Policy Statement on Rare Diseases

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Rare Disease: A Global Health Issue

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Background

Rare diseases are defined in Europe as those affecting less than 1 in 2,000 people [1]. However, since over 7,000 such conditions have been described, this leads to a paradox as although each rare disease is uncommon, together they affect a significant proportion of the population. In fact, it is estimated that collectively around 1 in 17 people in the UK [2] and 1 in 10 people in the US [3] will be affected by a rare disease at some point in their lives, amounting to over 350 million people around the world living with a rare disease [4].

Although each rare disease affects patients in a unique way, many struggles they face are strikingly similar. This is not surprising as the reasons behind it stem from the very nature of the diseases, i.e. the small number of patients with each condition and their dispersion around the globe, which makes them prone to not receive sufficient attention. The resulting common challenges include long, arduous journey to diagnosis ("diagnostic odyssey"), difficult access to specialist care and limited treatment options [2, 4, 5].

Overall, patients living with a rare disease are at a significant disadvantage in accessing high quality healthcare as well as at an increased emotional and physical disease burden. Therefore, in the context of aspiring to achieve the third Sustainable Development Goal (SDG3) of 'ensuring healthy lives and promoting well-being for all at all ages'' [6], rare diseases patients, as a disadvantaged populations, deserve additional efforts to ensure equitable access to care. Viewing rare diseases as a global health issue, crossing countries' borders and requiring international efforts, is needed, especially raising awareness, fostering more robust research efforts and legislature changes, in every country around the globe.

Struggles of patients with (undiagnosed) rare diseases

Rare disease patients face barriers at each step in accessing healthcare. In a large survey encompassing the voice of over 12,000 individuals of the former patients, EURORDIS (an NGO uniting the voice of European rare disease patients) investigated their experiences, needs and expectations [7]. It confirmed how challenging the pursuit of a diagnosis can be - a fourth of surveyed patients had to wait between 5 and 30 years to receive a diagnosis, after having consulted many physicians, underwent many (sometimes unnecessary and invasive) investigations and having suffered from significant psychological and financial burden. During their diagnostic odyssey 40% have received misdiagnoses and some also inappropriate treatments, which not only in itself can be deleterious to health, but also causes further delays in starting appropriate management (if it exists). Even once the correct diagnosis is reached, around a third of the patients are not content with the way it is delivered and how much support was offered. Additionally, despite the fact that 80% of rare diseases have a genetic basis, around 25% of patients were not informed about this and only half received appropriate genetic counselling [7]. Therefore, many patients are left to research their disease by themselves and although excellent information and support is available from many patient support groups, during such distressing time it would be reasonable to expect more guidance and support from the clinicians .

As it comes to living and managing a rare condition, it is important to know that they are commonly complex and chronic forcing patients to rely on the help from a specialist multidisciplinary team [5]. However, again they face multiple challenges with accessing the care they need due the cost and inconvenience of travelling to appointments at distant specialist centres and long waiting times [7]. Combined with the progressive nature of many rare diseases and resulting significant disability, many rare disease patients have limited options for employment. Not uncommonly, both paediatric and adult patients need to rely on their family for support, both financial and in performing daily activities [5].

Effective treatments are available only for around 5% of rare disorders [8], but again their availability varies regionally and nationally. This statistic is particularly striking as around half of rare diseases have an onset in childhood [5] and 30% die beyond the age of 5 [8]. The dismal prognosis together with isolation and the challenges described above all contribute to significant mental health burden for rare disease patients and their families [5]. Some parents refuse to give up and become extremely invested in advocating for their children's condition and liaising with researchers to try to find a cure and in some notable cases these efforts turn into success stories ending with finding new treatments for the condition (e.g. with adrenoleukodystrophy [9] and alkaptonuria [10]).

Additional struggles of patients with undiagnosed rare diseases

Some rare disease patients might never receive a diagnosis and they will continue to live in anxiety of what future might hold (sometimes called 'undiagnosed purgatory'). Because of that they endure additional challenges including isolation and helplessness as well as barriers to accessing coordinated medical and social care just because their problems do not have a name. Additionally the parents of undiagnosed children face difficult reproductive decisions [7]. Such unmet needs of undiagnosed rare disease patients have been recognized in the US and some other countries, which offer clinical evaluations at a national expert centres for these patients [11].

