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Addressing diagnostic gaps and priorities of the global rare diseases community: Recommendations from the IRDiRC diagnostics scientific committee

David R. Adams [a,*,1], Clara D.M. van Karnebeek [b,1], Sergi Beltran Agulló [c,d,1], Víctor Faùndes [e,1], Saumya Shekhar Jamuar [f,g,1], Sally Ann Lynch [h,1], Guillem Pintos-Morell [i,j,1], Ratna Dua Puri [k,1], Ruty Shai [l,1], Charles A. Steward [m,1], Biruté Tumiene [n,1], Alain Verloes [o,1], members of the IRDiRC Diagnostic Scientific Committee

[a] National Human Genome Research Institute, National Institutes of Health, USA
[b] Departments of Pediatrics and Human Genetics, Emma Center for Personalized Medicine, Amsterdam Gastro-enterology Endocrinology Metabolism, Amsterdam University Medical Centers, the Netherlands
[c] Centre Nacional d'Anàlisi Genòmica (CNAG), Spain
[d] Departament de Genètica, Microbiologia i Estadística, Facultat de Biologia, Universitat de Barcelona (UB), Spain
[e] Laboratorio de Genética y Enfermedades Metabólicas, Instituto de Nutrición y Tecnología de los Alimentos, Universidad de Chile, Chile
[f] Genetics Service, KK Women's and Children's Hospital and Paediatrics ACP, Duke-NUS Medical School, Singapore
[g] Singhealth Duke-NUS Institute of Precision Medicine, Singapore
[h] Children's Health Ireland, Ireland
[i] Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital, Spain
[j] MPS-Spain Patient Advocacy Organization, Spain
[k] Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, India
[l] Pediatric Cancer Molecular Lab, Sheba Medical Center, Israel
[m] Genomics England, United Kingdom
[n] Vilnius University, Faculty of Medicine, Institute of Biomedical Sciences, Lithuania
[o] Département de Génétique, CHU Paris – Hôpital Robert Debré, France

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ABSTRACT

The International Rare Diseases Research Consortium (IRDiRC) Diagnostic Scientific Committee (DSC) is charged with discussion and contribution to progress on diagnostic aspects of the IRDiRC core mission. Specifically, IRDiRC goals include timely diagnosis, use of globally coordinated diagnostic pipelines, and assessing the impact of rare diseases on affected individuals. As part of this mission, the DSC endeavored to create a list of research priorities to achieve these goals. We present a discussion of those priorities along with aspects of current, global rare disease needs and opportunities that support our prioritization. In support of this discussion, we also provide clinical vignettes illustrating real-world examples of diagnostic challenges.

1. Introduction

Establishing a correct diagnosis for a person with a rare disease is not a cure or therapy. However, diagnosis does provide direct benefits and may be required to optimize medical care. The benefits of a diagnosis may include improved estimation of prognosis, direction of rational therapy, opportunities for genetic counseling, refinement of supportive care plans, and the end of a potentially expensive and/or invasive series of diagnostic investigations ("diagnostic "odyssey"). An accurate diagnosis may allow participation in relevant clinical trials and prevent consideration of potentially harmful, ineffective treatments. Multiple barriers to rapid diagnosis exist, and each comprises a set of research opportunities. We have separated our recommendations for research priorities into three large aspects of the rare disease odyssey:

* Corresponding author.
E-mail address: david.adams@nih.gov (D.R. Adams).
[1] All listed authors contributed equally.

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1. Clinical Aspects
2. Laboratory Testing and Technology, and
3. Ongoing Care and Transition to Therapy

2. Clinical aspects

The clinical aspects of diagnosis encompass diverse activities and topics. Fundamental to all are pathways for educating new and existing stakeholders about known and emerging rare diseases (RD) (Tumiene et al., 2022). Educational planning must include all members of the rare disease community, with a focus on the inclusivity of affected individuals. New and innovative training methodologies, including asynchronous learning, problem-based learning, and interactive content, offer the potential for improved uptake by learners when compared with static and didactic approaches. Content and delivery methods in rare disease education should highlight areas of need for ongoing research.

Regarding clinical aspects of diagnosis, we propose three areas for research prioritization: rare disease recognition, rare cancers, and improvement of access to rare disease resources.

2.1. Rare disease recognition

Persons affected by rare diseases report appropriate clinical referral as a substantial early barrier to appropriate care. The individual must be recognized as having a remaining undiagnosed condition after the differential diagnosis has been exhausted. The person must then be successfully connected with the expertise and resources to identify and confirm the correct medical condition. Approaches to improving referral success rates can include improvements in education, referral infrastructure, and availability. Additionally, the empowerment of affected individuals can allow them to discover and engage potentially useful clinical resources on their own.

