Barriers to timely diagnosis of rare diseases

How healthcare systems in Europe shape time to rare disease diagnosis

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Contents

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Europe has made substantial progress in establishing the conditions for timely rare disease diagnosis. Advances in research, particularly in genomics and next-generation sequencing technologies, have improved diagnostic rates[1] and expanded the ability to identify rare diseases.

These advances have been supported by investments in genomic infrastructure, data sharing, and cross-border collaboration through initiatives such as the 1+ Million Genomes Initiative[2], Screen4Care[3], and the European Reference Networks. Policy developments and the growing number of orphan medicinal products authorised in the EU have also increased the benefits of obtaining a timely diagnosis, creating stronger incentives for timely patient identification and referral. Together, these developments have strengthened the scientific, organisational, and policy foundations for timely rare disease diagnosis.

However, despite this progress, **millions of Europeans with rare diseases continue to experience long and avoidable diagnostic delays**, with time to diagnosis averaging nearly five years from symptom onset to confirmed diagnosis[4]. Such delays not only worsen patient outcomes but also generate avoidable healthcare and societal costs.

In this White Paper, we investigate the barriers that exist across the EU to timely diagnosis of rare diseases by looking at factors associated with time to diagnosis (i.e. time from symptom onset to confirmation of diagnosis with appropriate medical tests or clinical criteria) and with time to diagnosis *in the healthcare system* (i.e. time from first medical contact to confirmed diagnosis), in line with the EURORDIS Rare Barometer study. We rely on the existing literature, the reanalysis of data from the EURORDIS Rare Barometer survey on the diagnostic odyssey of people living with a rare disease, as well as in-depth interviews with experts to identify the key barriers and provide practical examples of how these barriers emerge in healthcare systems and contribute to delayed diagnosis in rare diseases.

We have identified seven barriers that contribute to delayed diagnosis of rare diseases within European healthcare systems, see Figure 1. These barriers operate at different stages of the diagnostic pathway and reinforce one another.

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1 While traditional diagnostic pathways (e.g. sequential genetic tests, imaging, clinical work-up) often yield <10–15 per cent diagnoses in many rare disease cohorts. Genomic sequencing typically achieves ~25–40 per cent diagnostic yield, depending on the population and disease area. See for example Hayeems, R. Z., Bernier, F., Boycott, K. M., Hartley, T., Michaels-Igbokwe, C., & Marshall, D. A. (2022). Positioning whole exome sequencing in the diagnostic pathway for rare disease to optimise utility: a protocol for an observational cohort study and an economic evaluation. *BMJ open*, 12(10), e061468. https://link.springer.com/article/10.1186/s13073-023-01240-0

2 For details see: https://digital-strategy.ec.europa.eu/en/policies/1-million-genomes

3 For details see: https://www.screen4care.eu/

4 Faye et al. (2024). Time to diagnosis and determinants of diagnostic delays of people living with a rare disease: results of a Rare Barometer retrospective patient survey. *European Journal of Human Genetics*, 32(9), 1116-1126. https://doi.org/10.1038/s41431-024-01604-z

5 Ibidem.

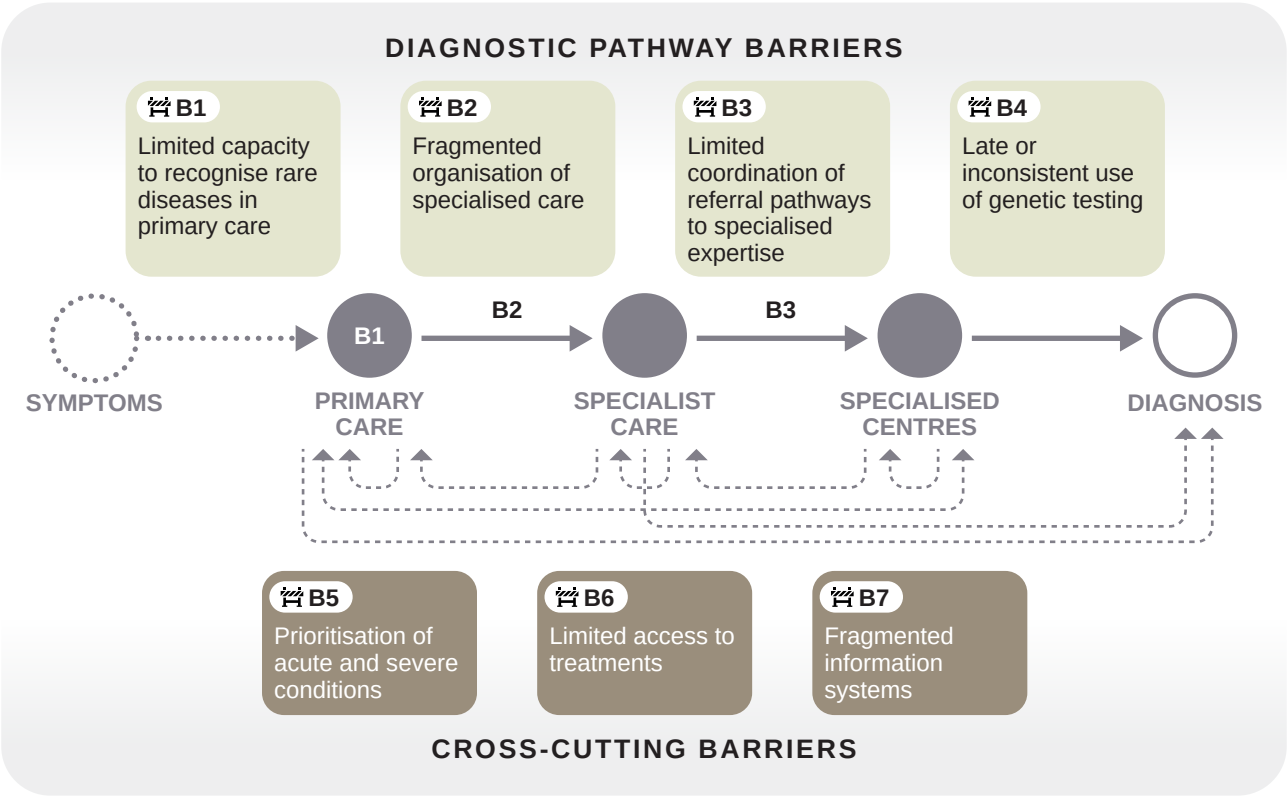
The identified barriers can be grouped into two broad categories.

The first group consists of barriers directly affecting the main diagnostic pathways themselves. These include limited capacity to recognise rare diseases in primary care (B1), fragmented organisation of specialised care (B2), limited coordination of referral pathways to specialised expertise (B3), and late or inconsistent use of genetic testing (B4). Together, these barriers slow the progression from the first presentation of symptoms to referral, testing, and confirmation of diagnosis. Delays emerging at one stage of the pathway often accumulate at subsequent stages, extending the overall diagnostic journey.

The second group consists of broader healthcare system and disease-related characteristics that reinforce these pathway-level barriers. One is the prioritisation of acute, severe, permanent and visible conditions (B5), whereby conditions with slow progression, non-specific symptoms, or predominantly long-term burden are less likely to trigger immediate investigation or referral. Another is limited access to treatments (B6), which can reduce the perceived value of early diagnosis and weaken incentives to invest in diagnostic capacity, screening, or proactive case identification. Finally, fragmented health information systems and incomplete implementation of rare disease coding standards (B7) limit the ability of healthcare systems to identify patterns across providers, aggregate patient data, and support timely clinical decision-making.

While these barriers are similar across Europe, the avoidable healthcare costs they generate may differ between countries. Therefore, European-level initiatives alone are unlikely to be sufficient to address these barriers; instead, a stronger evidence base on where and how barriers and costs arise across the diagnostic pathway in different healthcare systems will be needed to formulate country-specific recommendations on where targeted investment in timely diagnosis is likely to generate the greatest value for patients, healthcare systems, and society.

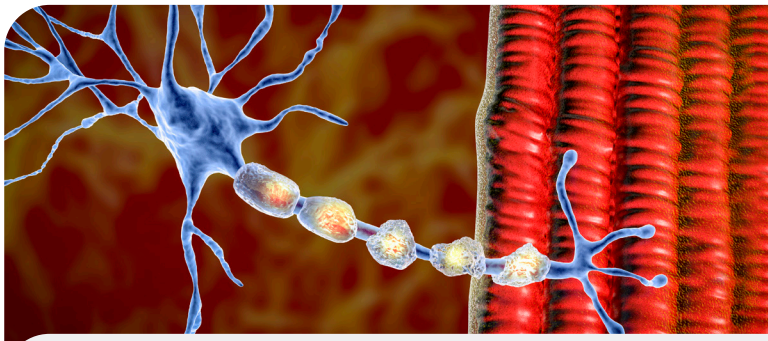
FIGURE 1: BARRIERS TO TIMELY DIAGNOSIS



Delayed diagnosis worsens patient outcomes and creates avoidable costs for healthcare systems and society

Delayed diagnosis in rare diseases has consequences for patient outcomes and healthcare system efficiency. Many rare diseases are progressive, with disease processes worsening over time and potentially leading to irreversible tissue damage. At the same time, the effectiveness of available treatments is often time-sensitive, with greater benefits when therapy is initiated early in the course of the disease. Even in cases where irreversible damage is not present, late diagnosis may worsen patient outcomes by leading to complications that make disease management less effective and may in some cases result in the use of inappropriate or contraindicated treatments that fail to address the underlying condition or exacerbate disease progression.

