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ARTICLE

Diagnostic delay in inherited metabolic diseases: Insights from the U-IMD registry

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ABSTRACT

Purpose: Early diagnosis and timely initiation of treatment have been shown to be crucial to improve clinical outcomes in individuals with inherited metabolic diseases (IMDs). However, comprehensive data on the diagnostic process and the potential diagnostic delay in IMDs are scarce. This study aims to systematically investigate the diagnostic process in IMDs.

Methods: Data were obtained from the Unified European registry for Inherited Metabolic Diseases (U-IMD), the patient registry of the European Reference Network MetabERN.

Results: Data were available for 3747 individuals with confirmed diagnosis of one of 345 IMDs. Median age at symptom onset was 120 days. The majority of participants were diagnosed after presenting with symptoms, median diagnostic delay in this group was 270 days, with 47.6% experiencing a diagnostic delay of at least 1 year. Diagnostic delay did not seem to have changed substantially within the last 2 decades in this cohort; however, it varied greatly among single IMDs and different IMD disease groups.

Conclusion: Diagnostic delay and concomitantly delayed start of specific therapies is a significant risk of poor outcome for individuals with IMDs, highlighting the urgent need to expand newborn screening programs and to establish (ultra-)rapid genome sequencing in critically ill children.

Introduction

More than 2000 inherited metabolic diseases (IMDs) have been identified to date, many of which present with a heterogenous spectrum of symptoms.[1] This clinical variability poses significant diagnostic challenges for all clinicians. However, early diagnosis, particularly through newborn screening (NBS) and subsequent early start of

The names of the U-IMD Consortium will appear at the end of the article.

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treatment have been shown to be important to improve clinical outcomes in different IMDs.[2-6] This benefit is expected to become even more important in the future, considering the increasing development of new therapies.

Despite the expansion of NBS programs, most IMDs currently remain outside the scope of these programs. Moreover, data on the diagnostic process for IMDs and the potential diagnostic delay in IMDs are scarce. Existing evidence from selected IMDs and other rare diseases suggests that the time from onset of symptoms to a confirmed diagnosis may span several years, often referred to as a "diagnostic odyssey," or that children are not correctly diagnosed at all, increasing the risk of recurrence for future pregnancies.[7-14] Several factors have been shown to influence the diagnostic process in rare diseases, such as sex or the age at onset of symptoms.[7,8]

In recent years, the diagnostic odyssey of individuals with rare diseases is thought to have shortened because of improvement in diagnostic technologies, especially next-generation sequencing, and increased awareness and knowledge. Nonetheless, delayed diagnosis remains a substantial health care burden.[7,13,15,16] Of note, 33 IMDs have recently been identified as priority rare diseases in which a delay in diagnosis would be particularly detrimental to the patient.[17] Acknowledging the burden of a diagnostic delay, The International Rare Diseases Research Consortium has made it one of its 3 goals for 2027 that "all patients coming to medical attention with a suspected rare disease will be diagnosed within one year" and highlighted the role of rare disease networks in measuring and evaluating the time to diagnosis to reach this ambitious goal.[18] The European Rare 2030 Foresight Study even aims at a diagnosis within "six months of coming to medical attention."[19]

The Unified European Registry for Inherited Metabolic Disorders (U-IMD), the official registry of the European Reference Network for Hereditary Metabolic Disorders (MetabERN), was established to systemically and prospectively collect clinical data on individuals with all known IMDs according to the Findable, Accessible, Interoperable, and Reusable (FAIR) principles.[20] Patient registries, such as U-IMD, are increasingly recognized as essential resources to evaluate diagnosis, treatment, and prognosis in rare diseases[21] and through the collaborative efforts of health care centers across Europe, U-IMD offers a unique, comprehensive data set.

This study evaluates the diagnostic process across a large, pan-European cohort of individuals with IMDs and therefore can provide valuable up-to-date insights for the international IMD research community and clinicians involved in diagnosing IMDs. Using structured data from U-IMD, this study aims to quantify diagnostic delay in IMDs and to identify potential determinants that contribute to this delay.