2.1.1. Identification of rare diseases based on phenotype

The identification of a rare disease requires either recognition of a phenotype or detection by clinical testing. Published rare disease phenotypes are often based on an ascertainment bias arising from the initial cohorts used to describe the disorder. In addition, age-dependent penetrance and evolution of phenotypes over time may obscure the similarity between described and observed descriptions. Agnostic testing, such as exome or genome sequencing, may generate evidence of disease-consistent DNA variation in the absence or partial absence of the expected gene-associated phenotype. There is a clear need for so-called "reverse phenotyping" to clarify the full phenotype of many rare diseases (Wilczewski et al., 2023). If a phenotype is not documented correctly or adequately, both genetic testing and subsequent clinical evaluation may fail to consider associated medical conditions. Standardizing medical notes with ontologies such as the Human Phenotype Ontology (HPO) (Kohler et al., 2021) and the Orphanet Rare Disease Ontology (ORDO) (Mohtashamian et al., 2022) enables machine readability, facilitating applications such as phenotype driven gene prioritization and patient matchmaking based on phenotypic similarity (Robinson et al., 2014). However, these tools must be updated and widened to cover fields of knowledge that are still lacking harmonization. In practice, many electronic medical record (EMR) systems do not incorporate standard phenotyping ontologies. Alternately, they may use ontologies optimized for public health statistics, economic and billing applications, *e.g.* International Classification of Diseases (ICD) coding. This can cause them to underperform for rare disease diagnosis (Gunne et al., 2021). Ontologies may be limited by the number of available language translations. Aligned with this objective, machine learning based methods (*e.g.*, Phenobert, Phenotagger) can facilitate the extraction of ontology terms from medical records containing unstructured text (Feng et al., 2023; Luo et al., 2021). Tools like Cliniface, Face2Gene and GestaltMatcher have emerged to facilitate capturing of facial phenotypes (FDNA Inc., 2011; Hsieh et al., 2022; Palmer, 2021). Further research to develop these technologies is needed to maximize both utility and the evidence needed to advocate for adoption in EMR systems.

Even with adequate phenotyping, the successful diagnosis of a rare disease is not guaranteed. Reduced penetrance, atypical presentations, provider knowledgebase limitations, genetic heterogeneity, and other factors may cause delay or failure of disease identification. It is unlikely that any individual medical provider will be aware of all existing and emerging rare diseases. Therefore, infrastructure for diagnostic augmentation (both by human experts and computational tools) is both essential and incompletely developed. Computational tools, such as those described, are important and useful examples but not comprehensive. In addition, networks of experts need to be developed alongside data sharing policy that allows communication across geographic and language barriers. Continuing development of diagnostic algorithms and standards and refinement of disease classifications will be essential both to educate emerging providers and to allow for optimized use of diagnostic resources. Expansion of newborn screening, perhaps to include genome sequencing, will both exacerbate diagnostic challenges and provide critical new data for genotype-first improvements to our understanding of gene-associated phenotypes.

2.1.2. Clinical diagnosis and related tools

The role of the primary care physician is critical in identifying patients who need to be referred for evaluation of a rare disease. Affected persons may be evaluated by specialists who concentrate on specific aspects of an illness rather than looking for a unifying genetic diagnosis. Education of physicians regarding cues for rare disease consideration is critical. A 2020 Irish study showed that both specific rare disease-specific coding and the use of the relevant rare disease information sources (*e.g.,* Orphanet) are lacking in general practice, demonstrating a gap in the education of RDs amongst primary physicians (Byrne et al., 2020). With the increasing prevalence of electronic health records, mining electronic health records for patients with rare disorders is an emerging topic of research interest. Indeed, such an approach has been shown to improve the diagnostic yield for patients with Mendelian diseases (Bastarache et al., 2018).

Genome and exome sequencing have provided critical new tools for the diagnosis of rare diseases. However, the fraction of clinical sequencing studies that yield a definitive diagnosis remains around 30% or less (depending on the population) (Slavotinek et al., 2023). More recent advances, including long read sequencing, optical genome mapping (OGM), transcriptomics, proteomics, metabolomics, and methylation profiles, as well as the continued discovery of new genetic diseases, are helping to improve the diagnostic yield, but the overall anticipated increase is less than 10%. In some cases, non-genetic or genetic plus environmental factors are responsible. In others, yet to be determined, genetic mechanisms will be causative. The fact that estimates of remaining Mendelian disease to be discovered are in the 1000s underscores the fact that new disorders will continue to be described in the near future (Ferreira, 2019). Frameworks for the consistent re-evaluation of persons with undiagnosed disease are haphazard and need standardization.