The implications of late diagnosis can be illustrated by rare neurological disorders such as Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), see Box 1. Patients who present with more advanced nerve damage at diagnosis are more likely to experience long-term disability. The consequences of misdiagnosis and inappropriate treatment can be illustrated by adult hypophosphatasia (HPP). Because HPP can present with symptoms similar to osteoporosis, patients may be incorrectly diagnosed and treated with bisphosphonates. However, these medicines are generally not appropriate for patients with HPP and may increase the risk of atypical femoral fractures and worsen skeletal outcomes.[6] Reducing time to diagnosis and avoiding inappropriate treatments are therefore critical for limiting disease progression and preserving treatment effectiveness.



BOX 1

DELAYED DIAGNOSIS MAY LEAD TO IRREVERSIBLE DAMAGE – THE CASE OF RARE NEUROLOGICAL DISORDER

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a rare, progressive neurological disorder in which the body's immune system attacks the peripheral nerves, leading to muscle weakness, sensory loss, and reduced mobility. The condition is often difficult to diagnose, as early symptoms are non-specific and can resemble more common neurological or musculoskeletal conditions. This frequently results in delayed referral to specialised care and postponement of appropriate treatment.

Evidence shows that such delays have important clinical consequences. Patients who already have more nerve damage at the point of diagnosis, and those who start treatment later, are more likely to experience long-term disability. This reflects the progressive nature of the disease: ongoing, untreated inflammation can lead to damage of the nerve fibres themselves, which is less likely to be reversible. As a result, delayed diagnosis increases the risk of permanent functional impairment, as damaged nerves have limited capacity to recover.[7]

6 Rassie, K., Dray, M., Michigami, T., & Cundy, T. (2019). Bisphosphonate use and fractures in adults with hypophosphatasia. *Journal of Bone and Mineral Research Plus*, 3(10), e10223. https://onlinelibrary.wiley.com/doi/10.1002/mus.27722

7 Al-Zuhairy, A., Jakobsen, J., Moldovan, M., & Krarup, C. (2022). Axonal loss at time of diagnosis as biomarker for long-term disability in chronic inflammatory demyelinating polyneuropathy. *Muscle & Nerve*, 66(6), 715-722. https://doi.org/10.1002/jbm4.10223

Delayed diagnosis of suspected rare diseases is associated with substantially higher healthcare system costs due to repeated consultations, misdiagnoses, unnecessary testing, and late referral. A German claims-data study, covering the period between 2014 and 2019, indicates that direct medical costs related to diagnosis incurred prior to referral to a specialised centre are, on average, **more than seven times higher** for patients with suspected rare diseases than for comparator patients. The study reports average direct medical costs of EUR 26,999 per patient with suspected rare diseases, compared with EUR 3,563 for patients without suspected rare diseases[8]. This indicates that prolonged diagnostic pathways generate significant and potentially avoidable expenditure for health systems.

The costs associated with prolonged diagnosis should also be considered in the context of the **wider healthcare system and socio-economic burden of rare diseases**. A recent study documents an average per-person-per-year overall economic cost of EUR 121,900 for people living with a rare disease, with 65 per cent attributed to direct medical costs, 19 per cent to direct non-medical costs such as supportive therapies and formal or informal care, and 16 per cent to indirect costs related to lost work productivity. The per person per year cost for people with a rare disease is reported to be **six times greater than the average annual per person healthcare expenditure** in the reference group without a rare disease (EUR 20,200)[9].

Another study across Germany, France, and Italy shows that the average rare-disease burden amounts to **EUR 107,000 per patient per year**, about **15 times the burden of common conditions**[10]. Crucially, when treatment is not available, indirect family-borne costs increase from 29 per cent to 45 per cent of the total, and the overall burden rises by roughly 28 per cent[11].

These findings indicate that, where delayed diagnosis also delays treatment, it also creates wider, avoidable socio-economic costs.

Across Europe, we identify seven barriers to timely diagnosis of rare diseases embedded in the organisation of healthcare systems

Delays in the diagnosis of rare diseases can arise at both the patient and healthcare system levels. Patient-level delays refer to the time between symptom onset and the first medical consultation. On average, these delays account for only 10 per cent of the total diagnostic delay calculated as the time between symptom onset and confirmed diagnosis.[12]

The remaining **90 per cent reflects delays in the healthcare system** (time between first medical consultation and confirmed diagnosis).[13] In Europe, healthcare systems are typically organised in steps, see Box 2. Patients should progress through multiple levels of care before they can access advanced diagnostics or rare disease expertise. In such a system, diagnosing complex rare diseases with non-specific, heterogeneous symptoms that overlap with more common conditions is more challenging.

8 Glaubitz, R. et al. (2025). The cost of the diagnostic odyssey of patients with suspected rare diseases. *Orphanet Journal of Rare Diseases*, 20(1), 222. https://doi.org/10.1186/s13023-025-03751-y

9 Wilsdon, T. et al. (2024) The Economics Cost of Living with a Rare Disease Across Europe. https://media.crai.com/wp-content/uploads/2024/10/28114658/CRA-Alexion-Quantifying-the-Burden-of-RD-in-Europe-Exec-Summary-October2024.pdf

10 Andreu, P., John Atay N., Piccinini, E., Chiesi, G., & Cioffi, G. (2023) *Rare disease burden of care and the economic impact on citizens in Germany, France and Italy.* https://chiesirarediseases.com/assets/pdf/rare-disease-burden-of-care-and-the-economic-impact-on-citizens.pdf

11 Ibidem.

12 Faye, F. et al. (2024) Time to diagnosis and determinants of diagnostic delays of people living with a rare disease: results of a Rare Barometer retrospective patient survey. *European Journal of Human Genetics* 32, 1116-1126. https://doi.org/10.1038/s41431-024-01604-z

13 Geng, LN, Sum-Ping, O, & Geng, YJ. (2019). Phases of the Diagnostic Journey: A Framework. *International Archives of Internal Medicine*, 3:013. https://www.clinmedjournals.org/articles/iaim/international-archives-of-internal-medicine-iaim-3-013.php?jid=iaim

BOX 2

TYPICAL DIAGNOSTIC PATHWAY FOR SYMPTOMATIC PATIENTS[14]

The diagnostic pathway for symptomatic patients typically begins in primary care, with a general practitioner (GP) consultation. During the initial consultation, the GP collects clinical information through medical history-taking and physical examination and formulates a preliminary diagnostic hypothesis. Where the hypothesis about the condition can be confirmed based on clinical findings, appropriate treatment may be initiated in primary care. Where diagnostic uncertainty remains, the GP may request diagnostic testing or refer the patient to a specialist for further assessment.

At specialist level, additional clinical evaluation and more advanced or condition-specific tests may be performed. The working diagnostic hypothesis is refined based on new evidence. Where results remain inconclusive, patients may undergo further testing, be referred to additional specialists, or be directed to specialised rare disease centres. And even after this point, when all possibilities in healthcare system have been exhausted, the patient may remain undiagnosed.

We have identified seven barriers that drive diagnostic delays in the healthcare system (see right).

The seven barriers can be grouped into two broad categories. The first group consists of barriers operating directly within the diagnostic pathway and includes barriers B1 to B4, see Figure 2. The second, consists of broader healthcare system characteristics that reinforce delays across the pathway and includes B5 to B7.

While we recognise that patients may not always progress through the typical diagnosis pathway - as illustrated by the Solve-RD illustration of the patient journey to diagnosis[15] and by the smaller arrows below the steps of the diagnosis journey in Figure 2 – the typical diagnostic pathway provides a useful analytical framework for understanding where barriers arise. The following sections therefore locate the identified barriers along this pathway and examine their contribution to delayed diagnosis across European healthcare systems.