Research

The very nature of being rare means that not uncommonly such conditions do not receive all the research interest and funding they require and if they do many challenges need to be overcome. First and foremost any research efforts, from describing the natural history or mechanisms of the condition to attempting to devise therapeutic approaches, are hampered by geographical dispersion of patients. Not only does it pose challenges for recruitment, but also for logistics around study appointments and results in many small fragmented studies, which have low statistical power [3]. Additionally, because of the small population of patients, the competition between pharmaceutical companies and academic institutions for trials participants can be heightened [12]. Therefore, given the scarcity of patients, regional and international collaborations like the International Rare Disease Research Consortium are an essential part of rare disease research [3, 13].

Other issues around rare disease research include funding (discussed below) and consideration of patients' input at all stages. The latter is especially important in assessing the study tolerability, the choice of targeted disease manifestations and final outcomes relevant to patients [3]. Additionally, attention needs to be devoted to study advertising as around half of 1,200 UK-based rare disease patients recently surveyed felt that they do not get sufficient information about research opportunities into their own condition by their doctors, despite 80% of them being eager to participate. Moreover, only 18% were aware of a registry for their condition, which is another mean of improving recruitment to clinical trials, therefore increased knowledge of their existence would be desirable [2].

Orphan drugs

Development of a new therapeutic takes on average 10 years and costs over 2.5 billion dollars [14] and less than 10% of the compounds entering phase 1 clinical trials are eventually approved for marketing and hundreds are discarded at the pre-clinical stages [15]. Therefore, investment in any drug development project carries a significant risk for pharmaceutical companies. In case of rare diseases the risk is compounded by the fact that the target patients population is small and therefore the scope for return of investment and profit for the pharmaceutical companies is limited. Additionally, not only are there thousands of rare conditions and each is caused by a unique pathophysiological mechanism, but also some of the genetic diseases are caused by many different mutations (e.g. Duchenne muscular dystrophy) and thus requiring different targeted therapies. With limited funds, resources and time this only adds to the challenges for development of therapies for rare diseases.

To overcome such barriers, policies incentivising development of medications for rare diseases (‘orphan drugs’) through offering tax incentives, support with marketing approval and market exclusivity have been introduced. The first, the Orphan Drug Act, was passed in 1983 in the United States (US) [16] and similar legislature followed in other countries [17, 18], including the Orphan Drug Regulation, which was passed in the European Union in 1999 [1]. Together with the rapidly developing genomics technologies, these policies have allowed for devising new targeted therapies that successfully reached the market. One recent example is onasemnogene abeparvovec (Zolgensma), which is the first gene therapy for spinal muscular atrophy (SMA) approved in the US in 2019 [19] and is being considered by the European Medicines Agency [20].

Another approach to finding effective therapies for rare diseases is drug repurposing, i.e. finding new uses for already approved medications which are known to be safe. Such approach, therefore, circumvents the need for pre-clinical and early human trials, thus saving both time (taking an estimated 6.5 years) and money (~300 million dollars) [17, 21]. In the past, drug reposition relied solely on serendipitous off-target effects, which were further investigated. This approach, although inefficient, resulted in repurposing of, for instance, thalidomide from its initial indication for managing nausea in pregnant women to its effective use in the treatment of a two rare diseases, leprosy and multiple myeloma [17]. Currently, more systematic methods using computational and experimental approaches to drug repurposing exist, which have the potential for bypassing the lacks of knowledge in the pathophysiology of rare diseases, although they have still not delivered the hyped surge in new treatments.

Despite the undeniable potential for drug repositioning to uncover treatments for rare disease, many challenges exist too. They include insufficient sharing of data and compounds, issues with patenting especially if other usable formulation of the drug are already available on the market and limited market exclusivity. Therefore, the is an argument for revising the current drug repurposing legislations in the US and Europe [17].

Funding for available orphan drugs

As previously described, enormous progress has been in recent years in developing more orphan drugs than ever before. In fact, between 1983 and 2018, the FDA approved over 800 medications for rare diseases [22], for instance alglucosidase alpha for Pompe’s disese and algasidase beta for Fabry disease. Despite this success, an important challenge has emerged – the drug pricing. Many of the approved medications are very costly with an estimated price of over 200,000$ [23], with the new gene therapy for SMA reaching over 2 million dollars and being the most expensive drug in history [24].

