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Rare diseases: challenges and opportunities for research and public health

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Rare diseases remain a formidable public health challenge. The key to unlocking breakthroughs in diagnosis and treatment is fostering dynamic international partnerships and streamlined data sharing. The empowerment of patient advocacy groups is essential, as they are pivotal in driving innovative research and elevating health-care standards for these often under-represented conditions.

The definition of a rare disease is based on the frequency of the disorder. The European Union defines a rare disease as one that affects <1 in 2,000 persons and, in the USA, the 1983 Orphan Drug Act considers a disease rare if it affects <200,000 people in that country. Rare diseases are characterized by challenges in diagnosis, their potential severity, which can often be life-threatening, and the scarcity or absence of effective treatments. For example, individuals with infantile Tay–Sachs disease, caused by biallelic mutations in *HEXA* encoding the α-subunit of hexosaminidase A, have a life expectancy of 3–5 years and there is currently no treatment.

Remarkably, the ~8,000 known rare diseases are estimated to affect ~6% of the global population, amounting to hundreds of millions of people worldwide[1]. Patients with rare diseases and their families face considerable physical, psychological and social challenges.

Reducing the burden of rare (often genetic) conditions remains a major challenge with economic considerations. For instance, in Australia, individuals with single-gene or chromosomal disorders accounted for 0.5% of the population but 1.9% of hospital admissions and 1.5% of hospital costs[2], much of which could be reduced by factors such as earlier diagnosis. In the USA, the costs of treatment for the rare disease phenylketonuria have been documented to be a considerable burden for affected families[3].

Current initiatives

Fortunately, the biomedical and public health communities increasingly recognize rare diseases as a considerable health burden. The scarcity of individuals with the same disorder necessitates global information exchanges. Data-sharing platforms such as Gene Matcher, Matchmaker Exchange and MyGene2 have emerged to disseminate knowledge on rare diseases. Physicians and scientists who encounter a patient who has an apparent new disease with a variant in a candidate gene not currently associated with a disease can list the gene or variant on one of these platforms, which alerts others who know of a similar patient or gene variant; this fosters collaboration. Further achievements have been made, especially in high-income countries, with the establishment of 24 Reference Networks for rare diseases in Europe by the European Commission, the Division of Rare Diseases Research Innovation at the US National Institutes of Health and the expedited drug approval processes for clinical trials involving orphan drugs by both the EMA and the FDA. Many countries have implemented newborn screening for genetic diseases, which brings substantial benefits to patient well-being and health-care sustainability, including cost savings. For low-income and middle-income countries (LMICs), additional barriers exist in improving diagnosis and treatment. These include a paucity of experts in rare diseases, insufficient diagnostic and laboratory resources, reduced access to care, owing to high costs or long distances, and sometimes cultural stigmata attached to an illness.

> "The scarcity of individuals with the same disorder necessitates global information exchanges"

Challenges in diagnosis have been formally addressed with initiatives, such as the NIH Undiagnosed Diseases Program (UDP)[4] and the NIH Undiagnosed Diseases Network[5] in the USA. These have fostered the creation of a global Undiagnosed Diseases Network International (UDNI), which now has >160 members from >50 countries, with ~20 UDPs worldwide, including a champions initiative to promote the creation of UDPs in LMICs[6]. Advocacy groups for rare and undiagnosed diseases have multiplied, and the scientific community recognizes the crucial role of patients in sharing experiences and advocacy. UDNI includes several patient associations and has a Patient Engagement Working Group with representatives of the European Organisation for Rare Diseases (EURORDIS), the Wilhelm Foundation and the National Organization for Rare Disorders (NORD). In the USA, the Undiagnosed Diseases Network Foundation (UDNF) has a Participant Engagement and Empowerment Resource (PEER). Change is happening, but it must be sustained and enhanced at both personal and institutional levels, as caring for individuals with rare diseases is a moral imperative.

Challenges and opportunities

Establishing care for patients with rare diseases has both challenges and opportunities. Many rare diseases have not yet been discovered, and describing a new disorder requires the elimination of known diseases, the elucidation of a distinct phenotype in more than one affected individual, the identification of pathogenic gene variants and cellular or biochemical studies illustrating a functional defect. Similarly, the discovery of a new disorder provides new insights into mechanisms, pathways and interventions. For example, the discovery of the basic defect in cystinosis, that is, failure to transport cystine out of lysosomes due to deficiency of the carrier protein cystinosin, led to the discovery