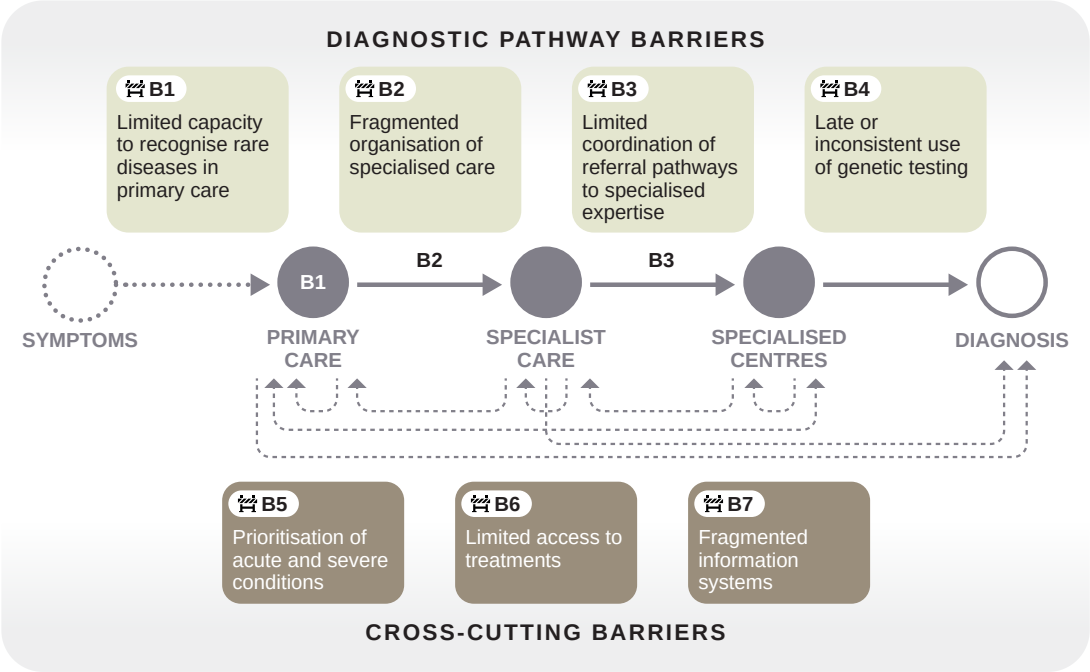
- **B1** Limited recognition of rare diseases in primary care
- **B2** Fragmented specialised care
- **B3** Limited coordination of referral pathways
- **B4** Late or inconsistent use of genetic testing
- **B5** Prioritisation of acute, severe, permanent and visible conditions
- **B6** Limited access to effective treatments
- **B7** Fragmented health information systems alongside incomplete implementation of rare disease coding standards

14 Geng, LN, Sum-Ping, O, & Geng, YJ. (2019). Phases of the Diagnostic Journey: A Framework. *International Archives of Internal Medicine*, 3:013. https://www.clinmedjournals.org/articles/iaim/international-archives-of-internal-medicine-iaim-3-013.php?jid=iaim

15 https://www.eurordis.org/publications/solve-rd-infographic-on-the-patient-journey-to-diagnosis/

FIGURE 2: BARRIERS TO TIMELY DIAGNOSIS

Source: Copenhagen Economics



B1 Limited capacity in primary care

In most European healthcare systems, primary care typically serves as the main entry point to the diagnostic pathway. General practitioners (GPs) are responsible for initial assessment, interpretation of symptoms, and referral to specialist care. The timeliness of diagnosis therefore depends on their ability to recognise patterns consistent with rare diseases and initiate appropriate diagnostic pathways.

Limited exposure to a specific rare disease

In practice, **GPs do encounter people living with a rare disease in routine care but are rarely exposed to the same specific condition repeatedly**, limiting opportunities to build diagnostic experience. Although rare diseases collectively affect an estimated 6 to 8 per cent of the European Union population, these patients are distributed across more than 6,500 distinct conditions. A GP with a patient list of around 2,000 individuals may care for approximately 120–160 patients living with a rare disease, but only a very small number of people living with the same rare condition. For a rare disease affecting 5 in 10,000 people, a GP may encounter approximately one patient at any given time. For diseases with a prevalence of 1 per 10,000 or lower, a GP may encounter at most one case in their clinical practice[16]. Opportunities to develop experience with specific rare diseases are therefore limited.

Limited awareness

This **limited exposure is compounded by gaps in medical education and training**. In the EU, rare diseases are not systematically covered in undergraduate medical education, postgraduate training, or continuing professional development programmes[17,18]. Historically, limited treatment options and the low prevalence of rare diseases

16 See Calomme, A., De Prez, V., De Schreye, R., & Wuyts, J. (2025). In-depth analysis of the results of the European Parliament's public consultation on rare diseases. Policy Department for Transformation, Innovation and Health, European Parliament. PE 778.583. https://www.europarl.europa.eu/supporting-analyses

17 Domaradzki, J., & Walkowiak, D. (2021). Knowledge and attitudes of future healthcare professionals toward rare diseases. *Frontiers in Genetics*, 12, 639610. https://doi.org/10.3389/fgene.2021.639610

18 Tumiene, B. et al. (2022) Rare disease education in Europe and beyond: time to act. https://doi.org/10.1186/s13023-022-02527-y

have likely contributed to their limited inclusion in medical education[19], as both factors reduce their perceived clinical priority within training curricula. While the past two decades have seen a significant increase in treatment options for some rare diseases[20], medical education and training have not yet fully adapted to this evolving therapeutic landscape. As a result, clinicians lack familiarity with diagnostic guidelines, red-flag symptoms, and available referral pathways.

Studies across Europe consistently document limited capacity to recognise rare diseases among healthcare professionals. Healthcare professionals in Germany often have limited knowledge of rare diseases. Clinicians in Italy frequently report poor awareness and knowledge of rare diseases[21]. In Spain, primary care professionals see few rare disease patients, often lack specific training[22]. GPs and other clinicians in the UK frequently do not recognise red flag symptoms and rarely suspect rare disease timely[23]. In Poland, most physicians rate their knowledge of rare diseases as insufficient or very poor, and over 90 per cent do not feel prepared to care for rare disease patients, underlining major gaps in medical education[24]. This is also the case in other Central and Eastern EU Member States, including Hungary and Romania[25].

BOX 3

AGE- AND GENDER-RELATED FACTORS AFFECTING TIMELY DIAGNOSIS

Symptom recognition and attribution

- In adolescents, symptoms may be normalised or misattributed to growth, puberty, fatigue, or psychological factors[26].
- In females, symptoms such as pain and fatigue, are more often interpreted as non-specific or benign[27].

Health-seeking behaviour

- Adolescents have lower healthcare utilisation autonomy and depend on parents/guardians, which can delay presentation[28].
- Gender differences in health-seeking can work both ways, but for certain conditions, women may delay escalation if symptoms are recurrent or previously dismissed[29].

System interaction and prior experience

- For younger populations, fragmented care pathways (paediatric vs. general practice) may contribute to delays.
- Previous experiences of not being taken seriously, reported more frequently by women, can lead to delays[30].

19 Medical education curricula are developed under time constraints and therefore prioritise conditions based on factors such as prevalence, burden, and clinical impact, as reflected in established curriculum design frameworks

20 Aartsma-Rus, A., Dooms, M., & Le Cam, Y. (2021). Orphan medicine incentives: how to address the unmet needs of rare disease patients by optimizing the European orphan medicinal product landscape guiding principles and policy proposals by the European expert group for orphan drug incentives (OD expert group). *Frontiers in pharmacology*, 12, 744532. https://doi.org/10.3389/fphar.2021.744532

21 For evidence in Germany and Italy see Calomme, A., De Prez, V., De Schreye, R., & Wuyts, J. (2025). In-depth analysis of the results of the European Parliament's public consultation on rare diseases (Study PE 778.583). European Parliament, Policy Department for Transformation, Innovation and Health. https://www.europarl.europa.eu/RegData/etudes/STUD/2025/778583/ECTI_STU(2025)778583_EN.pdf

22 Gimenez-Lozano, C. et al. (2022) Rare Diseases: Needs and Impact for Patients and Families: A Cross-Sectional Study in the Valencian Region, Spain https://doi.org/10.3390/ijerph191610366

23 Hay, E. et al. (2021) The diagnostic odyssey in rare diseases; a task and finish group report for the department of health and social care. https://doi.org/10.3310/nihropenres.1115171.1

24 Domaradzki, J. & Walkowiak, D. (2021) Knowledge and Attitudes of Future Healthcare Professionals Toward Rare Diseases. *Frontiers in Genetics ELSI in Science and Genetics*. Volume 12. https://doi.org/10.3389/fgene.2021.639610

25 Calomme, A., De Prez, V., De Schreye, R., & Wuyts, J. (2025). In-depth analysis of the results of the European Parliament's public consultation on rare diseases (Study PE 778.583). European Parliament, Policy Department for Transformation, Innovation and Health. https://www.europarl.europa.eu/RegData/etudes/STUD/2025/778583/ECTI_STU(2025)778583_EN.pdf

26 See for example: Cardinali, P., Migliorini, L., & Rania, N. (2019). The caregiving experiences of fathers and mothers of children with rare diseases in Italy: Challenges and social support perceptions. *Frontiers in psychology*, 10, 1780.