Some of the reasons for such a preposterous price are the small market and a need for return of the investment in drug development to the Novartis company. Other reason is the fact that there is no unified worldwide system for assessing the value of a developed drug and thus pharmaceutical companies are free to artificially inflate the prices. Some governments have started requesting release of information about costs incurred for drug development, however without binding legislation, this is only done on a voluntary basis by pharmaceutical companies. Drug prices should be regulated and set based on agreed and legally-binding criteria [23]. Some of those could include the cost of development, extend of the effect measured by for example added quality-adjusted life years (like used by the UK's National Centre for Health and Care Excellence, [25]) and the size of the target patient population [23]. Additionally, where possible counties should collaborate in price negotiations since this significantly increases the market for the medication and therefore the scope for decreasing the price, which has been done successfully in the past by Belgium and the Netherlands [26]. Following it would be desirable to include as many countries in such negotiations as possible, e.g. at the level of the European Union, which together comprised a market of over 500 million people [23] or also including low and middle income countries (LMICs) too [27].

Progress in the rare disease agenda in the high income countries (HICs) & the reality in LMICs

Since the introduction of the notion of 'rare diseases' almost 50 years ago [28], great progress has been made in raising their profile, improving patient care and developing new treatments. Some of the most important milestones that fuelled change were undoubtedly the orphan drug policies. Following on from those, new legislature from the European Union acknowledged the unique needs of rare disease patients and importance of improving their care through a call for introduction of national rare disease policies in the EU member states [29, 30]. All those achievement were fuelled by strong advocacy from determined patient support groups and international NGOs (e.g. EURORDIS, Rare Disease International (RDI)), whose members usually have lived experiences of rare disease and are highly motivated to achieve better access to high-quality care. In other words, progress is largely driven by the patients and their families themselves.

Some of the more recent advances include acknowledgment from the WHO [31] and the recognition of rare diseases as a pressing public and global health issue, both following strong advocacy efforts from patients organisations. Overall, currently rare diseases are a prominent public health priority in most HICs in Europe, North America, Australia and Japan, however, the reality is very different in LMICs.

Briefly it is estimated that not only over 300 million people are suffering from a rare disease in LMICs, which is 10 times more than in either Europe or the US [32], but also suffer the highest burden of congenital anomalies of various aetiologies, including rare and genetic causes [33, 34]. Yet, rare conditions are not uncommonly dismissed in those countries, in terms of research, orphan drug policies [35] and rare disease policies although exceptions exist [36, 37]. Some of the factors contributing to this this include lack of sufficient diversity in genomic data [38], limited funding for genomic technologies, staff training and research [39] and limited healthcare funding in general.

Overall, making high-quality care available for all patients living with a rare disease is undeniably challenging in resource-poor settings, where changes in the structure of the healthcare system driven by epidemiological and demographical transition force emphasis to be put on common conditions to ensure efficient use of the scarce available resources [40]. Therefore, in this context, the addition of rare disease to the United Nations' universal healthcare coverage agenda and declaration adopted by all 193 countries is especially important saluted. Not only does it draw attention to rare diseases at the level of international policy, but also allows the communities to demand action from their country's

government and hold it accountable to their declaration [41]. Devising feasible strategies for improving care of patients with rare diseases while working on achieving universal healthcare will be a challenge, however some success stories from Colombia, Philippines and Fiji are a useful resource and source of inspiration [42]

Teaching and training on rare diseases

Some of the previously described challenges that rare disease patients face can be ameliorated by improved education of the (future) healthcare professionals.

Until today, no large comprehensive studies have been conducted to assess how much teaching on rare diseases is included in the undergraduate curricula in medical schools. Published articles on the topic are rather selective with their focus and come almost exclusively from HICs. Data from Poland suggests that students know very little about rare diseases, e.g. the definition or examples of diseases, although a 30-hour-long facultative course improved their knowledge [43]. Non-compulsory courses on rare disease are also offered in the UK and other countries including France [44], Ireland [45] and Australia [46] among others [47]. Many of the courses include input from patients in the teaching sessions, given their expert knowledge of the topic and unique insight [44, 45, 48]. The scarce literature from LMICs also highlights the underrepresentation of the topic in the curricula [49, 50].

Regarding postgraduate education of the healthcare staff more focus is put on it in HICs, for instance in the UK the National Health Service staff have access to a funded Master's degree in Genomic Medicine [51] and the UK Strategy for Rare Diseases emphasizes this aspect in the implementation plan [52-54]. The situation is, however, different in many LMICs, which have few or no genetics training programme, limited genetics services and less than 50 genetic councillors in the whole of Africa, most working in South Africa [55]. The field is, however, rapidly developing especially in the Asia-Pacific region [56], South America [57] and in recent years also some African countries [58] with training programmes and services being developed.

