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Human Genomics

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Translating multi-omics into healthcare: requisites for scalable and equitable implementation

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Abstract

Multi-omics in combination with advanced computational methodologies synthesizes diverse omics data to provide deeper insights into molecular interactions and offers transformative potential for unravelling phenomenon behind disease complexities, improving diagnostics, disease prevention, and personalized treatments. This integrative strategy enables our understanding of gene-environment relationships, chronic disease progression, and the intricate molecular pathways involved in health. Effective multi-omics analyses require robust data sharing, accessibility, interoperability, and governance, which are critical for linking genomic elements to phenotypic traits. The Global Alliance for Genomics and Health advocates for responsible data-sharing practices, by promoting key principles such as transparency and equity. By emphasizing a collaborative approach to data utilization, our proposed framework seeks to advance improved disease prevention and treatment strategies. Multi-disciplinary collaboration, encompassing researchers, clinicians, policy makers, and patient representatives, is pivotal for driving innovation and addressing rare disease diagnostics. The success of multi-omics applications hinges on the establishment of comprehensive datasets, understanding the functional implications of multi-omic variation, adherence to findable, accessible, interoperable, reusable (FAIR) and Collective Benefit, Authority to Control, Responsibility, and Ethics (CARE) principles, and the strengthening of global genomic commons, benefiting scientific research, drug development, and broader health initiatives. Our review highlights essential components of multi-omics integration, underscoring its potential to transform the landscape of precision medicine and improved patient outcomes worldwide.

Keywords Omics, Health data, Multi modal data, Rare diseases, Health equity

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Introduction

Omics techniques provide thorough evaluations of various biological molecules, including RNA and metabolites. These methods have transformed modern medicine by enhancing our knowledge of the functional implications of molecular intricacies involved in health and disease. Recent advancements in various omics technologies, including proteomics and metabolomics, alongside improved computing capabilities, have facilitated a new approach known as multi-omics. This approach synergistically combines different types of omics data, allowing for a deeper understanding of the intricate molecular interactions involved in health and disease. The resources, methods, and technologies can be effectively utilized, and the existing challenges of integrating multiomics analyses into practice can be addressed by involving proper management and sharing of data, collaboration among multiple stakeholders, the establishment and ongoing enhancement of standards, as well as the empowerment, education, and motivation of individuals. It is imperative to ensure equity, inclusion, and accessibility.

The exposome is a comprehensive framework that includes all physical, chemical, biological, and psychosocial factors, as well as their interactions, that influence biology and health [1]. It encompasses all environmental exposures throughout an individual's life, from preconception to death, that may affect health and disease outcomes. This concept also addresses multigenerational and transgenerational exposures, wherein environmental factors experienced by parents or grandparents may affect the health of future generations through mechanisms such as modifications in epigenetics, changes in maternal physiology, or heritable transmission of effects caused by environmental factors [2, 3].

Human disease development, progression, and various biological processes are due to a complex and rigorous interplay of molecular corrugations involving elements such as proteins, epigenetics, genetics, mRNA, etc., swayed by different environmental agents. Elements such as the human genome, epigenome, exposome, metabolome, transcriptome, and proteome can be measured at the individual level, facilitated by the advancement of technology; however, their interrelationship can be established by multi-omics data-driven studies. Gene-environment relations, molecular processes, and chronic disease progression can be better deciphered by assimilating multi-omics measurements into analyses. This integrative approach can enhance disease pathophysiology understanding in greater detail and unravel better strategies for prevention and precise treatment. Our review aims to extrapolate key building blocks of this approach.

Data sharing and management: sine qua non condition for today and tomorrow

The success of contemporary big data science depends on early and open sharing of scientific research, often beginning at the project's inception, leveraging extensive comprehensive datasets. To meet growing demands, it is essential to identify all functional genomic elements, along with their natural and pathological variations. These elements must be reliably linked to phenotypic traits to better understand biological processes and disease mechanisms, inform drug development, and address various health challenges. Research on the exposome builds upon genomic studies. Decoding the human genome has significantly enhanced our understanding of disease mechanisms. However, it is important to recognize that the genome represents just one aspect of the overall disease burden experienced by the population [4, 5].

Achieving this will require the sharing and enrichment of a diverse array of data, including individual genotype and phenotype information, at an exponentially larger scale (Fig. 1).

Data sharing principles and exchange platforms

The Global Alliance for Global Health (GA4GH) establishes principles and tools to support data sharing implementation. The GA4GH published the Framework for Responsible Sharing of Genomic and Health-Related Data in 2014, targeting regulators, funders, patient groups, IT professionals, industry representatives, publishers, and research consortia. This framework delineates the essential elements of responsible data sharing, which include transparency, accountability, recognition, attribution, and sanctions for misuse [6].