27 Women and Equalities Committee (2024). Women's reproductive health conditions. https://committees.parliament.uk/publications/45909/documents/228040/default/

28 World Health Organization (2021). Assessing and supporting adolescents' capacity for autonomous decision-making in health care settings: A tool for health-care providers. https://www.who.int/publications/i/item/9789240039568

29 Westergaard, D., Moseley, P., Sørup, F. K. H., Baldi, P., & Brunak, S. (2019). Population-wide analysis of differences in disease progression patterns in men and women. *Nature communications*, 10(1), 666.

30 UN (2026). From misdiagnosis to medical bias: Why women are living longer but not better. Accessed on 28 April 2026. https://news.un.org/en/story/2026/04/1167259

Clinical recognition biases and challenges

Clinical recognition of rare diseases may be further complicated by age- and gender-related factors, see Box 3. Differences in symptom presentation, interpretation, healthcare utilisation, and interactions with healthcare professionals can affect whether symptoms are investigated and whether patients are referred for specialist assessment. Consistent with this, the EURORDIS Rare Barometer survey found substantially longer diagnostic delays among children and adolescents (8.8–10.4 years on average) and found that women receive a diagnosis almost two years later than men. The survey also shows that those differences mostly come from the health system[31].

Limited familiarity with red flags and appropriate diagnostic pathways

Limited awareness of rare diseases can reduce the effectiveness of diagnostic tests that are already available in routine care. For some rare diseases, timely diagnosis depends not only on access to specialised or genetic testing, but also on the correct interpretation of routinely measured laboratory parameters in the context of patient-specific characteristics such as age. This is particularly relevant for conditions where diagnostic signals are based on deviations in common biomarkers. If age-specific reference ranges are not applied, or if laboratory reporting systems do not appropriately flag abnormal values, clinically relevant findings may be interpreted as normal and opportunities for timely diagnosis may be missed, see examples in Box 4 which illustrate how such diagnostic gaps can occur in practice with examples of Hypophosphatasia[32] (HPP) and X-linked hypophosphataemia[33] (XLH). The consequences can be substantial: among adults with HPP,

BOX 4

CASE STUDY: MISSED SIGNALS IN ROUTINE LABORATORY TESTING

Two rare bone diseases, Hypophosphatasia (HPP) and X-linked hypophosphataemia (XLH), are characterised by abnormalities in routinely measured laboratory parameters, namely alkaline phosphatase (ALP) and serum phosphate. Clinical guidance emphasises the importance of applying age-specific reference ranges when interpreting these parameters, particularly in paediatric populations where physiological values differ substantially from those in adults.

Evidence from Austria points to substantial gaps in the implementation of age-specific reference ranges. In a study of extramural laboratories interpreting a paediatric sample, only 18.2 per cent of laboratories used appropriate paediatric reference ranges for serum phosphate and 40.9 per cent for ALP. Despite accurate measurement of absolute values, 54.5 per cent of laboratories interpreted the phosphate level as normal and 36.4 per cent did so for ALP, even though both were pathological for a child.[34]

Furthermore, persistently low ALP values may be overlooked in clinical practice, despite being widely available as a routine measurement in many parts of primary and specialty care. Laboratory reporting systems and clinical workflows often place greater emphasis on elevated results, which can result in low ALP values not being recognised as a potential hallmark of HPP.

31 Faye et al. (2024). Time to diagnosis and determinants of diagnostic delays of people living with a rare disease: results of a Rare Barometer rerospective patient survey. *European Journal of Human Genetics*, 32(9), 1116-1126.

32 X-linked hypophosphatemia (XLH) is a rare inherited condition where the body cannot properly retain phosphate, a mineral that is essential for building strong bones. As a result, phosphate levels in the blood are too low, leading to soft or weak bones, growth problems in children, and pain or fractures later in life. It is usually diagnosed through blood and urine tests that measure phosphate levels and how the kidneys handle it, along with clinical signs and sometimes genetic testing. Haffner,et al (2019). Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nature Reviews Nephrology*, 15(7), 435-455.

33 Hypophosphatasia (HPP) is a rare inherited condition in which the body lacks sufficient activity of alkaline phosphatase, an enzyme that is essential for building and maintaining strong bones and teeth. As a result, bones can become soft or fragile, leading to skeletal abnormalities, fractures, muscle weakness, and premature loss of teeth. It is usually diagnosed through blood tests showing low alkaline phosphatase level. See Orphanet, https://www.orpha.net/en/disease/detail/436

34 Steininger, J., Jablonska, M., Sagmeister, S., Mindler, G., & Raimann, A. (2025). Inadequate pediatric reference ranges impede the diagnosis of X-linked hypophosphatemia and hypophosphatasia in Austria. *Wiener klinische Wochenschrift*, 137(23), 764-767. https://link.springer.com/article/10.1007/s00508-025-02546-2

studies report average diagnostic delays of around 10 years, nearly twice the average diagnostic delay reported across rare diseases more broadly[35].

This issue extends beyond routine laboratory testing to specialised diagnostic pathways. Fabry disease provides a relevant example as enzyme activity testing is commonly used as an initial diagnostic tool; however, it has limited sensitivity in women, for whom genetic testing is required for confirmation. Evidence indicates that the recommended diagnostic approach to Fabry disease is not always applied consistently in clinical practice. As a result, reliance on enzyme testing alone can lead to missed or delayed diagnoses in female patients[36].

Finally, when primary care lacks the capacity and tools to consider rare diseases early in the diagnostic pathway, diagnostic decisions tend to be driven by statistical probability rather than clinical possibility. As a result, patients are commonly channelled into more prevalent disease pathways, and rare diseases are being systematically overlooked. The case study of lipodystrophy illustrates this dynamic, see Box 5.

Evidence from the EURORDIS Rare Barometer survey further underscores the scale of the issue: 60 per cent of participants report having been misdiagnosed with another physical condition, and 60 per cent report being misdiagnosed with a psychological condition or having their symptoms dismissed[37].

BOX 5

CASE STUDY: MISDIAGNOSIS IN LIPODYSTROPHY

Lipodystrophy is a group of rare disorders characterized by the partial or complete loss of adipose (fat) tissue, often leading to metabolic complications like insulin resistance and diabetes. It can be inherited (genetic) or acquired through autoimmune conditions or HIV medication, resulting in an abnormal, often muscular, appearance.

Delayed diagnosis in lipodystrophy is primarily driven by misdiagnosis within common disease pathways, reflecting non-specific clinical presentation and limited physician awareness. Patients typically present with heterogeneous symptoms, including insulin resistance, diabetes, and abnormal fat distribution, which do not clearly indicate a single underlying condition.

These features are frequently misdiagnosed as type 2 diabetes, given the presence of poor glycaemic control and high insulin requirements. As a result, patients are managed within standard diabetes pathways. While such treatment may provide partial glycaemic (symptomatic) control, it does not address the underlying pathophysiology, and patients often remain poorly controlled and continue to accumulate metabolic complications.

Evidence suggests that correct diagnosis is often reached only after referral to a clinician with greater familiarity with the condition or following a change in healthcare provider. In many cases, patients undergo multiple investigations and referrals across specialties before the underlying condition is identified, and key clinical “red flags” are acted upon[38].

35 Brandi, M. L., et al. (2024). The challenge of hypophosphatasia diagnosis in adults: results from the HPP International Working Group Literature Surveillance. *Osteoporosis International*, 35(3), 439-449.

36 Wilcox, W. R., Oliveira, J. P., Hopkin, R. J., Ortiz, A., Banikazemi, M., Feldt-Rasmussen, U., et al. (2008). Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. *Molecular Genetics and Metabolism*, 93(2), 112–128. https://doi.org/10.1016/j.ymgme.2007.09.013

37 EURORDIS (2025) Results of the Rare Barometer survey: The diagnosis odyssey of people living with a rare disease https://download2.eurordis.org/rarebarometer/Webinar_RB_Diagnosis_Results_30_01_2025.pdf

38 Platt, F. M., d’Azzo, A., Davidson, B. L., Neufeld, E. F., & Tifft, C. J. (2018). Lysosomal storage diseases. *Nature reviews Disease primers*, 4(1), 27.

B2 Fragmented organisation of specialised care

In most European health systems, specialised care is organised along single medical disciplines, typically focused on specific organ systems. This fragmentated organisation often suffers from lack of integration across providers, levels of care, and information systems, which prevents the consolidation of clinical information limiting specialists' ability to recognise rare diseases.

