Zebra Diagnosis Coalition
Health Economics for RD Dx

BARRIERS TO TIMELY DIAGNOSIS OF RARE DISEASES

FINDINGS FROM THE ZEBRA DX COALITION WHITE PAPER

Report from the Webinar

25 june 2026 • 14:00-15:15 CEST • Online

Moderated by Flaminia Macchia, Senior Advisor, FIPRA

On 25 June 2026 the **Zebra Diagnosis Coalition** hosted the **webinar** to present the findings from our White Paper "Barriers to timely diagnosis of Rare Diseases - How healthcare systems in Europe shape time to rare disease diagnosis".

Moderated by Flaminia Macchia *(Senior Advisor, FIPRA & Zebra Diagnosis Coalition Knowledge Partner)* the event welcomed **over 35 participants online**, including representatives of patient advocacy groups, healthcare professionals, researchers, policymakers, consultants and industry stakeholders.

Opening remarks

Flaminia Macchia explained the positioning the Zebra Dx Coalition within the broader landscape of rare disease diagnosis in Europe, acknowledging the growing number of European and global initiatives in this field, such as HLM4RD and Aspire4Rare. She then underlined the Coalition's own distinctive contribution, translating diagnostic delay into an investment case for health systems, while clarifying what the Coalition is not: neither a broad rare disease policy platform, nor a genomics or newborn screening initiative, nor a product-specific market access exercise. Its added value lies instead in building the health-economic case for early diagnosis of rare diseases at national level, thereby shifting the diagnosis agenda from awareness to investment.

Rare disease diagnosis should no longer be seen primarily as a clinical challenge but as a systemic one. Yet, despite real advances in genomics, the development of European Reference Networks (ERNs), and growing political attention, rare disease patients in Europe still face an average diagnostic delay of nearly five years, 90% of which occurs within the healthcare system itself rather than before patients even seek care. **Hence, the need for stronger evidence on where these barriers arise, what they cost, and where targeted investment would generate the greatest value**: **a gap the Coalition sets out to address**.

> *"The contribution of Zebra Dx Coalition is to move the diagnosis agenda from awareness to investment: from knowing that diagnosis takes too long, to understanding what delay costs and where action would create the greatest value".*
>
> **Flaminia Macchia, Senior Advisor,**
> **FIPRA & Zebra Diagnosis Coalition Knowledge Partner**

Building on this framing, **Jessie Dubief** (Social Research Director & Rare Barometer Lead, EURORDIS - Rare Diseases Europe & Zebra Diagnosis Coalition Knowledge Partner) and **Malwina Mejer** (Senior Economist, Copenhagen Economics & Zebra Diagnosis Coalition Knowledge Partner) presented the White Paper's methodology and findings.

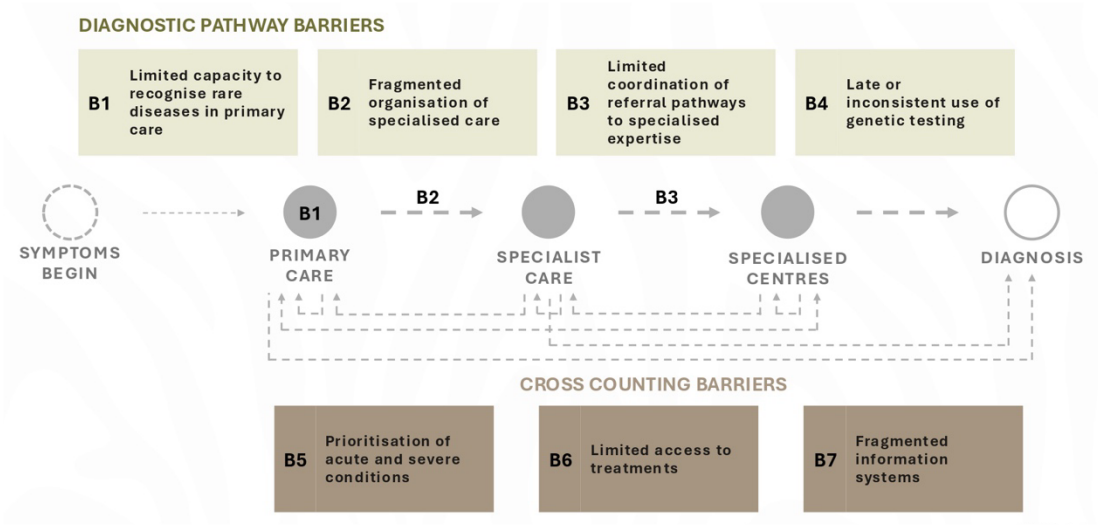
Malwina and **Jessie** highlighted that diagnostic delay in rare diseases is a predictable system failure, not a random clinical phenomenon as 90% of delays occur within the healthcare system itself[1]. On average, the direct medical costs related to diagnosis incurred prior to referral to a specialised centre are more than seven times higher for patients with suspected rare diseases (EUR 26,999 per patient) than for comparator patients (EUR 3,563). These inefficiencies further increase the overall burden, with annual per-person costs for people living with a rare disease estimated at EUR 107,000–121,900 per patient per year[2]. Consequently, delayed diagnosis may increase the financial and caregiving burden on families. Therefore, improving timely diagnosis in rare diseases will likely produce wider system benefits.

