DIAGNOSTIC RESEARCH NEEDS RECOMMENDATIONS

RARE DISEASE MOONSHOT

This paper provides recommendations to funders, researchers, patients, industry, and other stakeholders on where public-private partnerships (PPPs) would bring most value in optimising diagnostic research in rare diseases and points to consider when setting up such collaborations.

Introduction

While rare diseases have an inherently low point prevalence within populations, recent estimates indicate that 26 million people in the EU could be affected by a rare disease during their lifetime[1], and these diseases thus collectively constitute a significant healthcare problem[2]. The clinical manifestations and underlying causes of different rare diseases vary widely and due to their individual low prevalence, there is often a lack of knowledge and a scarcity of expertise to diagnose and treat them as well as a lack of integrated multi-disciplinary teams which would allow a full pathway to diagnosis and treatment. Despite significant advances in exome and genome sequencing that facilitated rare disease diagnosis over the last decade, the overall diagnostic rates remain below 50%[3]. Furthermore, the reported average time for accurate diagnosis of a rare disease in 2022 is still about 4–5 years and in some cases, it can take over a decade, with many patients going through long "diagnostic odysseys"[4]. During this journey, patients are often subjected to unnecessary tests and procedures or ineffective treatments due to no diagnosis and/or misdiagnosis, while the accompanying uncertainty can cause an added burden of psychological distress for them and their families and carers. In addition, most rare diseases are chronic and progress over time, so that delayed diagnosis may lead to irreversible damage as the condition progresses or may move patients out of a treatment window altogether. The current paper outlines key challenges and recommendations on where public and private sectors could pool efforts to address diagnostic research needs to implement changes that no stakeholders' group can achieve alone.

1 1 in 17 people in the EU has a rare disease (based on an estimated 26 million patients with rare diseases out of a population of 447 million in the EU. Source: EUROSTAT 2022) - https://www.ema.europa.eu/en/documents/leaflet/leaflet-orphan-medicines-eu_en.pdf

2 Tisdale, A., Cutillo, C.M., Nathan, R. et al. The IDeaS initiative: pilot study to assess the impact of rare diseases on patients and healthcare systems. Orphanet J Rare Dis 16, 429 (2021). https://doi.org/10.1186/s13023-021-02061-3 and https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf

3 Hartin SN, Means JC, Alaimo JT, Younger ST. Expediting rare disease diagnosis: a call to bridge the gap between clinical and functional genomics. Mol Med. 2020 Nov 25;26(1):117. doi: 10.1186/s10020-020-00244-5. PMID: 33238891; PMCID: PMC7691058.

4 EURORDIS Diagnosis Survey, 2022

BBMRI-ERIC Biobanking and BioMolecular resources Research Infrastructure · CRITICAL PATH INSTITUTE · eatris European infrastructure for translational medicine · ecrin · efpia · EUCOPE European Confederation of Pharmaceutical Entrepreneurs AISBL · EuropaBio · EURORDIS RARE DISEASES EUROPE

Critical improvements are required for rare disease diagnosis

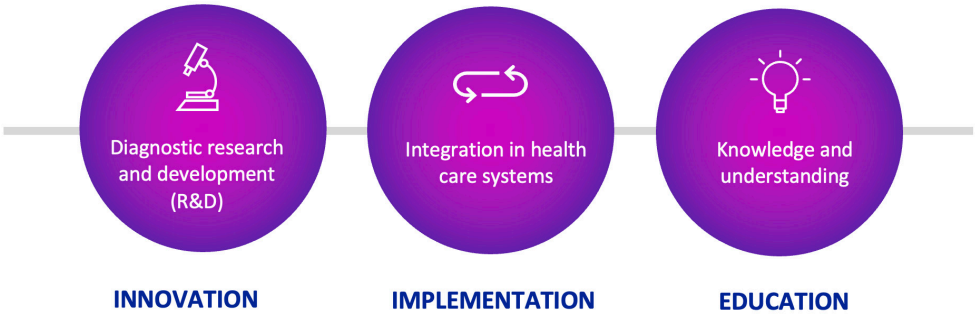
Diagnosing accurately and timely the undiagnosed, misdiagnosed, and unknown people affected by a rare disease remains a top public health priority. Although approximately 3 out of 4 rare diseases have a genetic basis[5], the low prevalence of individual diseases, their varying manifestation due to genetic interactions or interplay with the environment, and the lack of expertise makes diagnosis difficult.

To pave the way for earlier and better therapeutic interventions in rare diseases, diagnostic improvements are critically required across four main and complementary domains: i) accuracy, ii) time and access, iii) classification and iv) prevention and screening.