Many rare diseases are characteristically **multi-system**, meaning they affect multiple organs, tissues, and bodily systems simultaneously. While often originating from pathogenic variants in a single gene (monogenic), the protein produced by that gene may be required throughout the body, or disruption of its function may cause a cascade of malfunctions across different organ systems. Lysosomal storage disorders are examples of such multisystem disorders, caused by the accumulation of undegraded substrates within cells, leading to progressive dysfunction across multiple organs, see Box 6.

EURORDIS Rare Barometer data shows that time to diagnosis is significantly longer when rare diseases are multi-system, proxied by rare disorders that affect more than eight body parts, and when they have a genetic origin, see Figure 2. In such cases, time to diagnosis in the healthcare system are significantly longer, i.e. 7.8 years for multi-system diseases and 5.3 years for diseases with genetic origin, when compared to the average time of 4.3 years for all rare diseases.

The same survey indicates that one in four people living with a rare disease have more than eight medical consultations before they receive diagnosis. For people with multi-system diseases, this burden is even common: more than half, 54 per cent, report over eight medical consultations.

BOX 6

CASE STUDY: LYSOSOMAL DISEASE AS A MULTISYSTEM DISORDER[39]

Lysosomal storage disorders (LSDs) are a group of rare, genetic metabolic diseases caused by problems in lysosomes, which are responsible for breaking down and recycling substances within cells. When lysosomal function is impaired, certain materials accumulate inside cells, leading to progressive damage.

Because lysosomes are present throughout the body, this accumulation can affect multiple organs at the same time. LSDs therefore often involve several systems, including the brain and nervous system, bones and muscles, and organs such as the liver and spleen. The heart, lungs, vision, and hearing may also be affected. Symptoms vary between patients and typically worsen over time.

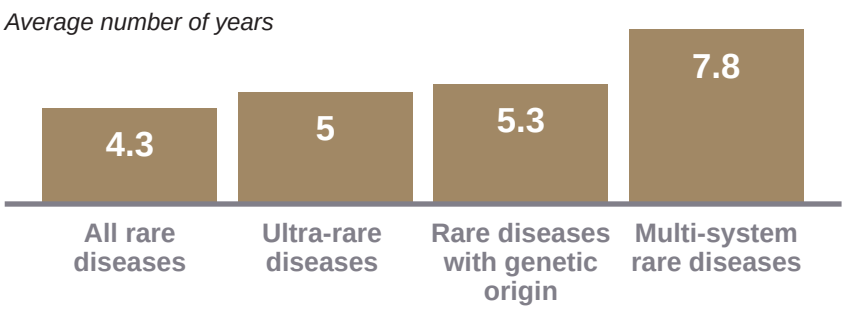
This multisystem and variable presentation can make LSDs difficult to recognise. Patients may present to different specialists depending on their main symptoms, which can delay identification of the underlying condition. Common misdiagnoses for LSDs include rheumatologic and orthopaedic conditions.

Fragmented organisation of specialised care contributes to delayed diagnosis in multisystem rare diseases. For such conditions, referral decisions are often driven by dominant symptoms rather than consideration of an underlying metabolic

39 Platt, F. M., d'Azzo, A., Davidson, B. L., Neufeld, E. F., & Tifft, C. J. (2018). Lysosomal storage diseases. *Nature reviews Disease primers*, 4(1), 27.

or genetic disorder. As a result, patients are assessed by multiple specialists, each focusing on isolated symptoms rather than the underlying disease. In the absence of clear ownership of the diagnostic pathway and integration of clinical information across specialties, recognition of a unifying diagnosis is delayed and often depends on chance encounters with clinicians familiar with the condition.

FIGURE 3: TIME TO DIAGNOSIS IN THE HEALTHCARE SYSTEM



Note: Ultra-rare diseases are defined as diseases with a prevalence of fewer than 1 in 100,000 people. Multi-system rare diseases are defined as rare diseases affecting more than eight body parts.

Source: Authors based on EURORDIS Rare Barometer Data

B3 Limited coordination of referral pathways to specialised expertise

In many European healthcare systems, access to specialised expertise in rare diseases is constrained by how such expertise is organised and accessed.

In many European countries, including France, Germany, Italy, Portugal, Romania, the Netherlands, Finland, Sweden, Spain, and the UK, specialised centres are formally recognised under national legislation and constitute a key component of the diagnostic and treatment pathways for rare diseases[40]. These centres concentrate expertise in a limited number of locations and typically adopt multidisciplinary approaches, enabling healthcare professionals to build experience in rare and complex conditions and improving diagnostic accuracy. Many of these centres are part of European Reference Networks (ERNs)[41], although their organisation varies across countries.

Evidence from Germany on rare inflammatory systemic diseases indicates that, once patients reach a specialised centre, the average time from initial presentation to an expert to confirmed diagnosis is 55 days; however, patients typically arrive at such centres late in the diagnostic pathway, with an average time of 4.2 years from the onset of first symptoms[42]. EURORDIS Rare Barometer data further support this finding. Among the 60 per cent of participants who were eventually referred to a rare disease centre of expertise, the mean time from first medical contact to referral was 3.3 years.[43]

First, **weak coordination between primary and secondary care and specialised centres delays referral to appropriate expertise**. Even when a rare disease is suspected, general practitioners may not know, or may not have visibility of, which centre to refer patients to and may instead follow traditional (organ-specific) referral pathways. Evidence from Germany and the Netherlands shows that clinicians lack clear referral

40 Cannizzo, S., Lorenzoni, V., Palla, I., Pirri, S., Trieste, L., Triulzi, I., & Turchetti, G. (2018). Rare diseases under different levels of economic analysis: current activities, challenges and perspectives. *RMD open*, 4(Suppl 1), e000794.

41 For details see European Reference Network website: https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks_en

42 Willmen, T., Willmen, L., Pankow, A., Ronicke, S., Gabriel, H., & Wagner, A. D. (2023). Rare diseases: why is a rapid referral to an expert center so important?. *BMC Health Services Research*, 23(1), 904. https://pmc.ncbi.nlm.nih.gov/articles/PMC10463573/

43 Dubief J., Faye F., The journey to diagnosis for people living with rare diseases. Dashboard with detailed results of the Rare Barometer survey. EURORDIS-Rare Diseases Europe. May 2024. http://tiny.cc/RB_diag

pathways and awareness of European initiatives such as ERNs[44].

Expert interviews indicate that the **organisation of specialised centres**, beyond their mere availability, systematically **shapes diagnostic timelines for rare diseases, through a trade-off between concentration of expertise and ease of access**. In Italy, the Nordic countries, and the Netherlands rare disease expertise is concentrated in designated centres of expertise. In Belgium and Spain rare disease expertise is shared across multiple hospitals alongside specialised centres. These structural differences influence how and when patients access appropriate expertise.

In centralised models, centres of excellence tend to see a higher volume of rare disease patients, which facilitates learning by doing, strengthens pattern recognition, and may also support multidisciplinary collaboration. This accumulation of experience improves diagnostic accuracy and efficiency once people living with a rare disease reach specialised centres. However, the same concentration of expertise can create access constraints. Referral thresholds may be higher, patients may need to travel to other regions, and limited capacity in specialised centres can lead to waiting times, delaying access to appropriate diagnosis.

In distributed or hybrid models, geographical access to expertise is generally broader, potentially lowering initial barriers to specialist consultation. However, because patient volumes are spread across multiple providers, individual clinicians may encounter fewer rare disease cases. This can limit opportunities for experiential learning and weaken the development of institutionalised expertise. Furthermore, the relevant expertise may be less visible within the healthcare system.

These coordination challenges are often amplified in regionalised health systems.[45] Differences in referral procedures across regions, limited visibility of centres of excellence, and administrative complexity (such as uncertainty over cross-regional funding responsibilities) can further delay referral to specialised centres. Together, these factors reduce timely access to expertise and prolong diagnostic pathways.

B4 Late and inconsistent use of genetic testing

An estimated 72 per cent of rare diseases are of genetic origin[46], making genetic testing a key diagnostic tool. Advances in genomic technologies have expanded the potential for earlier and more accurate identification of rare diseases. Evidence suggests that comprehensive genomic testing, particularly whole-exome and whole-genome sequencing, can improve diagnostic yield and shorten the time to diagnose rare diseases.[47]

However, genetic testing does not improve diagnosis automatically. Its impact depends on how it is used in the healthcare system.