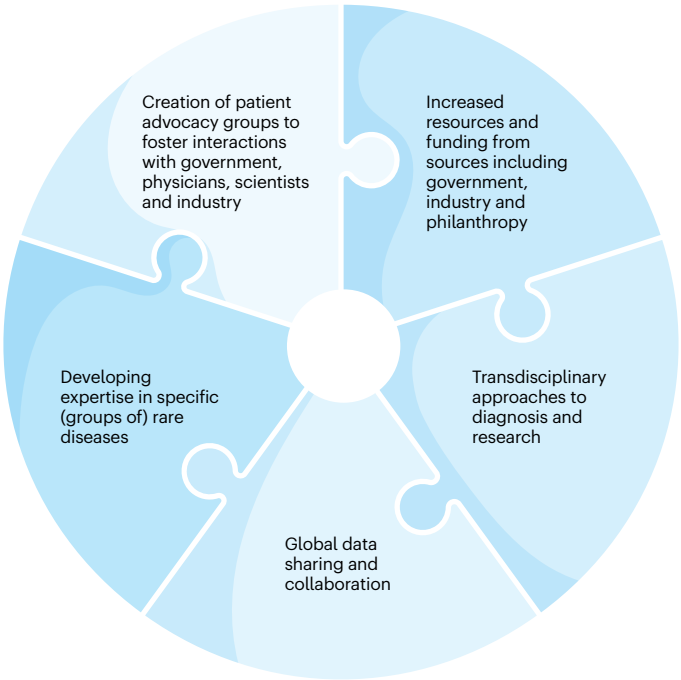

Fig. 1 | Opportunities to address the challenges faced by patients with rare diseases and their families and caregivers. The roles of government, advocacy groups, rare disease experts and industry are intertwined, with data sharing and collaboration unifying the efforts.

of the mechanism of action of cysteamine in depleting cystinosis lysosomes of cystine. Oral cysteamine has been the treatment of choice for cystinosis since 1994 (ref. 7).

Reaching a rare disease diagnosis can be difficult, and many affected individuals remain undiagnosed for years. For example, an analysis of a 3,304-member Spanish rare disease registry revealed that >20% of individuals waited ≥10 years for a diagnosis[8]. The rarity of each disorder challenges the expertise of individual physicians and institutions, and political and financial considerations often limit support for relevant research. Yet, once a diagnosis is made, it can lead to life-changing genetic counselling, improved health care and escape from the isolation surrounding individuals and families who cannot name their malady.

> **"Reaching a rare disease diagnosis can be difficult, and many affected individuals remain undiagnosed for years"**

A considerable challenge for diagnosis is that many rare diseases are multifactorial, involving both genetic and non-genetic factors. Focusing solely on monogenetic disorders may overlook epigenetic components and leave multifactorial conditions among the most neglected undiagnosed rare diseases. Transdisciplinary approaches, incorporating expertise in infectious diseases, toxicology and nutrition, can help address this problem[9]. Artificial intelligence might be useful in integrating vast omics data from various networks to address unusual disease aetiologies.

Equity in rare disease health care remains an issue. The likelihood of reaching a diagnosis varies substantially by country and socioeconomic status, leading to disparities among diagnosed and non-diagnosed patients. The UDNI's LMIC Working Group and Diagnostics Working Group aim to mitigate this issue, with partners acting as ambassadors to strengthen the global effort against undiagnosed rare diseases, considering cultural and societal specificities.

Finally, resource limitations are a major barrier to equating the care of rare and undiagnosed individuals with that for common disorders. The United Nations Sustainable Development Goal 3 for 2030 is to: "Ensure healthy lives and promote well-being for all at all ages". The United Nations Resolution on "Addressing the Challenges of Persons Living with a Rare Disease and their Families" urges member states to implement, as appropriate, national measures to ensure that persons living with a rare disease are not left behind. Data sharing is one way for global networks to address this goal. An example is the Free Sialic Acid Storage Disorders (FSASD) Consortium, supported by the advocacy group Salla Treatment and Research Foundation (STAR), which facilitates global collaboration on FSASD research[10].

Improving this situation is a collective responsibility and calls for actions. Physicians who practice in an amenable health-care system can establish referral patterns to rare disease experts or even specialize in a rare disease, providing care and disseminating their findings. This opportunity can be enhanced by early education and training in rare diseases. Scientists can explore rare disease mechanisms through gene function and mechanistical studies. Collaboration between health-care professionals and industry can lead to new therapies. Data and information sharing can create synergistic outcomes. Further opportunities include serving on expert panels and advocacy group advisory boards, offering expert opinions to government agencies, connecting with scientific or clinical counterparts over rare diseases and sharing expertise, teaching about rare diseases in medical schools and inspiring young people to enter the field (Fig. 1). The medical and public health communities must work together to implement these strategies to improve the lives of patients with rare diseases.

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Competing interests

The authors declare no competing interests.