- **Accuracy**. Increasing the accuracy of diagnosis may require specification down to the precise pathophysiology and/or clinical phenotype, requiring utilization of the full biochemical and molecular armamentarium (e.g., genetic testing and multi-omics) and increasing efforts in deep phenotyping[6].
- **Time & access.** Decreasing the time from the initial symptom(s) to accurate clinical and molecular diagnosis and subsequent therapy remains a critical objective[7]. The diagnostic delay for rare diseases varies from months to decades, depending on the patient's phenotype, age, geographical location, access to expert centres and affordability of the most recent diagnostic tools and technologies.
- **Classification & further understanding of the rare diseases.** Better and more granular identification, delineation, and definition down to the molecular pathophysiology as precise phenotype is required to match modern classification based on the emerging scientific understanding. This will foster the transition from a traditional, more descriptive medicine towards modern taxonomy, precision medicine and tailored treatment pathways and further research.

- **Prevention & screening.** An earlier identification of risk-patterns, early and subclinical symptoms is needed to allow for preventive measures and intensified monitoring (e.g., in at-risk groups as well as to pre-empt complications, exacerbations or progression), and earlier primary therapeutic intervention. Screening measures should also be implemented at population-level together with appropriate monitoring and scanning strategies.

A three-fold approach is required to tackle these challenges, encompassing not only diagnostic research but also its implementation into healthcare systems as well as adequate awareness and education measures to speed up the path towards implementation and adequate utilization.



Diagnostic research would identify and establish a new methodology, biomarker, prediction model, etc. The new knowledge obtained would ultimately be translated into healthcare systems (implementation), by offering ready-to-use diagnostic kits or validated schemes, supply-chain logistics as well as listing and reimbursement, as necessary. This integration of advanced diagnostics into clinical practice can also be accelerated via public-private partnerships, allowing better communication and data sharing between the industry, genomic centers, and

5 Nguengang Wakap, S., Lambert, D.M., Olry, A. et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 28, 165–173 (2020). https://doi.org/10.1038/s41431-019-0508-0

6 Marwaha, S., Knowles, J.W. & Ashley, E.A. A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. Genome Med 14, 23 (2022). https://doi.org/10.1186/s13073-022-01026-w

7 IRDiRC Goal 1: "All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline" - from: https://irdirc.org/about-us/vision-goals/

clinics, accelerating patients' access while supporting further research and development.[8] To ensure all relevant stakeholders know about the new opportunity - scientifically, clinically, practically – adequate measures will be needed to ensure education and awareness.

The below recommendations focus solely on diagnostic research while we recognize that synergistic efforts with other initiatives are required to implement those research outputs in healthcare systems.

Recommended areas for PPP in Rare Disease diagnostic research

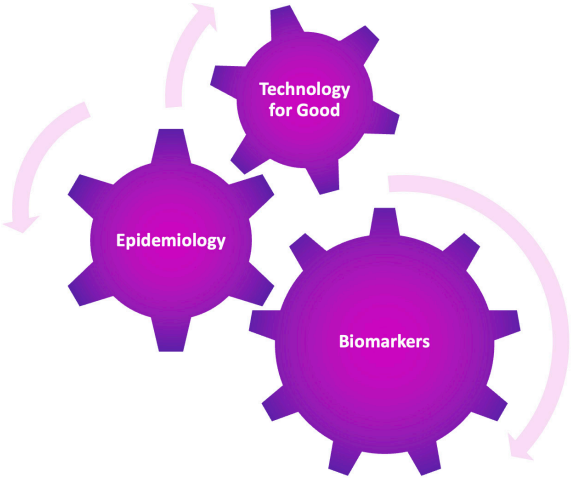
Public-Private partnership efforts should be sustained and reinforced in three core areas to tackle key challenges in rare disease diagnostic research[9]: biomarkers, epidemiology, and technology for good.

AREA 1 - BIOMARKERS

Supporting research efforts on biomarkers' discovery through public-private partnerships are required through a three-fold complementary approach, encompassing molecular biomarkers, clinical biomarkers, and digital biomarkers.

Molecular biomarkers

PPP research efforts should focus on:



- Identification, clinical and regulatory validation of new candidate markers, trends, and patterns.
- Developing and implementing scalable genomics and "multi-omics" diagnostics approaches together with a reflection on how to cope with massive amounts of data instead of case-by-case assessments.
- Advancing European labs to implement Next Generation Sequencing (NGS) more routinely at higher capacity and with faster turnaround time.
- Facilitating the implementation of the EU in vitro diagnostic medical device regulation (IVDR) by developing methodology and minimum analytic performance validation and supporting access to samples that would enable labs to meet these requirements.
- Improving the interpretation of genetic variants by developing tools to assess bio-pathogenicity and by building/reinforcing the expertise in data analysis processes.
- Supporting research on the clinical and health economic utility of earlier and accurate detection of biomarkers and its impact on health care management.
- Articulating the approach to disease profiling in national strategies (e.g., for rare disease, cancer or personalised medicine) and considering the integration of advanced diagnostics into clinical practice by investing in public-private partnerships. This should facilitate uptake of home-brewed diagnostics – those developed in individual laboratories – and integrate the latest advances in commercial diagnostics technologies.