44 Calomme, A., De Prez, V., De Schreye, R., & Wuyts, J. (2025). In-depth analysis of the results of the European Parliament's public consultation on rare diseases (Study PE 778.583). European Parliament, Policy Department for Transformation, Innovation and Health. https://www.europarl.europa.eu/RegData/etudes/STUD/2025/778583/ECTI_STU(2025)778583_EN.pdf

45 In Spain being diagnosed in another region that that of the patient's residence contribute to diagnostic delay. See Benito-Lozano, J., Arias-Merino, G., Gómez-Martínez, M., Ancochea-Díaz, A., Aparicio-García, A., Posada De la Paz, M., & Alonso-Ferreira, V. (2022). Diagnostic process in rare diseases: determinants associated with diagnostic delay. *International Journal of Environmental Research and Public Health*, 19(11), 6456. https://pmc.ncbi.nlm.nih.gov/articles/PMC9180264/

46 Wakap, S.N., Lambert, D. M., Olry, A., Rodwell, C., Guydan, C., Lanneau, V., et al. (2020). Estimating cumulative point prevalence of rare diseases: Analysis of the Orphanet database. *European Journal of Human Genetics*, 28, 165–173.

47 Brlek, P., et al. (2024). Implementing whole genome sequencing (WGS) in clinical practice: advantages, challenges, and future perspectives. *Cells*, 13(6), 504. Vissers, L. E., at al. (2017). A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. *Genetics in Medicine*, 19(9), 1055-1063.

Genetic testing is often introduced too late

First, **comprehensive genetic testing is often introduced late in the diagnostic pathway**. Despite being one of the most effective diagnostic tools available for rare diseases, **access to genetic testing in many European countries is structurally constrained by specialised, referral-based pathways**, where genetic causes are investigated only after conventional diagnostic routes have been exhausted[48]. In the Netherlands, for instance, testing is typically performed in specialised centres, meaning that patients with disorders of suspected genetic origin are often referred for genetic testing only after initial clinical evaluations. In France, genetic testing is subject to strict legal and clinical oversight. Genetic tests must be prescribed by a clinical geneticist consulted directly after referral by a primary or secondary care professional. As a result, access to comprehensive genetic testing is frequently contingent on progressing through multiple stages of the healthcare system first. This delays the point at which patients can benefit from one of the most effective diagnostic tools available, extending the time required to reach a definitive diagnosis.

These referral requirements may be further compounded by workforce constraints. Access to genetic testing is often dependent on a limited number of specialised professionals. In many healthcare systems, genetic tests can only be ordered or interpreted by clinical geneticists, i.e. specialist physicians trained in the diagnosis and management of genetic conditions. As a result, shortages of clinical geneticists can create long waiting times for genetic consultations, delaying test ordering, interpretation of results, and ultimately diagnosis. Genetic counsellors can help expand the capacity of genetic services by supporting patients and families in understanding genetic information, assessing familial risk, and making informed decisions before and after testing. However, the genetic counselling profession is not formally recognised in all European countries,[49] limiting the extent to which these professionals can support genetic service delivery. In systems where genetic testing must be prescribed by a clinical geneticist, such as France, workforce constraints may therefore further delay access to testing and subsequent diagnosis.

Late use of genetic testing delays diagnosis. In a Dutch study of children with suspected genetic neurological disorders, patients first underwent a lengthy sequence of investigations, including laboratory testing, imaging, neurophysiological examinations, metabolic investigations and multiple rounds of gene-by-gene testing. Before reaching a diagnosis, patients experienced on average 23 physician contacts, 4 imaging investigations, 5 genetic tests and more than 50 routine laboratory tests. Yet despite this extensive diagnostic effort, only 7.3 per cent of patients received a diagnosis through the conventional pathway. Most diagnoses were identified only when comprehensive genetic testing was performed, suggesting that earlier access to such testing could have avoided a significant share of the diagnostic burden, without necessarily incurring higher overall costs[50].

By postponing access to comprehensive genetic testing, healthcare systems risk prolonging time to diagnosis and generating avoidable diagnostic costs. Introducing comprehensive genetic testing earlier in the diagnostic pathway can reduce the need for repeated investigations, specialist referrals, and invasive procedures. Evidence from Germany suggests that a substantial share of diagnostic investigations performed before exome sequencing may be avoidable. The study found that 31.8 per cent of metabolic investigations, 27.9 per cent of MRI examinations, and 72.7 per cent of simple genetic tests could potentially have been avoided

48 Vrijenhoek, T., Tonisson, N., Kääriäinen, H., Leitsalu, L., & Rigter, T. (2021). Clinical genetics in transition—a comparison of genetic services in Estonia, Finland, and the Netherlands. *Journal of Community Genetics*, 12(2), 277-290.

49 Pestoff, R., Cordier, C., Darmanin, D., Õunap, K., & van Asperen, C. J. (2026). Harmonizing the genetic counselor profession in Europe. *European Journal of Human Genetics*, 1-3.

50 Vissers, L. E., at al. (2017). A clinical utility study of exome sequencing versus conventional genetic testing in paediatric neurology. *Genetics in Medicine*, 19(9), 1055-1063.

through earlier use of comprehensive exome sequencing, corresponding to average avoidable diagnostic costs of approximately EUR 3,025 per patient[51]. These findings are consistent with recent reviews concluding that exome sequencing can replace lengthy sequential diagnostic pathways and is increasingly supported as a first-tier test for patients with suspected genetic disorders[52].

Delays may occur even when a genetic diagnosis has already been established within a family. For inherited rare diseases with a known affected parent or relative, timely diagnosis should ideally occur before symptom onset through genetic counselling, family mapping, and cascade testing of at-risk family members. In practice, however, these processes are not always implemented systematically in the healthcare system. As a result, children may undergo a conventional diagnostic journey and receive a diagnosis only after symptoms emerge, despite the presence of a known familial risk. This suggests that barriers to timely diagnosis extend beyond access to genetic testing itself and include the effective identification and management of individuals at elevated genetic risk.

Genetic testing is not performed consistently

In addition to delayed access, **variation in the content and interpretation of genetic tests can further affect diagnostic outcomes**. Gene panels are not fully standardised across laboratories, meaning that different providers may test for different sets of variants associated with the same condition. Evidence from the EuroGentest guidelines[53] highlights substantial heterogeneity in next-generation sequencing approaches across laboratories for identical clinical indications. While recent efforts have improved alignment, variation in panel composition and variant interpretation persists, which can affect diagnostic consistency and lead to differences in detection rates across laboratories. Patients receive 'negative' results not because the test failed, but because the database does not include recently identified actionable variants. As a result, a patient tested in one laboratory may receive a different result than if the same test were performed elsewhere. This reflects differences in panel design, curation practices, and the frequency with which panels are updated as new disease-causing variants are identified.

Access to advanced genomic technologies remains uneven

Finally, **access to more advanced diagnostic tools remains uneven across countries**. For instance, whole genome sequencing[54] enables a more comprehensive analysis of genetic variation compared to targeted gene panels and has been shown to increase diagnostic yield, particularly in complex or heterogeneous cases[55]. While some countries, including Germany, Switzerland and Norway, have incorporated genome sequencing into routine care, others continue to rely on pilot programmes or research-based access[56]. Even in systems with more advanced integration, such as England's Genomic Medicine Service, access is governed by formalised rules and predefined diagnostic thresholds, which can limit early or exploratory testing for rare diseases. As a result, the benefits of comprehensive genomic testing are not yet realised consistently across healthcare systems.[57]

51 Klau, J., Abou Jamra, R., Radtke, M., Oppermann, H., Lemke, J. R., Beblo, S., & Popp, B. (2022). Exome first approach to reduce diagnostic costs and time–retrospective analysis of 111 individuals with rare neurodevelopmental disorders. *European Journal of Human Genetics*, 30(1), 117-125.

52 Cirillo, L., & Becherucci, F. (2024). The evolving role of first-tier exome sequencing in medical diagnostics. *Nephrology Dialysis Transplantation*, 39(4), 560-563.

53 Matthijs, G., Souche, E., Alders, M., Corveleyn, A., Eck, S., Feenstra, I., et al. (2016). Guidelines for diagnostic next-generation sequencing. *European Journal of Human Genetics*, 24(1), 2-5. https://www.nature.com/articles/ejhg2015226

54 Advanced diagnostics refers to specialised technologies such as advanced imaging and molecular or genetic testing. See Sustainability Directory (2025) *Advanced Diagnostics Therapeutics*. https://pollution.sustainability-directory.com/term/advanced-diagnostics-therapeutics/ or StudySmarter (n.d.) Advanded diagnostics. https://www.studysmarter.co.uk/explanations/medicine/diagnosis-therapy/advanced-diagnostics/

55 Stark, R., Grzelak, M., & Hadfield, J. (2019). RNA sequencing: the teenage years. *Nature reviews genetics*, *20*(11), 631-656.