2.1.3. Family history

Adequate family history collection in the primary care setting remains limited (Dineen et al., 2022). Studies have shown that an accurate family history may be able to assign the probability of finding a causative variant during genetic testing (Shirts et al., 2016). Family history may often reveal clues to the possible inheritance pattern of the disease so that a more focused look for variants can be performed on the genomic data (for example, focusing on rare variants on the X chromosome for a suspected X-linked disorder). That said, it must be stressed that "old concepts" like dominant, recessive, or X-linked inheritance have been challenged (or at least complicated by) recent developments in biological understanding (Zschocke et al., 2023).

2.2. Rare cancers

2.2.1. Definitions

Rare cancers may be divided into rare, generally non-familial cancers such as hairy cell leukemia and rare germline conditions that generate elevated risk of cancer, *e.g.* Li-Fraumeni syndrome and Gorlin syndrome. Of note, germline cancer predisposition syndromes may cause cancer types that are not in themselves rare, such as colon cancer in Lynch syndrome. Rare cancer affects people of all ages, including children, making them a critical area of study in pediatric oncology.

2.2.2. Characteristics

One of the primary challenges in rare cancer syndromes is early detection. Some rare cancers present with atypical symptoms, including earlier than typical onset. In other cases, atypical features may lead to diagnostic delay. As with rare diseases in general, treatment options may be less well developed compared with more common entities. Treatment decisions often rely on extrapolating from data on more common forms of cancer. Recent advancements in genetic testing and molecular profiling have significantly improved the diagnosis of rare cancer syndromes. For heritable cancer predisposition syndromes, next-generation sequencing and genetic counseling play crucial roles in identifying individuals at risk. Additionally, liquid biopsies and non-invasive screening methods are emerging as promising tools for early detection. Tailored treatments based on the specific genetic mutations associated with rare cancer syndromes are a promising avenue. Collaborative efforts to collect and share data on rare cancer syndromes are essential. This can help researchers better understand the genetic basis of these conditions and identify potential therapeutic targets. Pediatric rare cancer syndromes add an extra layer of complexity and urgency to this field. Children are more vulnerable to the long-term effects of cancer and its treatment. Therefore, efforts to advance research, diagnosis, and treatment for these conditions in pediatric populations are crucial. Early detection, pediatric-specific treatment protocols, and psychosocial support tailored to children and their families are all areas that require attention and innovation.

Rare cancer syndromes represent a multifaceted challenge in oncology. Progress in understanding these syndromes, improving diagnostics, and developing targeted treatments holds promise for improving the outcomes and quality of life for individuals and families affected by these conditions, particularly in the pediatric population.

2.3. Barriers to access and infrastructure requirements

2.3.1. Access to geneticist/genetic testing facilities

Limitations in access to rare disease expertise, testing, and care are challenging for many families, contribute to morbidity and mortality, and occur in every country (Ward, 2023). Testing results may be complex, genome and exome sequencing being a good example, to the point where mainstream clinicians require support to interpret and return them. Without support, errors in interpretation can be made, resulting in harm to the patient. A study focusing on mortality during evaluation found 45 patients who died awaiting a clinical genetics appointment (Bradley and Lynch, 2021).

2.3.2. Diagnostic referral pathways

Referral pathways differ substantially depending on geographic location and associated health system. Optimally, there would be a smooth transition from primary clinicians to subject matter experts anywhere in the world. However, language, time, knowledge, and other factors frequently disrupt this process. For any given rare disease, specialists are often rare themselves. Potentially useful confirmatory testing covers myriad modalities, including biochemical, molecular (DNA), radiological, and others, all of which are susceptible to inequitable access. Practices such as multidisciplinary meetings can help to integrate expertise about diverse aspects of a disease presentation but may require time consuming coordination if consultants are in geographically dispersed locations. Asynchronous approaches ("chat" discussions, mailing lists, and other online tools) may help to fill this gap and help to lower barriers created by time zone differences. Standardization and infrastructure development for such encounters would benefit from additional research and development.