The eight Work Streams of GA4GH focus on developing policies and tools related to various issues such as ethical governance, consent, privacy, and security. The framework, translated into 14 languages, has shaped data-sharing policies globally [7]. Key functions of proper data governance encompass enabling data access, ensuring compliance with national laws and international agreements, supporting appropriate data usage and minimizing potential harms, promoting equity, and utilizing data for public benefit [8]. Proper governance is enhanced by the FAIR principles established in 2016 [9], which aim to make data Findable, Accessible, Interoperable, and Reusable for both humans and machines. These resources are often created by leading global scientific organizations and are supported by experts, including databases like OMIM, gnomAD, and PDB. Genomic commons—global repositories of accessible genomic data, including functional genomic elements and phenotypes [10]. Crowdsourcing platforms such as ClinVar, ClinGen, DECIPHER, and MatchMaker are

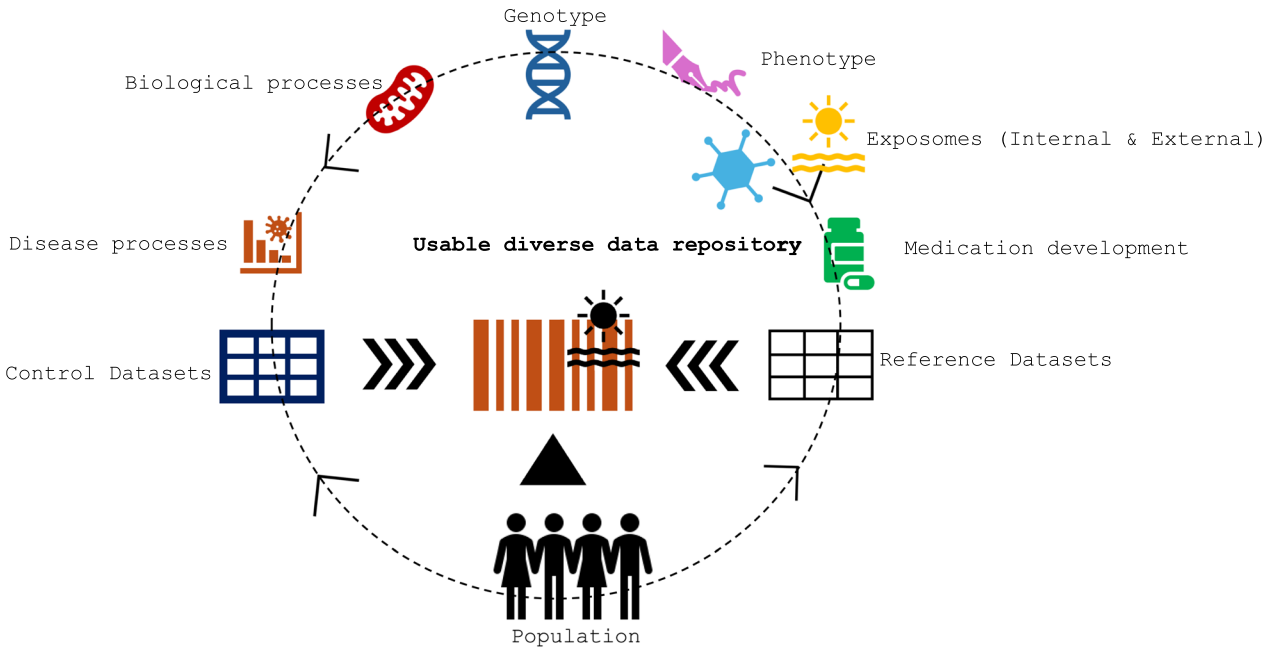

Fig. 1 Big data science success depends on leveraging extensive and comprehensive datasets as massive quantities of data are generated every second in both scientific and clinical contexts, accumulating in ever-expanding databases. To establish reference standards and control datasets that meet current demands, all functional elements of the genome along with their natural and pathological variations need to be identified and correlated these elements and their variants with phenotypic expressions, explore biological processes and disease mechanisms, develop effective medications, and tackle numerous other critical issues

democratizing data collection. DECIPHER—facilitates the sharing of diagnostic variants and phenotypic data from over 44,000 patients (as of 2023) [11].

In 2015, the MatchMaker Exchange (MME) was launched to unite eight existing platforms into a global resource that greatly enhances search efficiency. By 2022, the platform had recorded queries for over 13,520 genes and involved more than 12,000 medical professionals and scientists from 98 countries, resulting in over 120,000 case submissions. This initiative has enabled the identification of novel genetic disease genes and improved the diagnostic processes for patients with undiagnosed conditions [12]. Launched in 2013 by the National Human Genome Research Institute, the Clinical Genome Resource (ClinGen) is a collaborative effort with over 2,300 contributors from more than 67 countries (https://www.clinicalgenome.org/) [13].

Data accessibility

Data accessibility refers to the ease with which users can retrieve and obtain data without facing unnecessary obstacles. The General Data Protection Regulation (GDPR), which came into effect in 2018, particularly influences data sharing within the European Union (EU) and between the EU and other countries. While intended to harmonize data protection laws across the EU, the application of these regulations, especially concerning healthcare and research data, still brings about considerable uncertainty [8]. Investigations into the GDPR's implementation have revealed that consent requirements, research exemptions, and the permissibility of international data transfers are interpreted differently by various institutions and countries [14]. For Europe to create a common European Health Data Space (EHDS) and actively engage in data-sharing-based science on a global level, it's crucial to establish clear legal frameworks and appropriate governance measures to ensure data interoperability [15]. Various initiatives are being developed to safeguard data in the context of worldwide sharing. Protecting privacy and security entails maintaining control over data, which has led to a decreased reliance on centralized data pooling. Instead, data can be stored in the cloud alongside the necessary methods, workflows, and computing resources, facilitating secure international access and large-scale analyses [15]. A growing trend is the federated approach, where independent organizations host data in secure, separate processing environments while implementing technical measures for large-scale sharing and analysis [16]. Application Programming Interfaces (APIs) allow researchers to access databases, even when different computing environments are in play [16]. Data accessibility can be further improved through the use of "beacons," which enable users to check the existence of specific genetic variants across multiple datasets and contact the relevant dataset controllers upon confirmation [17]. The GA4GH

is also developing shared data protection standards, such as the Data Use Ontology (DUO), which provides a clear, machine-readable standard language for consent forms and data sharing policies [18]. Additionally, the GA4GH Passport is being used to define user permissions for data access [19].