56 Ibidem.

57 Hill S, D (2025) The NHS Genomic Medicine Service: achievements in 2024. https://www.england.nhs.uk/long-read/the-nhs-genomic-medicine-service-achievements-in-2024/

B5 Prioritisation of acute, severe, permanent and visible conditions

Healthcare systems prioritise patients based on medical urgency and severity to allocate constrained resources. As a result, conditions with acute and severe presentations are more likely to be assessed and diagnosed timely. By contrast, diseases with similar long-term burden but slow or non-specific progression are less likely to trigger immediate investigation, contributing to delayed diagnosis.

The nature and severity of symptoms influence how quickly a rare disease is diagnosed. Rare conditions that present acutely are more likely to be encountered in emergency or specialised settings, increasing awareness among relevant clinicians and supporting faster recognition. In contrast, rare diseases with slow or non-specific progression are encountered less frequently in a recognisable form, limiting opportunities for pattern recognition and contributing to delayed diagnosis. For example, acquired thrombotic thrombocytopenic purpura (aTTP), a rare blood disorder, is associated with high mortality if untreated and typically presents acutely. Due to the severity and urgency of the condition, clinicians, particularly in emergency and haematology settings, are trained to recognise its key features, enabling rapid diagnosis and treatment, see Box 7. Also, people with acute symptoms were found to be diagnosed faster in the EURORDIS Rare Barometer survey[58].

By contrast, patients experiencing transient or invisible symptoms experience longer time to diagnosis. Transient symptoms are episodic or intermittent, appearing and resolving over time, while invisible symptoms are not outwardly observable, such as fatigue or pain. Reanalysis of the EURORDIS Rare Barometer data shows that people living with rare diseases characterised by such symptoms are diagnosed approximately 1.5 years later than those without these presentations, see Table 1.

TABLE 1: TIME TO DIAGNOSIS IN HEALTHCARE SYSTEM PER TYPE OF SYMPTOMS

Average number of years

SYMPTOM TYPE	YES	NO	DIFFERENCE
Transient	5.0	3.4	1.6
Invisible	4.8	3.3	1.5
Acute	4.5	4.1	0.4
Behavioural	4.3	4.2	0.1
Intellectual disabilities	4.2	4.3	-0.1

Source: Authors based on EURORDIS Rare Barometer Data

BOX 7

CASE STUDY: RARE BLOOD DISORDERS WITH SEVERE PRESENTATIONS HAVE SHORTER TIME TO DIAGNOSIS

Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare, life-threatening haematological condition characterised where blood clots form in small vessels, reducing oxygen flow to organs and destroying platelets. Without prompt treatment, the mortality is up to 90 per cent in Germany[59].

Because aTTP can deteriorate quickly, emergency physicians are trained to recognise key red flags, including low platelets, renal impairment, and fever[60]. When aTTP is suspected, this typically triggers urgent specialist consultation and prompt initiation of treatment. In the UK, 61 per cent of patients commence plasma exchange treatment within 24 hours of hospital presentation[61].

58 Faye et al. (2024). Time to diagnosis and determinants of diagnostic delays of people living with a rare disease: results of a Rare Barometer retrospective patient survey. *European Journal of Human Genetics*, 32(9), 1116-1126. https://doi.org/10.1038/s41431-024-01604-z

59 Bommer, M. et al. (2019). Incidence of acquired thrombotic thrombocytopenic purpura in Germany: a hospital level study. *Orphanet Journal of Rare Diseases*, 14, 260. https://doi.org/10.1186/s13023-019-1240-0

60 Al-Housni, Z. et al. (2025). 2025 focused update of the 2020 ISTH guidelines for management of thrombotic thrombocytopenic purpura. *Journal of Thrombosis and Haemostasis*, 23(11), 3711-3732. https://www.sciencedirect.com/science/article/pii/S1538783625003605

61 Bull, T. et al. (2020). Factors Influencing Time from Initial Presentation to Start of Plasma Exchange (PEX) in Patients with Acute Thrombotic Thrombocytopenic Purpura (TTP). *Blood*, 136(1), 9-10. https://doi.org/10.1182/blood-2020-133371

B6 Limited access to effective treatments

Incentives to diagnose rare diseases in a timely manner are partly shaped by the availability of effective treatments. Out of more than 6,500 rare diseases currently identified, only around 12 per cent have at least one approved treatment option in the EU. More detailed estimates suggest that around 5 per cent benefit from an authorised orphan medicinal product, that is, a medicine with orphan designation that is approved for a life-threatening or chronically debilitating rare disease, where no satisfactory treatment exists, or where the medicine is expected to provide significant benefit over existing options. A further 10 per cent benefit from an approved medicinal product without orphan designation. By contrast, around 88 per cent of rare diseases still lack an authorised treatment option[62].

Recent evidence shows that **when a targeted EMA-approved treatment is available at symptom onset, the diagnosis can be as much as four times faster**[63]. The underlying driver of this pattern is likely to be the perception of the ultimate value of a diagnosis. Where treatments exist, timely diagnosis has clinical value, as timely intervention can improve outcomes and prevent irreversible damage. The availability of effective treatment may also increase disease awareness among clinicians and strengthen incentives to recognise symptoms and pursue diagnostic testing. In such cases, clinicians, patients, and healthcare systems have stronger incentives to pursue diagnosis proactively.

By contrast, when treatment options are limited or absent, the perceived value of timely diagnosis is lower. This affects behaviour across the diagnostic pathway. Clinicians may be less likely to consider rare diseases early in the diagnostic process or to initiate advanced diagnostic testing, particularly when such tests are costly, complex, or require specialist referral. Similarly, healthcare systems may be less inclined to invest in timely diagnostic capacity or screening for conditions where immediate clinical benefit is uncertain, delayed, or difficult to quantify.

However, the absence of effective treatment does not imply the absence of clinical value from timely diagnosis. In autosomal dominant tubulointerstitial

BOX 8

CASE STUDY: CLINICAL VALUE FROM TIMELY DIAGNOSIS, RARE KIDNEY DISEASE[64]

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a rare inherited kidney disease with non-specific and variable clinical presentation, often characterised by chronic kidney disease despite little or no protein in the urine, normal-sized kidneys, and no significant blood in the urine. As these features differ from more common kidney diseases, ADTKD is frequently overlooked or misdiagnosed. Diagnosis usually requires genetic testing using next-generation sequencing (NGS) panels.

Despite the absence of effective therapy, timely diagnosis remains clinically important. It enables implementation of kidney-protective measures, management of subtype-specific complications such as gout or anaemia, and earlier preparation for kidney transplantation before dialysis becomes necessary. It also supports genetic counselling and evaluation of related donors.

62 Orphanet Factsheet. Rare diseases in numbers from the Orphanet database. February 2026. https://www.orpha.net/pdfs/orphacom/cahiers/docs/GB/OrphanetRDFactsheet.pdf

63 Wilsdon, T. et al. (2024) The Economics Cost of Living with a Rare Disease Across Europe. https://media.crai.com/wp-content/uploads/2024/10/28114658/CRA-Alexion-Quantifying-the-Burden-of-RD-in-Europe-Exec-Summary-October2024.pdf

64 Bleyer, A. J., Kidd, K. O., Živná, M., & Kmoch, S. (2025). Autosomal Dominant Tubulointerstitial Kidney Disease: A Review. *American Journal of Kidney Diseases*

kidney disease (ADTKD), for example, timely diagnosis enables the implementation of kidney-protective measures that may slow disease progression, the management of complications, and earlier preparation for kidney transplantation. Because kidney function in ADTKD often declines gradually and predictably, timely diagnosis also allows prospective monitoring, donor evaluation, and transplantation planning before dialysis becomes necessary; see Box 8. Delayed diagnosis may therefore result in avoidable and irreversible renal damage despite the availability of clinically meaningful interventions.

Nevertheless, broader public healthcare system patterns continue to suggest that diseases with recognised and actionable treatment pathways are more likely to be prioritised for timely diagnosis. For example, conditions included in newborn screening programmes are typically selected where timely diagnosis enables effective intervention and improved clinical outcomes. **Diseases without clear or immediate treatment benefits are less likely to be prioritised for early diagnosis** and are instead diagnosed through symptom-driven pathways, which are associated with longer delays.

Whether or not these choices follow explicit policy, in practice they lead to delayed diagnosis, lower testing rates, and reduced prioritisation of rare diseases within clinical workflows. As a result, patients with conditions lacking effective treatments may experience longer diagnostic pathways, even when diagnostic tools are available.