2.3.3. In person evaluations

Direct clinical evaluation by experienced providers may be needed during the diagnostic process. If not available locally, travel to a referral center may be complicated by language, patient health/safety, financial considerations (both for the family and the center), and legal barriers. In high resource areas of the world, such as the European Union, progress has been made in establishing reference centers and mechanisms for rare disease patients to avail themselves of their services. The "Cross Border Act" includes rules for facilitating heathcare across the borders of member states (healthcare. et al., 2011). In parallel, systems must be developed to facilitate the discussion of complex cases without the need for the patient to move. The first level is teleconsultation (with an MD or a multidisciplinary team). The second level is the development of dedicated tools allowing discussion of complete cases between experts while respecting regulations like GDRP (in the EU) or other data/person protection. Although imperfect, the EU has even gone a step further by promoting a tool called the Clinical Patient Management System (CPMS) dedicated to expert deliberation at a European level (Fortunato et al., 2023). Access to reference centers and thus to regional or national structures of concentration of health care services can affect the quality of care and efficiency. One of the recommendations of the European Commission with respect to reference centers is to centralize rare disease expertise by promoting good clinical practice guidelines, training programs in diagnosis and treatment, and facilitate access to orphan drugs, and clinical-therapeutic assessment reports (Lynn et al., 2017).

2.3.4. Social and psychological support

Psychological and social support for families with RD is a critical part of a comprehensive care plan. A recent survey of 20 nations under the Undiagnosed Disease Network International identified needs, barriers, and opportunities to care for patients with rare diseases (Taruscio et al., 2023). The survey noted that patients self-reported anxiety and stress related to delayed access to diagnosis, clarity around recurrence risk, and follow-up management. The participants acknowledged that this had negatively impacted personal decisions around family planning, education, and employment and had a significant impact on family members seeking clarity on their own risk. The patient's journey to a diagnosis of a rare genetic disease is often long and tortuous, sometimes with many years of misdiagnosis and delay (diagnostic odyssey). In Fabry disease, the median age at diagnosis in men is 30 years, after up to 10 years of research and visits from up to ten different specialists. The psychological impact of late diagnosis can lead to significant depression even when a diagnosis is finally reached. Anxiety regarding the implications of the natural history of the disease and its treatment often replaces the initial relief of disease identification. Patients may express concerns regarding the availability of therapy, the reversibility of their symptoms or organ dysfunction, and the practicalities of receiving treatment. They will need support at every stage of diagnosis, evaluation, and treatment (Packman et al., 2010). Measuring the quality of care as perceived by patients is increasingly being used in clinical practice, but they are still relatively unknown. Evaluation of the care strategies by the patients is a new paradigm supported by the elaboration of Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs).

3. Lab aspects

Laboratory-focused research priorities can be grouped into data generation and data analysis. In the former, long-reads and single-cell

sequencing technologies (Oehler et al., 2023; Sreenivasan et al., 2022), optical genome mapping (Dremsek et al., 2021), multi-omics testing (Lunke et al., 2023; Wojcik et al., 2023) and massive, high-throughput functional assays (also called "Multiplexed Assays of Variants Effects", MAVEs (Spielmann and Kircher, 2022),) are becoming more frequently used in diagnostic laboratories in order to detect the missing heritability of some presumed genetic disorders (Sanchis-Juan et al., 2023) and to gain more clinical significance for variants that otherwise would be classified as uncertain. In the latter group, automatization of bioinformatic pipelines (Seo et al., 2022; Meng et al., 2023) and incorporation of deep-, machine-learning and artificial intelligence (AI) tools (Ma et al., 2022) are allowing iterative and quicker analyses of raw data along with the addition of novel and/or updated findings from literature or even from predictions. Also, *in-silico* predictors are increasingly using machine-learning approaches and AI to predict the pathogenicity of variants, especially missense ones (Cheng et al., 2023). Albeit all of these tools are closing some gaps in terms of detection and interpretation of genetic variants, the level of evidence that supports their broad use is still not enough, not just for measuring their impact on clinical management but also from other viewpoints (*e.g.,* ethics, economics, legal, etc.), which should be studied (Zhong et al., 2021).