They then presented the seven barriers to timely diagnosis identified in the White Paper *(see Annex for details)*:

- B1. Limited recognition of rare diseases in primary care
- B2. Fragmented organisation of 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

While barriers are similar across Europe, their impact and associated costs differ between countries and disease areas. The next step will be to document costs of delayed diagnosis and identify where policy action can have the greatest impact.

[1] 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. [Link]
[2] Wilsdon, T. et al. (2024) The Economics Cost of Living with a Rare Disease Across Europe. [Link]



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(Source: Zebra Diagnosis Coalition | Date: June 2025)

Building on these insights, **Jan Swiderski** (Senior Director, Government Affairs, Kyowa Kirin & Zebra Diagnosis Coalition Partner) explained why the Coalition decided to move from the European evidence base provided by the White Paper to country-level economic studies. The core argument: **national policymakers** (in this context, ministries of health, payers, and regional authorities) **require specific, system-level evidence to act**. They need to know which barrier matters most in their system, what it costs, and where investment would make the greatest difference. As such, a European description of barriers alone is insufficient, and this is exactly where the Zebra Dx Coalition aims to play its role.

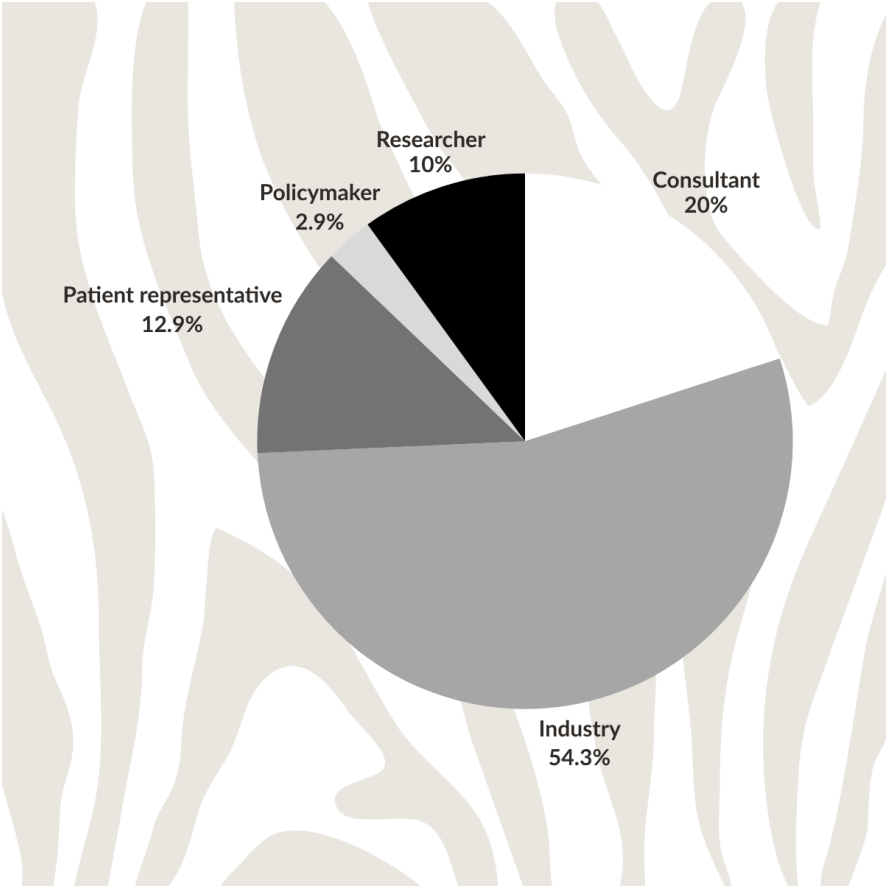
As the **same barrier can manifest very differently depending on how a healthcare system is organised in a given country**. For instance, in centralised systems, the main bottleneck may be patient access to concentrated expertise; in regionalised systems, variation between regions and administrative complexity may dominate; and in primary-care-pressured systems, general practitioners' capacity to recognise rare disease signals may be the binding constraint. And because the cost of diagnostic delay is inseparable from system structure, the Zebra Dx Coalition will draw on Aspire4Rare's healthcare system archetypes to build its own national studies.