No datasets were generated or analysed during the current study.

Data accessibility is significantly improved through the integration of various databases and tools, which facilitate effective navigation of complex data environments, as exemplified by MARRVEL [20]. The growing trend of applying systematic methodologies to explore intricate biological phenomena necessitates the collaboration of diverse specialties and the amalgamation of various datasets. This trend underscores the increasing importance of consolidating different knowledge bases and databases into cohesive platforms that allow for a comprehensive examination of biological questions or processes from multiple perspectives.

Data interoperability

Data interoperability bolsters the effectiveness and integration of information across diverse systems and platforms. This endeavor is complex and involves the implementation of standardized, machine-readable data formats and protocols, controlled vocabularies, ontologies, and metadata schemas. Notable examples of widely adopted ontologies include the Human Phenotype Ontology (HPO) [21], Orphanet Rare Disease Ontology (ORDO; https://www.orpha.net/), OMIM Ontology [22], and Gene Ontology (GO) [23]. Additionally, new ontologies are being developed, such as the Medical Action Ontology (MAxO), which is specifically designed to systematically organize medical procedures, therapies, and interventions, in close relation to the Mondo Disease Ontology (Mondo) and the Human Phenotype Ontology (HPO) [24].

The FAIR principles have become a widely accepted standard for data management across various institutions and organizations, both nationally and internationally. A notable example is the Canadian Distributed Infrastructure for Genomics (CanDIG) platform, which facilitates federated querying and analysis of human genomics and linked biomedical data across ten Canadian provinces [25]. Similarly, the FAIR Genomes project in the Netherlands connects 14 medical centers and institutes, developing a shared semantic schema for essential data elements. This initiative has enabled the sharing of over 168,000 variant classifications, significantly enhancing variant interpretation [26]. For fairness and respect, it is essential to embrace both FAIR and CARE principles. Concerns from Indigenous peoples about secondary data use and limited benefit-sharing opportunities underscore the tension between safeguarding Indigenous rights and supporting open data and big data initiatives. To address this, the International Indigenous Data Sovereignty Interest Group of the Research Data Alliance has developed the CARE Principles for Indigenous Data Governance (Collective Benefit, Authority to Control, Responsibility, and Ethics) in collaboration with Indigenous communities, scholars, non-profits, and governments [27]. These CARE Principles are focused on people and purpose, highlighting the significant role of data in advancing innovation, governance, and self-determination for Indigenous Peoples. They complement the existing data-centric FAIR principles, with the concepts of data FAIRification and CAREification being essential for enhancing efficiency, equity, and impact [28].

Standards and continuous cycles of quality improvement

Standards play a vital role in ensuring the accuracy and reliability of measurements, the reproducibility and credibility of methods, and the broader adoption of technologies. The creation of standards becomes necessary once sufficient data from a new method has been accumulated, enabling the identification of specific patterns. The International Rare Diseases Research Consortium (IRDiRC) has developed a quality label called "IRDiRC Recognized Resources" to highlight the standards, guidelines, tools, and platforms that should be utilized by those working in the rare disease research community [29]. In 2015, the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) published guidelines that have been adopted globally for interpreting germline sequence variations. These guidelines recognized functional annotation as evidence of pathogenicity or benignity (PS3/BS3); however, the guidelines at that time were somewhat general concerning the application of functional criteria [30]. In 2019, ClinGen assessed the use of functional studies for six diseases, identifying several challenges and the need for clearer guidance to standardize the approach and ensure consistency in applying functional evidence [31]. The ClinGen Sequence Variant Interpretation (SVI) Working Group released recommendations in 2020, which included refined rules for assessing the clinical validity of functional data. These recommendations provide a four-step provisional framework to evaluate the strength of evidence from functional assays, covering aspects such as experimental design, replication, controls, and validation using human data [32]. ClinGen's Gene Curation Expert Panels conduct systematic evaluations and curate annotations of variants in clinically relevant genes, including assessments based on specialized functional assays [33]. The systematic integration of information from functional studies into public resources like the ClinVar

database would greatly enhance global efforts in variant assessment.

In addition, other standards play a crucial role in accurately assessing gene-disease associations and variant pathogenicity, resolving VUS, and identifying functional genomic elements [34]. This includes developing standards for various types of genetic variants and reanalyzing genomic testing results. As omics studies become more prevalent, recent recommendations have emerged to capture evidence regarding the predicted and observed impacts on splicing, including data from RNA-seq studies [35]. The Genomics Research to Elucidate the Genetics of Rare Diseases (GREGoR) Consortium has created criteria for triaging, sharing, and reporting novel candidate genes in clinical settings [36].