Abbreviations

ANOVA – Analysis of Variance
FAIR – Findable, Accessible, Interoperable, and Reusable
Fig. – Figure
IMD – inherited metabolic disease
ICIMD – International Classification of Inherited Metabolic Disorders
NA – not available
NBS – newborn screening
NGS – next-generation sequencing
MetabERN – European Reference Network for Hereditary Metabolic Disorders
U-IMD – Unified European Registry for Inherited Metabolic Disorders

Materials and Methods

U-IMD registry

The U-IMD registry, the official patient registry of MetabERN, has been initiated in 2018 with funding of the EU Executive Agency for Consumer, Health, Agriculture, and Food and is coordinated by Heidelberg University Hospital (local ethics committee approval no S-387/2018). MetabERN and non-MetabERN health care providers are part of the project. The U-IMD registry is requiring each member to obtain an ethics committee approval for the study protocol and written informed consent forms according to local standards.[20] Twenty-five different metabolic centers in Europe contributed to the data set used in this study (Supplemental Table 1). Data were extracted from the U-IMD registry at a cut-off date of August 20, 2025.

Statistics

Pseudonymized data were extracted from the U-IMD registry and were used for the analysis. Diagnostic delay was defined as the time between the age of onset of symptoms and the age of diagnosis. For cases where symptom onset was indicated as "at birth," 0 days were used for the calculation and for cases where diagnosis was indicated as "at birth" or "prenatal," an age at diagnosis of 0 days was used for the calculation.

We performed a descriptive analysis of the following variables: sex (female/male, clinician assignment), disease, International Classification of Inherited Metabolic Disorders (ICIMD) disease group, diagnostic mode (NBS, prenatal high-risk screening, postnatal high-risk screening, and clinical presentation), age at onset of symptoms (defined as the age at which the first occurrence of clinical signs or symptoms attributable to the underlying metabolic disorder were recorded [eg, metabolic decompensation, neurological symptoms, or organ-specific manifestations]), age at

diagnosis, and age at first contact with a specialized metabolic center. Because of implausible data entries, data from 146 participants were excluded from the analysis.

Statistical analysis was done using the software R (version 4.5.1).[22] Nonparametric tests were used for group comparisons due to non-normal distribution of diagnostic delay (Whitney Mann U-Test). Correlations between age at symptom onset and diagnostic delay were assessed using Spearman's rank correlation.

Kaplan-Meier estimation of symptom onset: Participants with a documented age at symptom onset were classified as symptomatic (status = 1) at the recorded age. Participants without a recorded onset age were considered asymptomatic (status = 0) and censored at the age corresponding to the date of their last clinical record entry. The resulting data set was analyzed using Kaplan-Meier survival estimates and Cox proportional hazards models.

Temporal trends in diagnostic delay were assessed using quantile regression with year of symptom onset as a numerical variable (R package "VGAM," version 1.1-13).[23] To account for right censoring and to avoid underestimating diagnostic delays for more recent cases, a maximum delay period of 5 years and an endpoint (2019) at which the delay could be fully observed by the end of the study period was chosen. This ensures that all cases had sufficient follow-up time to be diagnosed and allows a statistically valid comparison across years. Because only few cases per year with symptom onset before 2000 were recorded, the analysis was restricted to cases from 2000 onward.

Results

Data were available from 3747 participants with a total of 345 confirmed IMDs. 52.1% ($n = 1950$) of them were male and 47.9% ($n = 1796$) female. As expected, Phenylalanine hydroxylase deficiency (phenylketonuria, $n = 603$), Medium-chain acyl CoA dehydrogenase deficiency (MCADD, $n = 204$), and Alpha-galactosidase deficiency (Fabry disease, $n = 141$) were the most frequently reported single IMDs in the study sample. Participants were identified through NBS (37.2%; $n = 1393$), high-risk family testing due to an index patient, performed prenatally (0.8%, $n = 30$) or postnatally (7.8%, $n = 293$), whereas the majority (54.2%; $n = 2031$) was diagnosed following the onset of symptoms (Supplemental Figure 1). A complete list of included participants per disease and distribution of mode of diagnosis for each disease is provided in Supplemental Table 2.