> *"The coalition should not simply say "Europe has a diagnosis problem." It should be able to say: in this kind of system, this kind of barrier creates this kind of delay, and that delay creates these costs."*
>
> **Jan Swiderski**
> **Senior Director, Government Affairs, Kyowa Kirin & Zebra Diagnosis Coalition Partner**

Looking ahead, now that the main structural barriers to timely diagnosis have been identified, the Zebra Dx Coalition is ready to move from general statements to concrete evidence. To that end, we will conduct a series of national studies (the evidence-generation phase of our work) aimed at providing real-world data for advocacy activities at both national and EU levels.

In short:

- The white paper tells us what is broken.
- The national studies will show what it costs.
- The next phase can then focus on what should change, which is planned to launch in Q2 2027.



Breakdown of the diversity of stakeholders registered for the Webinar.
(Source: Zebra Diagnosis Coalition | Date: June 2025)

Zebra
Diagnosis Coalition
Health Economics for RD Dx

ABOUT US

The Zebra Diagnosis Coalition is a European multi-stakeholder initiative launched on 21 April 2026, with the aim of advancing early diagnosis of rare diseases through rigorous health-economic evidence, translated into concrete policy action at national, regional and, ultimately, global level. To this end, it brings together, today, public affairs experts, health economists, clinicians, policymakers and representatives from the pharmaceutical industry, including EURORDIS-Rare Diseases Europe, Copenhagen Economics, FIPRA International, EUCOPE, Kyowa Kirin, AstraZeneca, Sanofi, Argenx and Chiesi Group, combining their expertise to build the evidence base and support its translation into, first, national health policy/policies across Europe.

Zebra Diagnosis Coalition
Health Economics for RD Dx

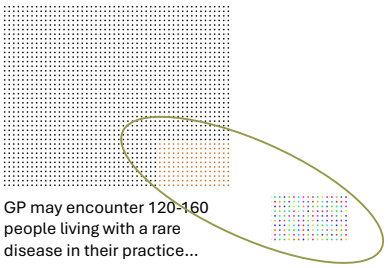
Annex: Barriers to Diagnosis

DIAGNOSTIC PATHWAY BARRIERS

B1 Limited capacity in primary care

- **Limited exposure of GPs to a specific rare disease[1]**
- Limited awareness of rare disease among GPs
- Clinical recognition biases and challenges
- Missed signals in routine laboratory testing

Opportunities to build diagnostic expertise in rare disease in primary care are limited[2]



GP may encounter 120-160 people living with a rare disease in their practice...

... but rarely two people living with the same rare disease

Note: (1) Calomme et al. (2025). / (2) Calomme et al. (2025).

DIAGNOSTIC PATHWAY BARRIERS

B1 Limited capacity in primary care

- Limited exposure of GPs to a specific rare disease
- **Limited awareness of rare disease driven among GPs[1]**
- Clinical recognition biases and challenges
- Missed signals in routine laboratory testing

Tumiene et al. Orphanet Journal of Rare Diseases (2022) 17:441
https://doi.org/10.1186/s13023-022-02527-y