Environmental factors play a crucial role in shaping health outcomes, and their influence can differ significantly based on the specific condition being examined. In many cases, these factors can be as impactful as, or even more significant than, genetic influences. Understanding this relationship can lead to more effective health interventions and improvements in public health. Research shows that environmental factors are responsible for about 70–90% of the risk associated with chronic diseases such as cardiovascular disease and certain types of cancer. In contrast, a much smaller percentage is linked to inherited genetic variation. Therefore, it is crucial to evaluate the relative contributions of both environmental and genetic risk factors to model diseases and develop effective prevention strategies [37–40]

Communities brought together for common purposes: multi-stakeholder collaboration

The projects and initiatives outlined here span multiple biological fields and specialties, engaging diverse communities of stakeholders. The research conducted by these collaborative groups is crucial for uncovering the intricate biological makeup of humans in both health and disease. For current clinical practices, multi-stakeholder collaboration is vital to address complex diagnostic challenges and accommodate the diverse needs of people living with rare diseases (PLWRD).

In the United States, the Undiagnosed Disease Network (UDN) connects clinical centers with a Model Organism Screening Center (MOSC) to explore candidate genes and variants functionally. In Canada, the Rare Diseases Models and Mechanisms (RDMM) Network fosters collaborations between model organism researchers—represented by a registry of over 500 Canadian scientists with expertise in more than 7,500 human genes—and clinicians who have identified new disease gene variants. These partnerships not only validate variant pathogenicity but also elucidate the molecular mechanisms underpinning rare diseases (RD) and test new therapies. Following this model, similar networks have emerged in Europe (Solve-RD—http://solve-rd.eu/rdmm-europe/), Australia (https://www.functionalgenomics.org.au/), Japan (https://j-rdmm.org/indexEn.html) and Singapore (Rare Disease Models and Mechanisms Network). Communication and collaboration have emerged as critical success factors across these initiatives. On a global level, collaborations between researchers and clinicians have been facilitated by ModelMatcher, which is part of the Matchmaker Exchange platform (https://www.modelmatcher.net), helping users identify potential partners. Additionally, the smooth integration of healthcare and research is supported by initiatives like NHS England's implementation of layered consent procedures within routine medical practice [7].

Exposomics is a field that utilizes high-throughput methodologies and employs a data-driven approach rather than a hypothesis-driven one. It integrates information from various methodologies and across different time points to thoroughly assess the impact of the exposome on health. This comprehensive analysis helps in evaluating risk and estimating the burden of environmental diseases. Additionally, exposomics seeks to uncover the cellular and molecular changes induced by the exposome, which can serve as potential biomarkers for diagnosis and create new opportunities for treatment [41].

The fundamental problems and solutions at the levels of all stakeholders is enumerated in Fig. 2.

Unfortunately, all too many RDs still suffer from a lack of foundational knowledge regarding their mechanisms, biomarker identification, and treatment development. Furthermore, the human genome and proteome contain many poorly studied or entirely uncharted areas. Currently, only 3% of the human proteome aligns with known drug targets linked through established mechanisms of action; an additional 6% bind to small molecules without such links. Meanwhile, 53% of proteins are connected to Mendelian diseases but lack further information necessary for clinical applications, and 38% are "dark" proteins, either minimally or not at all studied [42]. These categories include numerous potentially "druggable" proteins whose therapeutic prospects remain unexplored. Despite the surge of data from high-throughput omics studies and the rise of sophisticated computational resources, disparities in genome and proteome research, as well as functional annotation, continue and may even be worsening. Proteins that are well-researched are accumulating even more data, whereas others are experiencing stagnation in knowledge advancement. For instance, the widely studied p53 protein is featured in an average of two publications daily, while 95% of life science literature focuses on just 5,000 well-characterized human proteins [43]. Several factors contribute to the reluctance to

