (AI) in Rare Diseases: Is the Future Brighter? Genes (Basel). 2019 Nov 27;10(12). pii: E978.
- Editorial. Gene therapies for rare diseases. Nature Genetics, 1999, 22, 4: 313-314
- Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, Murphy D, Le Cam Y, Rath A. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020 Feb;28(2):165-173.
- EMPATHiE. Final report : https://www.eu-patient.eu/Members/Weekly-Mailing/empathie-finalreport