Orphanet Journal of Rare Diseases

POSITION STATEMENT Open Access

Rare disease education in Europe and beyond: time to act

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Abstract

People living with rare diseases (PLWRD) still face huge unmet needs, in part due to the fact that care systems are not sufficiently aligned with their needs and healthcare workforce (HWF) along their care pathways lacks competencies to efficiently tackle rare disease-specific challenges. Level of rare disease knowledge and awareness among the current and future HWF is insufficient. In recent years, many educational resources on rare diseases have been developed, however, awareness of these resources is still limited and rare disease education is still not sufficiently taken into account by some crucial stakeholders as academia and professional organizations. Therefore, there is a need to fundamentally rethink rare disease education and HWF development across the whole spectrum from students to generalists, specialists and experts, to engage and emp
a common coherent and complementary strategy
Special consideration should be also given to the r
training for integrated multidisciplinary care, patien
learning and fostering of social accountability to en
strategy has to be developed and implemented by
ties, medical and nursing schools and their associat
patient organizations, other organizations and instit
policy bodies.

Keywords: People living with rare disorders, Rare d
empowerment, Interprofessional learning, Highly-s

Level of rare disease knowledge and awareness among the current and future health workforce is insufficient.

Awareness of (existing educational resources) is still limited and rare disease education is still not sufficiently taken into account by some crucial stakeholders as academia and professional organizations.

Note: (1) Tumiene et al. (2022).

DIAGNOSTIC PATHWAY BARRIERS

B1 Limited capacity in primary care

- Limited exposure of GPs to a specific rare disease
- Limited awareness of rare disease driven among GPs
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- Missed signals in routine laboratory testing

Age- and gender-related factors affect timely diagnosis

Symptom recognition and attribution

In adolescents, symptoms may be normalised or misattributed to growth, puberty, fatigue, or psychological factors[1]

In females, symptoms such as pain and fatigue, are more often interpreted as non-specific or benign[2]

Health-seeking behaviour

Adolescents have lower healthcare utilisation autonomy and depend on parents/guardians[3]

Gender differences in health-seeking can work both ways, but for certain conditions, women may delay escalation if symptoms are recurrent or previously dismissed[4]

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 delayed re-presentation[5]

Note: (1) See for example: Cardinali, P., Migliorini, L., & Rania, N. (2019); (2) Women and Equalities Committee (2024); (3) World Health Organization (2021); (4) Westergaard, D., Moseley, P., Sørup, F. K. H., Baldi, P., & Brunak, S. (2019); (5) UN (2026)

DIAGNOSTIC PATHWAY BARRIERS

B1 Limited capacity in primary care

- Limited exposure of GPs to a specific rare disease
- Limited awareness of rare disease driven by educational gaps
- Clinical recognition biases and challenges
- **Missed signals in routine laboratory testing**

Missed signals in routine laboratory testing can delay time to diagnosis

Case study: Rare bone diseases[1]

- HPP and XLH can be identified through abnormalities in routinely measured laboratory parameters (alkaline phosphatase and serum phosphate)
- Accurate diagnosis requires age-specific reference ranges, particularly in children
- Evidence from Austria suggests that paediatric reference ranges are frequently not applied, leading to abnormal results being interpreted as normal
- Results of the study shows that
  - 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

Note: (1) Steininger et al. (2025).

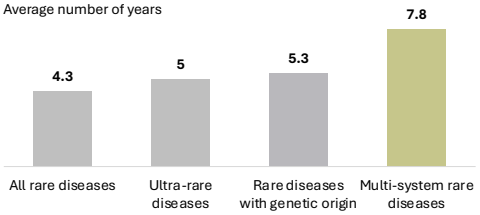
DIAGNOSTIC PATHWAY BARRIERS

B2 Fragmented organisation of specialised care

- In 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** limiting specialists' ability to recognise rare diseases

Patients with multi-system rare diseases, which affect multiple organs, tissues and body systems, experience longer times to diagnosis

Figure 1: Time to diagnosis in the healthcare system
Average number of years



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

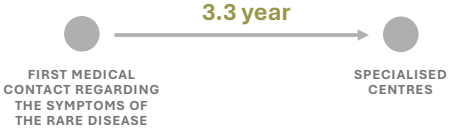
Source: Authors based on EURORDIS Rare Barometer Data.