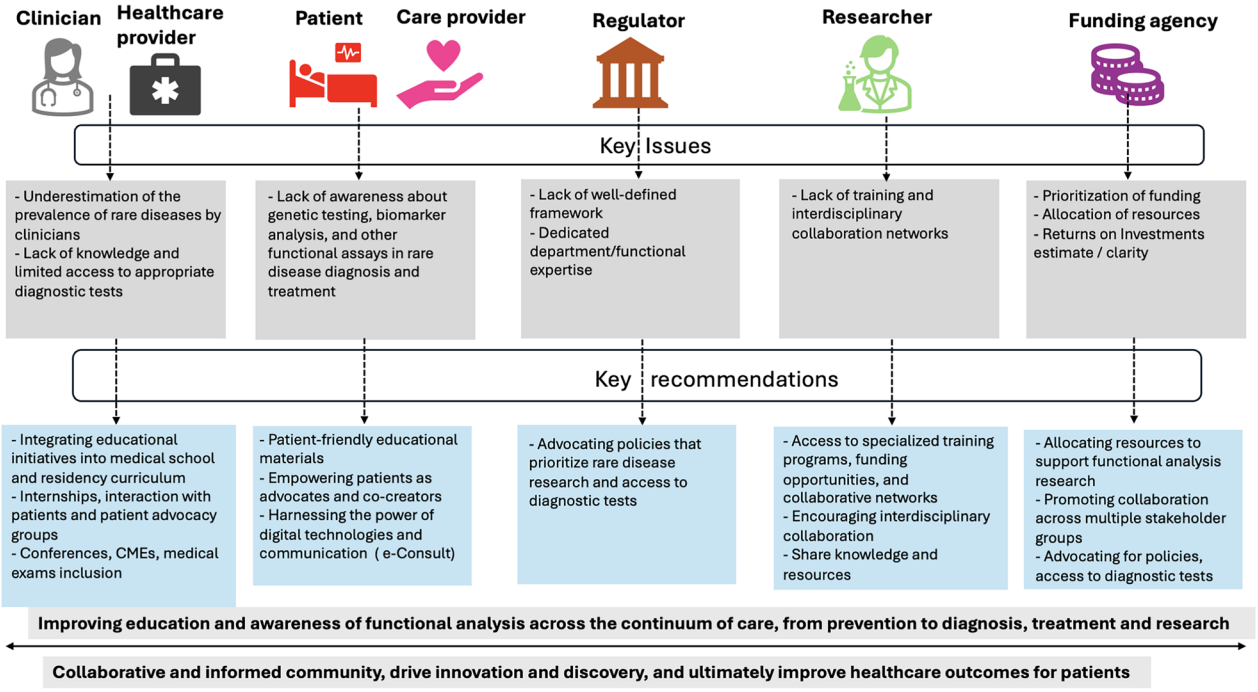

Fig. 2 Improving education and awareness of functional analysis across the continuum of care, from prevention to diagnosis, treatment and research including all relevant stakeholders (clinicians and healthcare providers, patients and caregivers, researchers, regulators and policy makers, funding agencies) is essential for addressing the challenges associated with RDs

explore these under-researched areas, including a lack of motivation driven by funding and prioritization norms, a tendency toward risk-averse, hypothesis-driven studies, career pressures for swift results, and misconceptions about the importance of frequently studied proteins. Other issues include inadequate promotion and awareness of understudied proteins, difficulties in accessing research tools and samples, and an over-reliance on standardized lab conditions that, while ensuring reproducibility, may impede innovation [44]. The vast potential of negative data remains largely untapped, despite attempts to shift traditional funding, prioritization, and publication practices. It typically takes 12 to 20 years for a human protein to garner enough information for clinical application. Breaking this cyclical pattern requires a collaborative approach among stakeholders, including targeted funding, training initiatives, incentives, and a unified effort to address research inequalities and bridge existing gaps [45].

Existing frameworks for data sharing

National plans and strategies are essential for fostering collaboration among multiple stakeholders and establishing shared responsibilities and accountability in the integration of genomic technologies into routine clinical practice. Numerous countries worldwide, including all EU nations except Malta and Sweden, as well as the UK, Switzerland, India, the Philippines, Japan, Australia, Canada, Brazil, Chile, and South Africa, have implemented national RD plans [46, 47]. Although some of these have expired, they generally address key issues such as RD codification, registries, diagnostics and screening, orphan drug access, research, and patient support and empowerment. However, there is significant variability in the effectiveness of these plans; some lack multi-stakeholder collaboration, financial support mechanisms, or effective implementation. On the other hand, genomic medicine plans are more recent developments. The Global Genomic Medicine Collaborative (G2MC) was introduced in 2016 to drive the adoption of genomic medicine in clinical settings. Between 2017 and 2020, G2MC assessed 65 genomic medicine initiatives globally and found that the full integration of genomic medicine into standard health services remains relatively limited, with many projects primarily serving as pilot studies exploring implementation options. Most of these strategies emphasize genomic sequencing, data management, workforce training, ethical and social concerns, and raising public awareness [48]. Insights from the National Human Genome Research Institute's (NHGRI) Implementing GeNomics In pracTicE (IGNITE) Network study indicated that key factors driving implementation included genomic clinical decision support tools within the electronic health record (EHR) and third-party reimbursement for genomic testing [49]. IRDIRC Functional

Analyses task force recommends the collaboration framework as outlined in Fig. 3.

In Europe, several prominent institutions and collaborative projects are dedicated to advancing our understanding of the exposome and its impact on health. Notable entities include Helmholtz Munich [50] and initiatives such as the Enhanced Exposure Assessment and Omic Profiling for High-Priority Environmental Exposures in Europe (EXPOsOMICS) [51] and the European Human Exposome Network (EHEN) [52]. The HERCULES Exposome Research Center [53] and the Institute for Exposomic Research at Mount Sinai [54] in the United States are contributing exposome research significantly. Exposomics is advancing rapidly due to significant technological developments in genetic and omics technologies, along with big data analytics [55]. The exposome influences various omics layers and is crucial in understanding disease etiology [56].

Exposomics focuses on measuring environmental exposures and their biological responses. The approach employs a diverse range of tools and methodologies, including omics technologies, sensors, mobile devices and applications, geospatial devices, and self-reported questionnaire responses, which are aptly facilitated by statistical and bioinformatics tools. This combination enables comprehensive data collection and analysis, enhancing our understanding of complex biological systems and their interactions in various environments [57].