Existing inequalities in rare diseases are reinforced by unequal access to treatment across European countries. The EFPIA W.A.I.T. Indicator measures the time between EMA approval and patient access through national reimbursement systems and shows substantial variation in access to innovative medicines across Europe. Availability varies significantly between countries, with Germany (93 per cent), Austria (85 per cent), and Italy (79 per cent) having considerably higher availability rates than Sweden (49 per cent) or Poland (46 per cent). These differences illustrate persistent cross-country disparities in access to innovative therapies within Europe.[65]

B7 Fragmented health information systems

Diagnostic delay arises not only from the clinical complexity of rare conditions, but from the inability of health systems to aggregate and interpret patient data longitudinally.

As already mentioned, rare diseases frequently present with non-specific, heterogeneous and evolving symptoms that mimic more common conditions. First manifestations may be mild, intermittent or involve multiple organ systems, leading to sequential referrals across different specialists. Each provider may assess isolated symptoms, while the underlying multi-system pattern remains unrecognised.

In such healthcare systems, **patients frequently become informal coordinators of their own care**. They repeat their medical history multiple times, transfer documentation between providers and undergo duplicative testing when prior results are inaccessible. While increasing digitalisation has improved patients' ability to access and share health information electronically, and initiatives such as the European Health Data Space (EHDS)

65 EFPIA (2026) Patients W.A.I.T. Indicator 2025 Survey. https://www.efpia.eu/media/mnfdwzax/efpia-patients-wait-indicator-2025.pdf

seek to further strengthen these capabilities, implementation remains uneven and many patients still lack seamless access to a view of their medical history across providers and care settings.

Beyond the burden placed on patients, **fragmented health information also limits the ability of healthcare systems to make effective use of patient data**. Although electronic health records (EHRs) have become increasingly widespread, interoperability remains incomplete in many European countries[66]. In 2020, Denmark, Estonia, and Finland were identified as the only EU countries with fully operational EHR systems covering almost all healthcare organisations across care sectors, while cross-sector electronic data exchange remained uneven and limited across much of the EU[67]. This means that data remain locked within institutions and cannot be shared or understood across providers, preventing clinicians from accessing a comprehensive, longitudinal view of an individual's medical history, which is a prerequisite for identifying complex rare disease patterns. Lack of interoperability also limits the use of artificial intelligence for incidental case findings.

Even where digital records exist, they are often not designed to support structured rare disease coding such as ORPHAcodes[68] or ICD-11 classification[69]. Rare conditions may be recorded under broad diagnostic categories, using ICD-10 coding, or documented only in free text. As a result, rare diseases become systemically invisible: they cannot be reliably identified across settings, flagged in clinical workflows, analysed for diagnostic pathways, or used to inform digital decision-support tools. The absence of structured rare disease coding prevents healthcare systems from analysing and improving diagnostic pathways.

Across Europe, **adoption of ICD-11 remains uneven and incomplete**. While some countries have initiated pilot implementation and integration into digital health systems, most healthcare systems continue to rely primarily on ICD-10 for clinical coding, reimbursement, and health reporting. The transition to ICD-11 is constrained by interoperability challenges, system adaptation costs, and the complexity of integrating new coding standards into existing health information infrastructures[70]. ORPHAcodes are relatively well established within specialised rare disease infrastructures, including ERNs, registries, and specialised centres, but implementation in routine national health information systems and across all hospitals remains uneven and incomplete across Europe, limiting their potential to systematically identify rare disease patients, support care coordination, generate reliable epidemiological data, and improve the visibility of rare diseases within healthcare systems[71].

66 European Commission, Directorate-General for Communications Networks, Content and Technology. (2021). *Study on Interoperability of Electronic Health Records in the EU (SMART 2019/0056)*. Publications Office of the European Union. https://digital-strategy.ec.europa.eu/en/library/interoperability-electronic-health-records-eu

67 Ibidem. Attached in the sources as a PDF: Thiel, R. et al. (2020) *eHealth, Interoperability of Health Data and Artificial Intelligence for Health and Care in the EU. Lot 1 – Interoperability of Electronic Health Records in the EU (2020).* https://www.orphacode.org/

68 ORPHAcodes are unique identifiers assigned to rare diseases within the Orphanet nomenclature, developed to improve the identification, classification and visibility of rare conditions in health systems. https://www.orphacode.org/

69 International Classification of Diseases (ICD-11) significantly improves rare disease classification, featuring over 5,500 rare diseases with unique identifiers, developed in collaboration with Orphanet. Effective since January 2022, it enables precise coding, enhancing tracking of disease prevalence, research, and reimbursement, offering 10 times more coverage for rare diseases than ICD-10. For details see> Aymé, S., Bellet, B., & Rath, A. (2015). Rare diseases in ICD11: making rare diseases visible in health information systems through appropriate coding. *Orphanet Journal of Rare Diseases*, 10(1), 35.

70 See Boussat, B., Jakob, R., Boyer, L., & Romano, P. S. (2025). Strategic pathways to International Classification of Diseases, 11th Revision, adoption in France and the United States. *Health affairs scholar*, 3(7), qxaf099; World Health Organization. (2024). Press release WHO Advances Implementation and Integration of ICD-11 and Related Medical Classifications and Terminologies. Retrieved May 28, 2024, from https://web.archive.org/web/20240528143046/https:/www.who.int/standards/classifications/classification-of-diseases

71 OD4RD Consortium. (2025). *ORPHAcodes adoption and implementation: State of play in Europe* (September 2025 version). https://od4rd.eu/communication-material/ORPHAcodes_Adoption_Implementation_State-of-Play_September2025_VF.pdf

Delayed diagnosis is a predicable outcome that can be addressed

Delayed diagnosis in rare diseases is not the result of isolated clinical challenges, but a predictable outcome of how healthcare systems are organised. In particular, limited capacity in primary care, fragmented organisation of specialised care, and weak coordination of referral pathways emerge as the most prominent barriers shaping diagnostic delays across Europe. These barriers determine whether rare diseases are considered early in the diagnostic process, how rapidly patients access specialised expertise, and whether clinical information can be consolidated across providers and care settings.

While the underlying barriers are broadly similar across countries, their magnitude may substantially differ depending on how healthcare systems are organised. Differences in the degree of centralisation, organisation and visibility of specialised rare disease centres, access to genetic testing, interoperability of health information systems, and availability of orphan medicinal products shape diagnostic outcomes across the Member States. As a result, similar rare disease patients may experience very different diagnostic pathways and delays depending on the healthcare system in which they are treated.

These findings suggest that European-level initiatives alone are unlikely to be sufficient to address these barriers. Although initiatives such as the European Reference Networks, rare disease education and training, the European Health Data Space data standardisation efforts can support coordination and knowledge sharing, many of the most important determinants of diagnostic delay remain embedded in national healthcare structures and financing arrangements. Reducing delays therefore requires Member State-level policies that improve capacity to diagnose rare diseases in primary care, strengthen referral pathways and integration across care levels, and support earlier and more consistent use of diagnostic tools.

Addressing barriers within national healthcare systems requires a stronger evidence base on where and how barriers and costs arise across the diagnostic pathway. Delayed diagnosis leads to avoidable healthcare expenditure through repeated consultations, misdiagnoses, unnecessary testing, and delayed treatment, while also worsening patient outcomes and increasing indirect and family-borne costs. Better evidence on these costs can help identify where investment in timely diagnosis is likely to generate the greatest value for patients, healthcare systems, and society.

Ultimately, improving timely diagnosis in rare diseases may produce wider system benefits beyond improving outcomes for people living with a rare disease and reducing avoidable costs to healthcare systems due to delayed diagnosis. The spillover effects of approaches and methodologies used in rare disease research, such as registries, regulatory flexibility, patient engagement, or newborn screening, already show a broader impact on healthcare systems[72]. In a similar vein, policies that improve coordination and strengthen diagnostic capacity can also improve the management of other complex and multi-system conditions, contributing to more integrated and resilient healthcare systems across Europe.

72 World Economic Forum. (2026). *Making rare diseases count: Addressing the hidden burden on healthcare systems and societies.* World Economic Forum. https://reports.weforum.org/docs/WEF_Making_Rare_Diseases_Count_2026.pdf

Zebra
Diagnosis Coalition
Health Economics for RD Dx

The Zebra Diagnosis Coalition is a **European multi-stakeholder initiative** that uses **health economic evidence and coordinated policy advocacy** to accelerate **early diagnosis and timely access to care** for people living with rare diseases.

Despite scientific progress, millions of Europeans still experience avoidable diagnostic delays because early detection is not structurally embedded in national health planning and financing systems.

The Coalition drives evidence-based advocacy to make the case for early diagnosis as a structural priority at the national level. We exist to demonstrate both economically and politically that early diagnosis is not a cost, but a high-value investment for patients, healthcare systems, and society, and provide actionable recommendations to policymakers.

Find out more about the work of the Zebra Diagnosis Coalition at

zebradxcoalition.eu

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