Clinical biomarkers (from Electronic Health Records)

PPP research efforts should focus on:

- "Unsolved cases" which should be made available from a European federated repository to capitalize on subsequent advances in knowledge and research[10].This repository should be flexible and accessible for research.
- Automated identification of clinical conditions and patterns of interest with relevant support and further development of Electronic Health Data interpretation software facilitating deep phenotyping, supporting Healthcare providers decision making, and patient empowerment[11].

8 EUCOPE (2021): Developing an advanced diagnostics ecosystem in Europe: A proposal for change.

9 This recommended set of actions has been issued further consultations amongst a group of 30 industry representatives.

10 This should be done in collaboration with the forthcoming ERN Joint Action and with appropriate support to the Undiagnosed Diseases Network International (UDNI) members.

11 Building upon and in complementarity with existing/under development solutions such as AccelRare - Rare Disease Knowledge – FindZebra or Screen4Care.

Digital biomarkers[12]

PPP research efforts should focus on:

- Developing models for data integration including the emerging "digital footprint realms" from wearables, mobile devices, and other digital health technologies.
- Developing mechanisms and processes to allow for deep phenotyping and pheno-mapping from multimodal digital footprint (EHR, patient trackers, big data).
- Harnessing artificial intelligence-driven hypothesis generation and discoveries using structured material information as well as unstructured health records while respecting privacy through federated learning approaches.
- Developing risk pattern recognition models and tools to enable early identification of the clinical condition.
- Identification and implementation of automated triggers for diagnostic follow-up, preventive measures, and earlier treatment intervention.

AREA 2 - EPIDEMIOLOGY

PPP research efforts should focus on:

- Supporting comprehensive registries for pattern recognition, disease characterization and understanding of patients current and future needs.
- Investing in the definition of improved methodologies for accurately determining the true prevalence of rare diseases at a population level[13].
- Supporting epidemiology efforts (including the disease itself, complications and comorbidities, and genetic and other risk factors) to better assess the number of patients with actionable diseases to improve care and treatment follow ups as well as informed decision making.
- Quantifying diagnosed patients with certain conditions quickly and early-on to incentivize industry involvement.
- Supporting socioeconomic research on the current and future health and economic burden of rare diseases with recommendations on where interventions (e.g., earlier screening) would have most impact.
- Speeding up the implementation of the legal environment/data use regulations with systematic EHRs in place as well as education measures and a reasonable balance of data protection and data altruism.
- Defining deep phenotyping standards for rare diseases.
- Accessing genetic and genomic profiles' databases and repositories while ensuring data protection.
- Interlinking functionalities (based on the International Classification of Functioning, Disability and Health) with rare diseases ORPHA codes to break the silos between the assessment of the impairment and disabilities, the clinical symptoms and the genetic information to reach earlier diagnosis.

AREA 3 - TECHNOLOGY FOR GOOD

PPP research efforts should focus on:

- Building a participatory medicine approach centred around individuals, with adequate measures to enable their participation and to equip, educate and empower them.
- Proactively engaging with the public to establish privacy and ethical guidelines for reassurance regarding the use of diagnostic data.
- Developing advanced analytics-driven patient alerts and recommendation for expert follow-ups
- Funding socio-economic research studies to evaluate and assess how diagnostic research outcomes are translated into the clinic and how they have a clear impact on patient care pathways together with increased opportunities to be enrolled in clinical research and to benefit from the most suitable treatment.

Conclusions

Public-private cross-sectoral collaboration is required to advance on how diseases are defined, on the diagnostic speed, accuracy, scrutiny as well as to access state-of-the-art diagnostic technology and automatization. This will result in cost-effectiveness, socio-economic improvements, greater individual benefits for patients in yet underserved populations as well as more tailored and personalised treatment approaches.

---

12 Vasudevan, S., Saha, A., Tarver, M.E. et al. Digital biomarkers: Convergence of digital health technologies and biomarkers. npj Digit. Med. 5, 36 (2022). https://doi.org/10.1038/s41746-022-00583-z

13 This is challenging due to a combination of factors including incomplete clinical data and sparse penetrance data, which results in potentially significant underestimates of the true scale of rare diseases. Genetic enable the frequency of occurrence of a given allele to be quantified and coupled with penetrance, this can give a more accurate estimate of the true burden of the disease by estimating both diagnosed and undiagnosed cases.