Empowered, educated and motivated people—the main driver forward

Education and training serve as vital instruments for empowering multi-stakeholder communities within the functional genomics ecosystem. This ecosystem encompasses a range of participants, including researchers, healthcare providers, allied professionals, funders, regulators, and patient representatives. The educational needs of these groups are diverse, requiring content that spans from basic information to highly specialized knowledge, and formats that range from traditional lectures and Massive Open Online Course (MOOCs) to hands-on training and mentoring programs. It is essential for all medical and specialty students, as well as the current healthcare workforce, to receive education in RDs and genomics. Professional organizations play a crucial role in establishing practice standards and educational goals, as well as providing ongoing professional training and medical education. It is essential that these organizations acknowledge the significance of RD and genomics education, integrating these topics into their agendas [58]. To enhance the diagnosis of RDs, all healthcare providers must be able to identify potential signs—known as red flags—that necessitate referrals for specialized genetic diagnosis. Translating these red flags into various languages, including Indigenous languages like those developed by Lyfe Languages ((https://www.lyfelanguages.com), is critical for promoting equity and inclusion. For individuals involved in genetic diagnostic services,

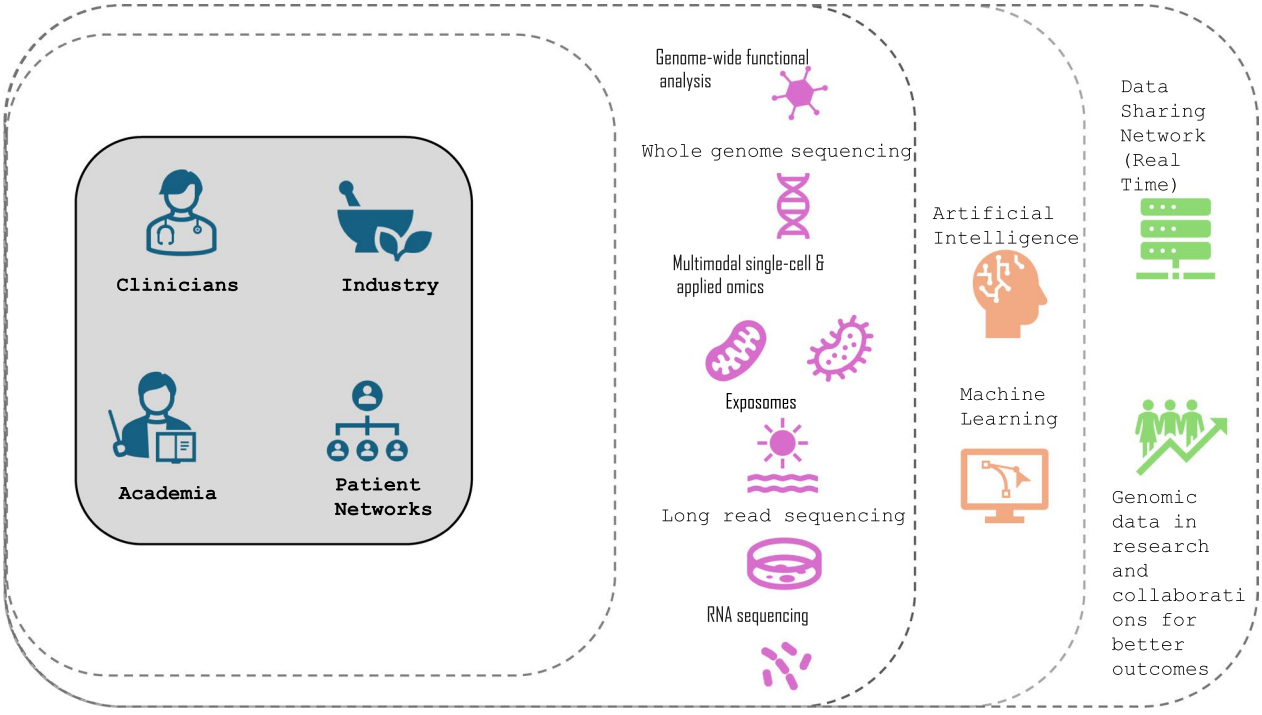

Fig. 3 Best practices collaboration model recommendation by IRDIRC Functional Analyses task force for global adaptation