Novel data generation technologies are changing the way that genetic variants are understood. Long-read sequencing techniques are allowing to identify hard-to-call variants such as structural ones and short-tandems repeats, and even epigenetic changes such as methyl-cytosines and methyl-adenines in a single assay (Oehler et al., 2023; Mastrorosa et al., 2023). Single-cell genomics coupled with long-read sequencing may unveil the consequence of a variant in a specific tissue and highlight the clinical impact of mosaicism and heteroplasmy (Hard et al., 2023). If coupled to transcriptomics, proteomics, metabolomics, and/or epigenetics, it is possible to obtain the full landscape of consequences from a variant at the cellular and molecular levels (Sreenivasan et al., 2022; Lunke et al., 2023; Smirnov et al., 2023; Su et al., 2023). MAVEs are clarifying at once the pathogenicity of hundreds of variants of uncertain significance (Spielmann and Kircher, 2022). However, these positive impacts of the mentioned technologies are still incipient (Lunke et al., 2023), and they possess the evident risk of overloading interpretation teams with uncertain data (Lahnemann et al., 2020), increasing the requisition of unnecessary examinations and their collateral cost (Wojcik et al., 2023), and increasing negative psychological impacts on families (Zhong et al., 2021). Along with studying the diagnostic yield of novel technologies with clinical trials, it will be necessary to delineate what features should be included in clinical settings in the short term and what requires further research.

Automatization of bioinformatic pipelines is decreasing the time required to re-analyse genomic data from unsolved cases and the requirement of a dedicated workforce to perform those re-analyses, with the consequent decrease in their costs and time to diagnosis (Seo et al., 2022; Meng et al., 2023). If coupled with AI, then it is possible to add novel gene-disease associations constantly, increasing the diagnostic yield of already-obtained sequencing data (De et al., 2021). The same technology is being applied to ameliorate *in-silico* predictors, which have the advantage of adding multiple and different sources of information to give a likelihood of pathogenicity (Cheng et al., 2023). Like novel wet laboratory technologies, automatization and AI lack proven clinical utility, which should be studied (Ma et al., 2022). Also, they pose other risks in terms of ethical and legal consequences. For instance, many AI tools cannot reveal their methodology of processing the information, not just because of corporations' interests, but also because of the unexplainable way that they can achieve a result, i.e. the "black box problem" (Voosen, 2017). There are incipient initiatives to regulate this and other aspects of AI in healthcare in the European Union (Meszaros et al., 2022), but it is still premature to say if it will work or not. Furthermore, the use of multiple sources of data it may have negative consequences on the privacy of sensitive information (Meszaros et al., 2022; Yuste, 2023), which may be sold to other corporations for profit purposes (Meszaros et al., 2022; Chiruvella and Guddati, 2021), affecting, for example, insurance fees and causing discrimination (Meszaros et al., 2022; Pierson and Tsai, 2023). Therefore, professionals such as bioethicists, lawyers, and others must be included in order to study the ethical, legal, and social impacts of novel technologies.

Finally, access to the aforementioned technologies and tools is also a challenging problem to solve, not just in financial terms but also regarding the required workforce and equipment involved in their use. Healthcare systems will need evidence of their cost-effectiveness to cover the implementation of those technologies, either by public or private insurance. Otherwise, the costs will likely be transferred completely to the patients and their families, as happened with older genomic tools (Wojcik et al., 2023; Riggs et al., 2014). Also, workforces will require to be trained in the use of these tools and, more critically, in the interpretation of multiple types of data. In that sense, clinicians, bioinformaticians, and clinical scientists must be trained not just to interpret a specific result (*e.g.* a genetic variant without additional information), but they will be required to interpret that variant considering multiple other results (*e.g.* a genetic variant that may cause a specific pattern of metabolites in mass spectrometry and have effects on splicing of multiple transcripts, in a specific spatial/temporal way) (Oehler et al., 2023; Wojcik et al., 2023; Plummer and George, 2023). This may unveil the need to create novel careers and professions in the future. Lastly, although those technologies and protocols have been published, they require multiple machines to be performed and massive storage devices, which are expensive and time- and space-consuming (Oehler et al., 2023; Sreenivasan et al., 2022; Wojcik et al., 2023; Spielmann and Kircher, 2022; Plummer and George, 2023), and therefore, limit their broad access. Thus, research focused on tackling these issues will be necessary to speed up the implementation of novel laboratory technologies and meet their promise of solving cases with undiagnosed rare diseases.

4. Ongoing care and transition to therapy

Persons with a rare disease face several epochs during their life journey. There may be a pre-symptomatic phase during which expectations are set that are then lost with disease-related disability. A pre-diagnostic phase is characterized by the uncertainty of experiencing signs and symptoms for which there is no explanation. After a diagnosis is made, families search for treatment, community, information, and resources for care. Each of these eras presents challenges and research opportunities for the rare disease community (providers and affected persons). Optimal care can be framed as "P4 Medicine:" predictive, preventative, personalized, and participatory. Counseling by a complex disease specialist or genetic counselor has utility in all diagnostic phases. Before diagnosis, individuals and families may need help understanding and prioritizing recommended diagnostic procedures. Returning a diagnosis may be complicated by familial implications and the spectrum of possible diagnostic certainty. After a diagnosis, a common question is, "What does my (my child's) future look like?" The answer to this question may evolve over time as a rare disease continues to be characterized. For diseases requiring palliative care, rare diseases may raise unique issues (Adams et al., 2016).