DIAGNOSTIC PATHWAY BARRIERS

B3 Limited coordination of referral pathways

- Clinicians lack clear referral pathways at national level
- Organisation of specialised centres, impact time to diagnosis, through a trade-off between concentration of expertise (Sweden, Italy) and geographical ease of access (Belgium)
- Coordination challenges are often amplified in regionalised health systems (Italy, Spain)

Patients reach a specialised centre on average 3.3 years following the first medical contact[1]



Source: Authors based on EURORDIS Rare Barometer Data. Based on responses from 60 per cent of participants who were eventually referred to a rare disease centre of expertise

Note: (1) Dubief J. & Faye F. (2024)

DIAGNOSTIC PATHWAY BARRIERS

B4 Late and inconsistent use of genetic testing

- Genetic testing is often structurally constrained by specialised, referral-based pathways, delaying the time to diagnosis (France, Netherlands)
- Referral requirements may be further compounded by workforce constraints (Spain, France)
- Genetic testing is not performed consistently as gene panels are not standardised and regularly updated
- Access to advanced genomic technologies in routine care remains uneven across countries

Late use of genetic testing can generate avoidable healthcare costs

Case study: Diagnosis of genetic neurological disorders, NL[1]

- 150 patients presenting with complex neurological disorders of suspected genetic origin
- Before reaching a diagnosis, patients experienced on average:
  - 23 physician contacts
  - 4 imaging investigations
  - 5 genetic tests
  - 50+ routine laboratory tests
- Only 7.3 per cent of patients received a diagnosis through the conventional pathway
- 29.3 per cent received diagnosis using whole genome sequencing

Note: (1) Vissers at al. (2017)

CROSS CUTTING BARRIERS

B5 Prioritisation of acute, severe, permanent and visible conditions

- Healthcare systems prioritise patients based on medical urgency and severity to allocate constrained resources
- Rare diseases with permanent or visible symptoms are also diagnosed faster
- **Prioritisation shapes clinical exposure and familiarity**

Rare conditions that present acutely are more likely to be encountered in emergency or specialised settings, increasing awareness and supporting faster diagnosis

Case study: Rare blood disorders with severe presentations have shorter time to diagnosis[1]

- Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare, life-threatening blood disorder causing small blood clots throughout the body
- Without prompt treatment, mortality can reach 90%
- Emergency physicians are trained to recognise key warning signs, including low platelet count, renal impairment and fever
- Suspected aTTP typically triggers urgent specialist consultation and immediate treatment
- In the UK, 61 per cent of patients start plasma exchange within 24 hours of hospital presentation

Note: (1) Bommer et al. (2019), Al-Housni et al. (2025) and Bull et al. (2020).

CROSS CUTTING BARRIERS

B5 Prioritisation of acute, severe, permanent and visible conditions

- Healthcare systems prioritise patients based on medical urgency and severity to allocate constrained resources
- Rare diseases with permanent or visible symptoms are also diagnosed faster
- **Prioritisation shapes clinical exposure and familiarity**

Patients with rare diseases presenting with transient or invisible symptoms experience longer time to diagnosis

Table 2. Time to diagnosis in healthcare system per type of symptoms
Average number of years

TYPES OF SYMPTOMS	YES	NO	DIFFERENCE
Transient symptoms	**5**	**3.4**	**1.6**
Invisible symptoms	**4.8**	**3.3**	**1.5**
Acute symptoms	4.5	4.1	0.4
Behavioural symptoms	4.3	4.2	0.1
Intellectual disabilities	4.2	4.3	-0.1

Source:: Authors based on EURORDIS Rare Barometer Data.

CROSS CUTTING BARRIERS

B6 Limited access to effective treatments

- Incentives to timely diagnosis are shaped by treatment availability
- Limited treatment options can reduce the perceived value of early diagnosis, making clinicians less likely to prioritise rare diseases or pursue advanced diagnostic testing
- Healthcare systems may be less likely to invest in diagnostic capacity or screening when the benefits of early diagnosis are uncertain, delayed or difficult to measure

When a targeted EMA-approved treatment is available at symptom onset, the diagnosis can be as much as four times faster.[1]

Notes: (1) Wilsdon et al. (2024).

CROSS CUTTING BARRIERS

B7 Fragmented health information systems

- Limited interoperability and data sharing
- Inadequate coding and classification of rare diseases
- System adaptation costs

Rare diseases often manifest across multiple consultations, providers and specialties

Because information is dispersed and disconnected, no single clinician sees the full picture to deliver timely diagnosis