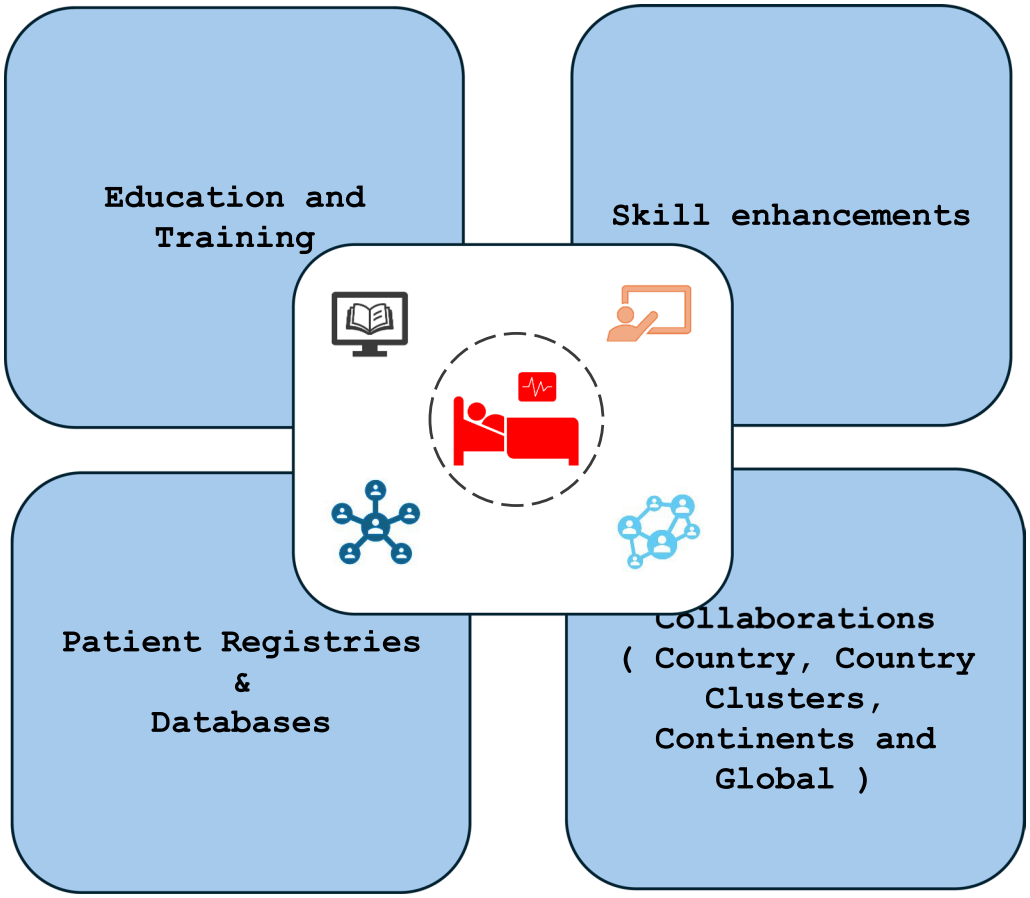

Fig. 4 With patient as the core of all initiatives towards skill enhancement for healthcare professionals it is essential that an integrated approach towards education and training with patient registries and data networks coupled with collaborative efforts built at grassroots, country and international level could be gamechanger for all stakeholders

understanding the principles of genomic variant analysis and interpretation, genetic counselling, and the associated ethical and legal challenges is paramount [59].

Key sources of this knowledge and training include European Reference Networks [60], international initiatives, infrastructures, and programs like the European Joint Programme on Rare Diseases (https://www.ejprarediseases.org/), ELIXIR [61], and the Global Nursing Network for Rare Diseases (https://www.gnnrd.org/), along with other global organizations [62]. Training is typically created by international experts and offered to a worldwide audience, highlighting the significance of online training formats that enhance access to specialized knowledge. The global interest in these webinars organized by European Reference Networks [63] underscores the importance of such educational opportunities. Care coordinators and case managers can improve access to RD diagnostics while bioinformatics and computational science specialists have become crucial members of genomic diagnostics teams. Additionally, data stewards and data managers play a vital role in ensuring the proper management and FAIRification of data. To tackle the complexities of emerging fields like functional genomics, knowledge in systems biology is increasingly being offered through master's programs. It is crucial to establish training objectives for these new fields, develop corresponding programs, and implement them in universities and educational institutions (Fig. 4) with active collaborations.

For years, successful training programs have been conducted by international patient organizations, including EURORDIS Open Academy, EUPATI, NORD, GARD, and NCATS [64]. These programs often include both patient representatives and researchers, which helps to promote mutual understanding and collaboration. However, it is crucial that training initiatives are also disseminated at the national level, ensuring they reach patient representatives through appropriate formats, such as simplified and visual resources, while accounting for multicultural, linguistic, and ethnic differences [65]. To promote equity and inclusivity for underrepresented populations, educational resources should be tailored to resonate with specific communities. For example, the Aboriginal Australian concept of songlines and their

singers has been used effectively to explain inheritance concepts and their relation to health. Cross-cultural narratives, like basket weaving, could also serve as useful avenues for conveying complex ideas related to genomic or functional analysis (https://www.lyfelanguages.com/). Furthermore, the Lyfe Languages initiative, a universal Indigenous medical translator project, is paving the way for technological solutions that include translations and educational resources for both clinicians and patients.

Exposome-wide association studies (ExWAS) are a data-driven logical architecture designed for large-scale exploratory studies in exposomics, applicable across various study designs, including cohort, cross-sectional, longitudinal, and case–control studies. The approach emphasizes interpretability and can utilize a range of methods grounded in regression and other statistical techniques. The core objective of ExWAS is to systematically reproduce all paired relationships between a single phenotype and numerous exposures, aiming to identify statistically significant associations while accounting for multiple analogies [66]. For instance, ExWAS has been deployed to investigate the association of 266 environmental factors with type 2 diabetes, revealing both risk factors (such as heptachlor epoxide) and protective factors (such as β-carotenes) [67].

Empowering patients effectively goes beyond offering training in leadership, advocacy, and general knowledge. It also encompasses education on all critical aspects of research and the application of innovations. This includes integrating patients into joint scientific projects, especially those addressing socioeconomic and clinical issues, as well as supporting RD research through non-governmental organizations and foundations. Patient advocacy groups play a pivotal role in this process, serving as bridges between researchers, clinicians, and the patient community, and ensuring that research agendas align with patients' real-world needs. Additionally, patient representatives are encouraged to take part in the translation of innovations, contributing to bioethical and regulatory committees, such as those at the European Medicines Agency, and participating in healthcare organization decisions, like those in hospital boards or national oversight committees for RDs.