Follow-up and care can and should be tailored to the diagnosis in close collaboration with the patient and their caregivers. To this end, care pathways (CPW) are required. Given the phenotypic heterogeneity and complexity typical for rare diseases, Tumiene and colleagues (Tumiene and Graessner, 2021) proposed a CPW should meet the following criteria (1) the intervention is a structured multidisciplinary plan of care; (2) the intervention is used to translate guidelines or evidence into local structures; (3) the intervention details steps in a course of care (i.e., the intervention has timeframes or criteria-based progression); and (4) the intervention aims to standardize care for a specific population (Lawal et al., 2016). In short, CPWs aim to have "the right person, in the right place, doing the right thing, at the right time, with

the right outcome and all with attention to the patient experience." CPWs are optimally implemented using multidisciplinary teams (MDT) and centers of excellence (CoE) (Valdez et al., 2016). These may incorporate cross-border healthcare, global collaboration, and data sharing. While excellent programs exist, they are not uniformly available globally. Integration of services on a local and global scale could be used to address significant existing disparities in healthcare access.

Increasingly, disease-modifying treatments are making their way into CPWs. Strategies vary from nutritional (medical diets, vitamin, or co-factor supplements), pharmacologic, stem cell and organ transplants, RNA and gene therapies. Therapy may stabilize, ameliorate, or reverse disease manifestations. Many rare diseases are progressive, meaning there is a window of therapeutic opportunity before irreversible damage is done; diagnostic and therapeutic delay should thus be minimized. Although definitive therapies are available for a minority of disorders, the number is increasing as new approaches are discovered and/or mature. Disease-modifying therapy is available for more than 250 inherited metabolic disorders. Identification of available treatments can be facilitated by emerging tools such as Treatable ID (Hoytema van Konijnenburg et al., 2021) and the Treatabolome Study of new therapies, which is often complicated by small numbers of geographically dispersed individuals, pre-clinical study costs, and small market economics. (Atalaia et al., 2020; Bonne, 2021). There is also a need to develop resources for related ethical frameworks and strategies for patient engagement (Ibrahim et al., 2023). Rare disease registries, novel trial methodologies, patient-reported and centric outcome measures, real-time data collection (wearables), and artificial intelligence show promise for addressing some of these issues. Ethical guidelines.

Healthcare costs for chronic disorders are often substantial and require appropriate prioritization models (Miller et al., 2020). In some geographies, families and patients are additionally burdened due to challenges of limited or absent compensation of the cost of care by insurance or discrimination based on genetic diagnoses (IAMC, 2023). This results in inequity in access to care and parental emotional stress and burden. Integrating models to develop those best suited to a location requires a collaborative conversation between stakeholders and continents to enable equitable management for patients. Economic models for rare disease therapies are in dire need of innovation based on patterns of access and cost for newer approaches (*e.g.,* gene therapy).

Family groups and advocacy organizations can be critical to the promotion of rare disease research but vary widely in terms of availability and organization. Example organizations dedicated to improved interaction with affected individuals include the Innovative Medicines Initiative (https://www.imi.europa.eu/), the European Patients' Academy (https://eupati.eu/), and its 18 EUPATI National Platforms, the Clinical Trials Transformation Initiative (https://ctti-clinicaltrials.org/), the Patient-Centered Outcomes Research Institute (PCORI, https://www.pcori.org/) National Consortium for Research and Development on Therapeutic for Rare Diseases (https://rdrdb.icmr.org.in/), FDA's Patient-Focused Drug Development (PFDD) Initiative (https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development), Cochrane, and others. Patient organizations may inform the creation of awareness, guideline development, regulatory processes, and improved understanding of specific care and living environments. Further work is needed to optimize stakeholder collaboration in a systematized manner (Boudes et al., 2018).

Networks of care centers can lower access barriers for diagnosis and treatment. An example of notable success to optimize care pathways is RarERN (Talarico et al., 2020). RarERN incorporates patient representatives, healthcare professionals including emergency medicine, healthcare organizers, and hospital policymakers. This forms a model of structured expert care within a patient-centered approach (Talarico et al., 2022). Expansion of such models to a diverse set of global settings remains a challenge for future research and policy development. An early step toward the goal of functional global networks would be the development of well-structured registries designed to follow, with adequate consent, individuals with unsolved, partially solved, and inadequately treatable rare diseases.