Conclusion

Rare diseases are collectively a common and important global health issue affecting over 350 million people worldwide. In spite of the stark heterogeneity of the conditions, rare disease patients face similar struggles and disadvantages when accessing healthcare including delays in diagnosis, limited access to specialist care and treatment options.

Although efforts to tackle those issues are undertaken on national and international level, they are not only nowhere near complete, but also mostly centred around Europe and Northern America. Someone once said that 'families affected by rare diseases represent a medically disenfranchised population that falls through the cracks of every healthcare system in the world' [46] and this statement is especially felicitous for rare disease patients living in resource-poor settings.

Access to high-quality healthcare should not be determined by patients' financial abilities, where they live or what type of disease they have. To ensure health equity for everyone, special attention needs to be devoted to those who are most disadvantaged, and that includes patients living with a rare disease. Viewing rare diseases as a global health issue, crossing international boarders and requiring more efforts in some regions, can help tackle this problem more efficiency.

Calls to Action

Students for Global Health National Committee to:

- Acknowledge that viewing rare disease as a global health issue can help the rare disease community achieve many of their goals more easily and more quickly
- Establish a working group on Rare Diseases, which aims would be to carry out an audit of rare disease and genomic education in medical schools, where SfGH has its branches
- Raise awareness about how common rare diseases are collectively and why medical students should seek opportunities to learn about them
- Advocate for acknowledgement of the disenfranchised population of patients living with a rare disease with little support, especially in LMICs
- Raise the issue of rare diseases at international meetings and discuss strategies for student advocacy and research with other IFMSA member organizations, and seek potential collaborations
- Consider organising clinical or research exchange opportunities for incoming students involving a rare disease aspect

Students for Global Health Local Branches to:

- Set up or support the efforts of the Rare Disease societies at their University in organising events that raise awareness about rare diseases amongst students including celebrations of the Rare Disease day (28/29th February)
- Run awareness campaigns about rare diseases, orphan drugs and their funding at their University
- Research local opportunities to get involved in rare disease patients communities, charities and other organisations supporting rare disease patients, and advertise them to the wider medical student community
- Consider inviting speakers with a special interest in rare diseases to the Global Health Short Courses or organize one off events to introduce this topic to medical students

Students for Global Health Local Members to:

- Actively seek opportunities to learn about rare diseases, including rare disease patients who are eager share expertise about their condition and the struggles they face
- Get involved in clinical, scientific and social science research on rare diseases, e.g. as part of a student selected module or an elective
- Provide constructive feedback on current rare disease teaching to the medical schools and suggest ideas for improvement to the teaching staff based on own experience

Medical Schools to:

- Consider granting permission and support students wishing to undertake audits on the quality and quantity of content about rare diseases and genomics in the medical schools' curriculum
- Establish a realistic curriculum for undergraduate education of medical students on rare disease and genomics based on evidence from audits and experts' opinion, and implement it
- Advertise and facilitate opportunities for medical students to take part in research in rare diseases

The UK Government to:

- Foster international collaborations negotiations of orphan drug prices with pharmaceutical companies
- Allocate funds to assist the work of patient support groups and finance basic, translational and clinical research and training in rare diseases (including scholarships for students from LMICs)
- Promote collaboration between researchers to conduct more robust and meaningful studies on rare diseases

Global Academic Community to:

- Support medical schools in developing desirable and realistic learning outcomes for undergraduate education of medical students on rare disease and genomics
- Support students in auditing current rare disease and genetics content at their medical school, fostering their interest in research and drive to change what they are passionate about
- Provide guidance, support and share expertise researchers less experienced in the field of rare disease, including those in LMCIs
- Ensure diversity of genetic research and foster training opportunities for researchers in LMICs to take lead in the design, conduct and analysis of data, rather than outsourcing of the projects to the HICs

Health Professionals and Heath Institutions to:

- Continuously seek to keep up to date with new developments in rare diseases especially pertinent to the specialty they work in
- Organise workshops to facilitate further professional development in the area of rare diseases amongst healthcare workers
- Conduct research into social and clinical aspects of rare diseases and offer eager medical students an opportunity to help
- Support and promote the engagement of patients and patient support groups at every step of the consultation, drafting and implementation of Rare Disease plans and strategies

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