Equity, diversity and inclusion

The opportunities available for PLWRD as well as for healthcare providers and researchers working in the field, are neither equal nor fair. A variety of factors contribute to these inequities, including financial constraints, cultural differences, language barriers, workforce shortages, stigma, and more [68]. Millions of individuals around the world suffer from undiagnosed RDs, not due to a lack of diagnostic technology, but because of the limited availability of modern and effective (genomic) diagnostic methods [69] and insufficient resources hindering the capacity to exchange crucial genomic and clinical data [7]. Additionally, public genomic databases like gnomAD are often unrepresentative of many populations, particularly those from African, Middle Eastern, and Oceanian communities, resulting in patients having rarer VUSs [70]. Although individuals of European descent account for around 16% of the global population, most of the genomic research originates from people of European ancestry [71]. This lack of representation exacerbates diagnostic uncertainty and delays access to appropriate treatments, particularly for historically marginalized populations. Fortunately, this gap can be partially addressed through unbiased high-throughput methods such as MAVE [72] and computational resources like AlphaFold [73], which offer functionally relevant information beneficial to communities worldwide. Genomic research in high-income countries often fails to adequately include participants from underrepresented communities, including rural populations and those from culturally and linguistically diverse backgrounds, unless specific steps toward inclusivity are taken [74]. Intentional efforts must be made to improve recruitment, community engagement, and culturally adapted informed consent processes to ensure that diverse populations are equitably represented in research. Initiatives aimed at enhancing representation include the Australian Indigenous Genomics Network (ALIGN), which features a Rare Diseases Flagship and focuses on functional analysis, as well as Australian Genomics projects that actively involve Aboriginal and Torres Strait Islander populations [75]. gnomAD has also made calls to increase genetic diversity in population-scale datasets [76]. Open-source tools provided by global genomic databases, such as the DECIPHER system, assist in data sharing and collaboration, with platforms like DDD-Africa (https://h3africa.org/index.php/ddd-africa) utilizing these resources [11].

Collaboration among resource-limited countries and global partnerships is crucial. While individual African or low-income Asian nations may lack national genomic medicine programs, multinational initiatives like the Human Heredity and Health in Africa (H3Africa) consortium (https://h3africa.org/) and the GenomeAsia 100 K consortium (https://genomeasia100k.org) promote the advancement of genomic medicine [48]. The H3Africa initiative aims to encourage research relevant to African contexts while building capacity for genomic research. It focuses on collecting and processing genomic and clinical data associated with various non-communicable and infectious diseases, creating high-quality biorepositories, and developing a bioinformatics network while offering training programs for healthcare professionals and researchers [77]. Another global partnership, the International Centre for Genomic Medicine in Neuromuscular

Diseases (ICGNMD) initiated to enhance the diagnosis of hereditary neuromuscular diseases, is a network of 18 centers across Brazil, India, South Africa, Turkey, Zambia, the Netherlands, and the UK. This centre collaborated to develop a cloud-based data solution, trained 17 international neurology fellows in clinical genomic data interpretation, and provided genomic diagnostics to thousands of NMD patients from understudied populations [78]. The Undiagnosed Diseases Network International connects centers worldwide to improve the diagnosis of RDs [79] and comprises active functional analysis and low- and middle-income country working groups. The GA4GH has established global standards for genomic equity, diversity, and inclusion, forming specialized groups focused on equity, diversity, and regulatory and ethical considerations [71].

Translational science related to exposomics can provide valuable insights for shaping public health policies and discourse aimed at reducing population-level risks and guiding essential regulatory actions. [80] Exposomics focuses on identifying environmental risks that impact specific population groups, allowing policymakers to concentrate with meaningful interventions on high-risk groups or areas [81]. This approach facilitates the development and implementation of focused regulations that take into consideration various factors influencing health risks [81]. Data derived from exposome studies can influence policies related to chemical exposure [82], air quality [51], and workplace safety [83]. Even though individuals with the same syndromic form of intellectual developmental disability (IDD) share the same genetic background, there is significant variability in their cognitive abilities and IQ scores. Research suggests that almost 80% of the differences in IQ among those with syndromic IDDs can be linked to non-genetic factors such as exposomes [84].

Conclusion

To successfully integrate functional multi-omics analyses into routine healthcare, it is imperative to focus on several key areas: establishing robust data sharing and management practices, adhering to standards with continuous improvements, fostering collaboration among various stakeholders, and empowering individuals through education and motivation. By ensuring data accessibility, interoperability, and reusability, along with the formation of international partnerships and the implementation of equitable, inclusive measures, we can maximize the potential of multi-omics technologies to enhance diagnostics and patient care for PLWRD. These efforts will contribute to the creation of a more efficient and comprehensive healthcare system that leverages the latest genomic advancements to address complex medical challenges and leverage precision medicine.

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Author contributions
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Declarations

Ethics approval and consent to participate
This review does not contain any studies with human subjects performed by any of the authors.

Competing interests
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