Lost in the System: The Labyrinth of Rare Disease Diagnosis

Authors:	Peter Fish[1] 1. Mendelian, London, UK *Correspondence to peter@mendelian.co
Disclosure:	Fish is the CEO and a shareholder of Mendelian, London, UK, a company that generates revenue from life science companies for projects aimed at shortening the diagnostic odyssey of rare diseases.

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One in 10 people may be affected by a rare disease (RD) in their lifetime.[1] This is the surprising paradox of RDs. While each disease is individually rare, when considered collectively, they affect a staggering portion of the population. This prevalence is expected to be even higher in those who frequently seek care. The full burden is often hidden and poorly understood. As a result, their impact on patients and healthcare systems is profoundly difficult to quantify, and expected to be substantially under-estimated.

In Europe, a disease is classified as rare if it affects less than one in 2,000 people. RDs that affect less than one in 50,000 people are termed ultra-rare. Most sources suggest there are 6,000–7,000 known RDs.[1] Recently, RARE-X estimated the number of distinct RDs at almost 11,000, noting that 2,000 of these are vaguely defined.[2] Around five new RDs are discovered and added to these lists every week.[1] This will accelerate as knowledge expands, and as we move to stratified and personalised care.

Most RDs lack an approved drug treatment, although the number of RD treatments is expected to increase rapidly.[3] Orphan drug (drugs developed to treat RDs) trials represent half of the active trials. Approved treatment or not, an accurate diagnosis is essential for optimal disease management, empowering patients to understand their condition and facilitating access to supportive care, advocacy groups, and clinical trials.

Unfortunately, the diagnostic process remains an odyssey for most: long, challenging, and rife with misdiagnoses and inefficiencies, allowing diseases to progress and irreversible complications to accumulate. Unnecessary tests and procedures are carried out, and inappropriate medication is prescribed.

Early and accurate diagnosis is noted as a priority by almost all relevant organisations, including the European Organisation for Rare Disorders (EURORDIS-Rare Diseases Europe),[4] and in various RD-focused government frameworks. Diagnostic odysseys appear to have been amplified by the strain that the COVID-19 pandemic placed on our healthcare systems.[5]

Our exposure to RDs has increased in recent years, driven by greater patient advocacy, novel diagnostic technologies, our expanded understanding, and the rise of orphan drugs. This aside, routine medical practice, in Europe and the rest of the world, still fails patients with RDs. We need to change this.

WHY THE LABYRINTH?

RDs are a vast and heterogeneous group of diseases. This leads to information complexity beyond simply the sheer number of diseases, which, in turn, delays recognition and diagnosis.

We Only Recognise What We Know

Unsurprisingly, most clinicians have limited experience with RDs, having rarely encountered patients with these conditions, particularly the ultra-rare RDs. Just 150 RDs account for 80% of all patients diagnosed with a RD.[3] Some, like cystic fibrosis, occur near the one in 2,000 threshold, while 85% of these diseases affect less than one in 1,000,000 people.[3] Some diseases have only ever been recorded in one or two patients worldwide. We generally recall some of the important or intriguing RDs that are more common, linked to famous people, or that present with unique or pathognomonic signs. Cystic fibrosis, sickle cell disease, haemophilia, Duchenne muscular dystrophy, achondroplasia, amyotrophic lateral sclerosis (Lou Gehrig's and Stephen Hawking's disease), fibrodysplasia ossificans progressiva ('stone man syndrome'), and progeria might all ring a bell.

Diverse Aetiologies

Over 70% of all RDs are genetic.[6] Others are infectious, autoimmune-driven, or rare cancers. Some RD databases even include diseases arising from toxin exposure. Wide diversity exists within each group. Genetic RDs can be the result of single nucleotide variants, insertions/deletions, structural variants, repeat expansions, and more.[7] These may occur in one of 20,000 genes, or numerous, now known to be important, non-coding sites.

This variation opens a huge search space for diagnosis, which requires diverse clinical expertise and testing methods. Frequently, a specific suspected RD, perhaps the most common, or one that was top of mind, turns out not to be the culprit, while another related RD is. This shifts the way we need to diagnose; instead of requesting a highly targeted test, it often pays to explore more broadly from the start.

New diagnostic technologies generally allow a greater 'catch' with a single test. As the costs decrease and availability improves, guidelines are swiftly updated to recommend tests covering a greater range of conditions. With genetic RDs, short-read whole genome sequencing should be considered in most circumstances,[7] while promising advances in long-read sequencing means it may supersede this in the years to come. Sadly, the diagnostic yield, even from the most advanced tests, may still leave most complex patients undiagnosed, or with a variant of unknown significance, which may or may not be pathogenic.[7] These modern tests generate huge amounts of data, and interpreting the results is often a substantial feat.

Population Background

Different populations are affected disproportionately. The discrepancies in disease prevalence may make a disease rare in certain populations, while fairly common in others. Thalassaemia is rare in Northern European patients, yet common in Mediterranean patients. Clinicians may miss diseases in populations they are only occasionally exposed to.

Temporal and System Fragmentation

RDs can present at any life stage, from birth to far later in life. Some present acutely, while many have insidious, progressive presentations. Almost 70% are known to start in childhood.[6] Not all these patients present clinically at this young age, yet on deeper evaluation or enquiry, early signs may have been there. As RDs progress, patients present with additional pathologies over time. Clinicians often only have the capacity to focus on the current presenting complaint in isolation. The temporal fragmentation of patient data obscures clinical patterns, highlighting the importance of comprehensive longitudinal reviews.