5. Conclusions

A review of the landscape of RD in 2023 reveals myriad opportunities for research funding. In many cases, strong examples are available to build upon. Creating systems with economic tractability and geographic equity presents formidable challenges. For the clinical practice of caring for individuals with a rare disease, funding priorities should include methods to deliver rare disease education at all levels, methods to improve access, and improved disease definitions to aid disease detection. Rare cancers present a special challenge that should be actively included in the search for new approaches. For new technologies, the rapid pace of innovation and development is creating inequities and highlighting the need for an expanded workforce. While in part a problem of economics, innovations in the structure and delivery of these tools have the potential to move costs closer to available resources. Finally, transitions from disease onset to diagnosis to care highlight the need for the development of uninterrupted care models that support individuals throughout the phases of rare illness with impact across a lifespan.

6. Clinical case vignettes

6.1. Case #1

A child is referred with multiple malformations, significant intellectual disability and autism. A singleton exome sequencing detects a variant in the *DSCAM* gene. Preliminary, limited evidence in the literature reports an association with autism. If the autism association is taken as given, a preliminary application of the American College of Medical Genetics (ACMG) guidelines yields a "likely pathogenic" categorization. The clinician, a clinical geneticist, reviews what is known about the gene and is not convinced that it explains the child's problems. A small number of loss of function variants in *DSCAM* have been described in association with autism and this variant, whilst novel, is a loss of function variant, hence the classification. The clinical geneticist meets with the mother, impresses on her the need to get DNA from both parents. They both agree. Neither parent has autism signs or symptoms. One of the parents tests positive for the presence of the variant seen in the proband. The clinician re-contacts the testing laboratory director who states that the interpretation of the report still stands. The clinician returns the result to the family, including their opinion that they do not find the diagnostic evidence compelling or a good explanation for the child's phenotype.

6.2. Lesson

The laboratory uses ACMG criteria for a gene with a tentative association with a human phenotype (it is not listed in OMIM, the literature is limited, and the association has not been evaluated through a formal process such as the ClinGen Gene Curation Expert Panel (GCEP) process. The ACMG criteria assumes an established gene-disease association. If the gene-disease association is correct, the clinician must consider whether the phenotypic differences between those described for the gene, and those observed for the patient, comprise reason to reject the result and counsel the family. This decision is complex, in part because few associated cases have been asserted in the available literature. Autism is also genetically heterogeneous, raising the possibility of alternate causation. This case illustrates the complex judgements often needed when considering a potential diagnosis.

6.3. Case #2

A child with short stature is seen by a pediatrician specializing in

growth. The *SHOX* gene is associated with familial short stature (OMIM 300582) and two skeletal dysplasias (OMIM 249700 and 127300). *SHOX* sequencing is requested. The report states "This report does not confirm a diagnosis of short stature due to *SHOX* rearrangement etc". The clinician reads this as the result being normal. They do not pick up the reference to a rearrangement within the region, which suggests that further analysis is needed to understand a potential association with the child's phenotype. In fact, a gain of genetic material has been noted in the *SHOX* region in the child and is described in technical language in the report. The recommendation is "it is important to investigate the relationship between this variant and the affected individual's diagnosis by doing segregation analysis". The clinician, a non-geneticist, is not familiar with this analysis, including the requirement for additional parental samples. The parental samples would be used to ascertain whether the even was *de novo* in the patient, which would constitute evidence supporting disease causation. In this case an additional factor is that a delay in diagnosis (if further follow up is not performed) would result in a delay in treatment and failure to take advantage of a time limited opportunity for successful treatment in this disorder.

6.4. Lesson

Genetic testing reports often use technical language for legal reasons. In addition, results may be complex, probabilistic and/or contingent on specific knowledge about associated medical conditions. In this case, use of "plain language" would have facilitated improved communication. Clinicians should also be aware of the limitations of their own knowledge base and have plans for consultation if additional expertise is required. An example here would be a recommendation to "test both parents" rather than the less clear term "segregation studies".

6.5. Case #3

A woman attends clinic to undergo predictive testing because of an inherited pathogenic variant in a breast cancer gene. Her sister is the proband. She herself, had a bone marrow transplant from an unaffected sibling for an unrelated disorder so a saliva sample is taken for analysis. The laboratory is due to proceed with testing but notes several papers alerting to the fact that blood-derived lymphocytes can be found in saliva. In this case, such lymphocytes may be derived from the transplanted bone marrow. A hair sample is subsequently tested.

6.6. Lesson

It is important to ensure if someone has had a bone marrow transplant which samples are required to avoid inadvertently testing the donor and result in a predictive test being done on the donor. Many rare disease tests have specific requirements and considerations. Optimally, testing is planned using expertise from the clinical laboratory, clinicians experienced in ordering the specific test or other sources of expertise.

6.7. Case #4

A 5-year-old child is referred for evaluation of mild developmental delay. Genetic testing detects a *de novo* copy number variant (CNV). The same CNV can be found in reference databases such as gnomAD and the Toronto Database of Genomic Variants (DGV). Strong weight is given to the *de novo* origin of the CNV and it is returned to the family as potentially related to their child's developmental challenges. The genetic testing documentation sent to the lab by the ordering provider indicates that the child was conceived by donor egg. When the parents are counselled in clinic, it becomes clear that the mother gave her own blood for CNV analysis rather than blood from the egg donor. In this case, based on the new information the assessment of the Geneticist downgrades the CNV to benign and gets the report re-issued as it is likely this is an inherited benign CNV.

6.8. Lesson

Donor egg or sperm pregnancies are becoming more prevalent and are likely to continue to do so given the expansion of genetic testing in general. In practice, it is rarely possible to access DNA samples from donors. One cannot assume a parent will volunteer the nature of the conception especially after years have passed. The nature of the conception will get lost over time and may lead to mis-diagnosis.

6.9. Case #5

A couple have a baby who is deceased at birth and found to have multiple malformations on examination. A diagnostic DNA array is requested by the pathologist. A small CNV of ~700 kb is found within a region known to be associated with a microdeletion syndrome. The genetic report is transcribed into the post mortem report, including the name of the microdeletion syndrome. Parental DNA testing is ordered, but the previous genetic testing results are not included. The laboratory performs chromosomal fluorescence in situ hybridization (FISH) testing and reports both parents results as normal (no deletion). However, the test results turn out to be false negatives as the probes used in the FISH analysis were not designed for a microdeletion matching the small size and position of the genomic lesion found in the proband. The couple have another baby with similar multiple malformations. An array reveals the same small deletion on array. The parents are tested by array and one of them carries the small deletion.

6.10. Lesson

Inadequate provision of information to testing laboratories can result false positives, false negatives, and incorrect interpretations. In this case, the ordering clinician should have included the original test results and if not, the testing laboratory should have requested a copy of the original test results to confirm design of the follow up FISH testing. Also, reports can be cited, but not be transcribed word for word. In rare disease diagnosis, the lack of interoperable medical record systems was not in place to mitigate human error.

6.11. Case #6

An adult patient presented for clinical evaluation and described an extensive history of abdominal pains, with diarrhoea and intermittent vomiting. He further related that his internet research suggested that theses symptoms might be related to peri-umbilical skin lesions also present on the buttocks and thighs. More than 10 years before, he underwent a kidney biopsy because of proteinuria, revealing "nonspecific' foamy kidney cells, and was lost of follow-up. The patient suggested a diagnosis of Fabry disease. This self-diagnosis turned out to be correct, being confirmed by genetic and enzyme studies. The genetic diagnostic was also confirmed in two young daughters (personal experience of GP-M).

6.12. Lesson

Persons with rare disease have increasing access to legitimate medical data and may have critical insights into the cause of their illness.

CRediT authorship contribution statement

David R. Adams: Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing. **Clara D.M. van Karnebeek:** Writing – original draft, Writing – review & editing. **Sergi Beltran Agulló:** Writing – original draft, Writing – review & editing. **Víctor Faùndes:** Writing – original draft, Writing – review & editing. **Saumya Shekhar Jamuar:** Writing – original draft, Writing – review & editing. **Sally Ann Lynch:** Writing – original draft, Writing – review &

editing. **Guillem Pintos-Morell:** Writing – original draft, Writing – review & editing. **Ratna Dua Puri:** Writing – original draft, Writing – review & editing. **Ruty Shai:** Writing – original draft, Writing – review & editing. **Charles A. Steward:** Writing – original draft, Writing – review & editing. **Biruté Tumiene:** Writing – original draft, Writing – review & editing. **Alain Verloes:** Writing – original draft, Writing – review & editing.

Data availability

No data was used for the research described in the article.

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