Some RDs affect isolated organ systems (retinal diseases), while others are multi-systemic (metabolic diseases). Specialist

care can be notoriously siloed, and as a result, clinicians may miss an underlying multi-systemic disease. A dermatologist may manage a skin rash; a month or two later, a hepatologist reviews abnormal liver function: both pathologies driven by a single, undiagnosed RD. In some settings, primary care electronic health records may house more complete data on the patient's journey.

The Wide Range of Severity

Some RDs have mild presentations, but many present acutely and severely. Various RDs are incompatible with life, leading to miscarriages and stillbirths during the antenatal and early neonatal periods. These may be diagnosed retrospectively after death, which may bring closure to some parents, useful knowledge for future pregnancies, and academic value. Sadly, many children with an RD will not survive to their fifth birthday.

RDs often exhibit significant inter-patient variability. Patients with the same genotype manifest with varied phenotypes, ranging from no signs at all to markedly severe. Diseases may have early- or late-onset subtypes. Less severely affected patients, and those with later-onset disease, often go undiagnosed until later in life.

HOW DO WE SOLVE IT?

Undiagnosed patients can be split into three stages based on symptom presence, patient engagement with the healthcare system, and whether an RD is suspected or not. There are mechanisms and levers that can be lent on to expedite diagnosis at each stage. Not every patient will pass through every stage.

Stage 1: Pre-symptomatic (or Subclinical Symptoms), No Healthcare System Engagement, Rare Disease Is Not Suspected

These patients may be diagnosed via cascade testing (testing of relatives when a family member tests positive with a relevant RD), or newborn blood spot (NBS) screening programmes.

NBS varies notably across the world. In Europe, the UK and Ireland screen for nine diseases, while Italy screens for over 40. Advocacy groups are calling for a more harmonious approach. Advances in mass spectrometry and molecular methods now allow far more diseases to be included, yet the downsides, mostly associated with false positives, need to be carefully weighed. The International Society for Neonatal Screening (ISNS) collaborates closely with various RD organisations, including the European Reference Network for Hereditary Metabolic Diseases and Rare Endocrine disorders (metabERN/EndoERN) and EURORDIS, to drive NBS forward via focused programmes like the first pillar of the Screen4Rare project.[8]

Genomic tests are being evaluated as screening tools. A research project being conducted in England, UK, called The Generation Study, looks to sequence the genomes of 100,000 newborns by March 2025. Pathogenic mutations will be reported on for around 200 carefully selected diseases, all of which present, and can be treated, in the early years of life.[9] Genomic screening programmes, if proven clinically useful, cost-effective, and ethically sound, may be routine in the future.

Additionally, early phenotypic detection, through routine health checks, and automated, somewhat objective, biomarker detection via patient wearables and other related technologies, may hold future promise in surfacing these hidden patients, and moving them into Stage 2 or 3.

Stage 2: Symptomatic, Healthcare System Engagement, Rare Disease Is Not Suspected

Patients may seek care for seemingly unrelated conditions over the course of years. Too often, clinicians focus on managing only the acute issue, rather than searching for a possible unifying root cause, a natural outcome of time pressure and limited knowledge of RDs.

Education programmes may yield some effect; yet due to the expansive (and expanding) list of RDs,

educating most patients and clinicians about individual RDs may be futile. Two approaches can be considered:

1. General 'Think Rare' education challenges patients and clinicians to always explore the potential that a patient's clinical pattern may be the result of an undiagnosed RD (hoof beats do not always mean a horse: it may be a zebra). Hopefully this article raises awareness in this way.

2. Phenotype-specific education integrates an RD consideration into day-to-day care, by including a 'Consider an RD' branch into diagnostic or management guidelines and algorithms (for instance, patients with early-onset, treatment-resistant epilepsy may warrant further investigation for an underlying, undiagnosed RD).

Health informatic and artificial intelligence approaches, including electronic health record case-finding technologies, and automated differential diagnosis generators, can identify patients who warrant a review, or suggest alternative diagnoses. Screen4Care's second pillar focuses on this aspect.

Additionally, we can ensure we break down silo walls, enhance health data standardisation and sharing, and ensure clinicians have a comprehensive view of every patient's health. The European Health Data Space (EHDS) initiative strives to do just this.

Stage 3: Symptomatic, Healthcare System Engagement, Rare Disease Is Suspected (Not Yet Diagnosed)

As previously noted, even when a RD is suspected, a successful and accurate diagnosis is far from guaranteed. Between 50–95% patients with suspected RDs who are put forward for whole genome sequencing remain undiagnosed.[7] Multimodal diagnostic pathway enhancements, diagnostic hardware and software improvements, and data-driven phenotype to disease and genotype search engines are levers in this phase.

Specialist units and organisations focused on these undiagnosed patients are purposefully being set up, such as Syndrome Without a Name (SWAN) clinics and Undiagnosed Disease Networks, with European organisations like Solve-RD driving this agenda forward.

MOVING FORWARD

Much of the diagnostic odyssey is the result of a massive information challenge. Clinicians (and humans in general) lack the tools to effectively integrate and interpret the vast amounts of disease and patient information required for earlier RD diagnoses. To address this, it would be beneficial to continue to invest and support coordinated European initiatives, harmonise and expand genomic and health data sharing, ramp-up cross-border research, and develop robust tech-enabled diagnostic technologies and decision support tools. Adopting new technologies is challenging, and these bring notable changes, so political support is an imperative. Continually evaluating diagnostic pathways, identifying and widening bottlenecks, and optimising resoource allocation, will maximise the impact of new technologies and specialised care.

I urge clinicians to 'Think Rare', and utilise the valuable RD resources at your disposal, to change patients' lives for the better.

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