Median age at diagnosis was 9 days in the NBS group and 1095 days in the clinical presentation group (Mann-Whitney U-test, $P < .001$). Notably, 53.2% of individuals diagnosed through NBS remained asymptomatic at last follow-up. Supplemental Table 3 compares median age at diagnosis and percentage of asymptomatic individuals between participants diagnosed through NBS or after clinical presentation (only diseases with data available for at least 10 individuals in each diagnostic group were included). Across all of these diseases, median age at diagnosis was consistently lower in the NBS group and a substantial proportion of individuals diagnosed through NBS remained asymptomatic.

Among individuals with documented age at onset of symptoms, median age at symptom onset was 120 days (mean 1504, IQR 0-730, range 0-29200; $n = 2406$). Figure 1 shows a Kaplan-Meier estimate of age at symptom onset, including all participants ($n = 3747$) and censoring participants without a recorded onset age at the age corresponding to the date of their last clinical record entry.

For all further analyses of diagnostic delay, only data from participants diagnosed after the onset of symptoms were considered ($n = 1670$). Among these participants, the median diagnostic delay was 270 days (mean 1136, IQR 6-1095, range 0-18,980, $n = 1670$). Overall, 795 of these individuals (47.6%) experienced a diagnostic delay of at least 1 year, whereas in 461 patients with IMDs (27.6%), diagnostic delays of at least 3 years was found (Figure 2).

The highest percentage of individuals experiencing a diagnostic delay was found (1) in the ICIMD subgroup "Complex Molecule and Organelle Metabolism," such as OPA1 deficiency, Heparan N-sulfatase deficiency (mucopolysaccharidosis Type III/Sanfilippo disease type A) and Iduronate 2-sulfatase deficiency (mucopolysaccharidosis Type II), (2) in the ICIMD subgroup "Intermediary Metabolism: Nutrients," such as Cystathionine beta-synthase deficiency (Classical homocystinuria) and Glucose transporter 1 deficiency, and (3) in Mitochondrial tRNA(Leu) 1 deficiency (ICIMD subgroup: "Intermediary Metabolism: Energy") (Table 1).

In contrast, IMDs with the lowest rates of diagnostic delay included disorders with acute metabolic decompensation, such as methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency, fumarylacetoacetase deficiency (Tyrosinemia Type I), trifunctional protein subunit alpha deficiency, propionic acidemia due to propionyl-CoA carboxylase deficiency (both alpha and beta subunits), galactose-1-phosphate uridyltransferase deficiency (Galactosemia), and glucose-6-phosphatase deficiency (Glycogen storage disease type Ia), all within the "Intermediary Metabolism: Nutrients" subgroup (Table 1).

To further characterize the diagnostic process, we assessed the interval between symptom onset and first contact with a specialized metabolic center. The median duration of this interval was even larger than the diagnostic delay (333 days, mean 1417, IQR 59-1449, range 0-21,661, $n = 1638$), with 69.8% of individuals being diagnosed only after contact with a specialized metabolic center.

Age at symptom onset and diagnostic delay were correlated. Although diagnostic delay showed considerable variability across age at onset, individuals with symptom onset later in life tended to experience longer delays (Spearman's rho = 0.18, $P < .001$; linear regression:

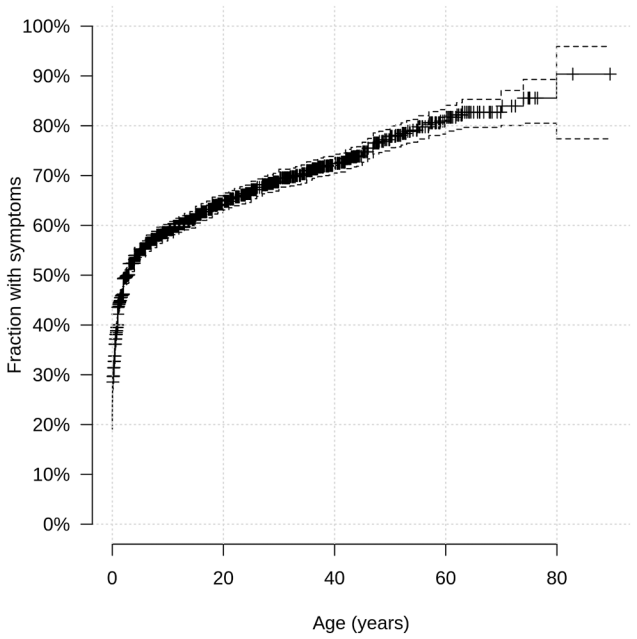

Figure 1 Kaplan-Meier estimate of age at symptom onset. The curve shows the cumulative proportion of individuals with symptoms ($N = 3747$) as a function of age at symptom onset, with 95% confidence intervals (dashed lines). Patients without a recorded onset age were censored (vertical lines) at the age corresponding to their last clinical record entry.

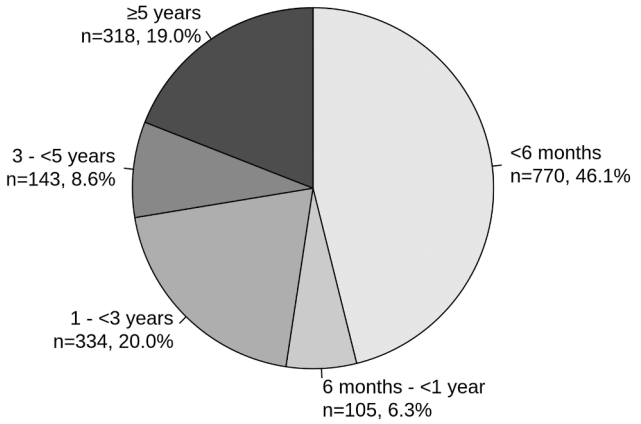

Figure 2 Distribution of diagnostic delay among individuals with IMDs diagnosed after symptom onset. Among 1670 patients diagnosed after clinical presentation with symptoms, 46.1% were diagnosed within 6 months, 6.3% within 6 months to 1 year, 20% within 1 to 3 years, 8.6% within 3 to 5 years, and 19% experienced a diagnostic delay of at least 5 years. IMDs, inherited metabolic diseases.

$\beta = 0.11$, $P = .001$; $R^2 = 0.04$). A stratified analysis by age at symptom onset revealed that individuals with childhood-onset (age at symptom onset below 18 years) had a significantly shorter median diagnostic delay (84 days) compared with those with symptom onset in adulthood (age at symptom onset $\geq$ 18 years), who experienced a median diagnostic delay of 365 days (Mann-Whitney U-test, $P <$ .001).

Diagnostic delay did not differ by sex (female: median 330 days, IQR 3-1168, range 0-18,980; male: median 243 days, IQR 8-1095, range 0-17,490, P value (Mann-Whitney U-test) = 0.56) (Supplemental Figure 2). When stratified by inheritance mode according to iembase.org,[1] diagnostic delay did not differ by sex in autosomal inherited IMDs (female: median 360 days, IQR 6-1228, range 0-18,980; male: median 213 days, IQR 8-1157, range 0-17,490, P value (Mann-Whitney U-test) = 0.56). Analyses restricted to X-linked disorders likewise did not show an overall sex difference in diagnostic delay (female: median 60 days, IQR 0-646, range 0-18,980; male: median 365 days, IQR 1-869, range 0-9855, Mann-Whitney U-test, $P = .07$).

To evaluate potential changes in diagnostic delay over time, we plotted the delay against the date of symptom onset. To minimize bias from right censoring in more recent years, only cases with a maximum possible delay of 5 years and symptom onset between 2000 and 2019 were included. Within this model, no temporal trend in diagnostic delay was observed (Figure 3), except that beginning with year 2016, diagnostic delays above the 75th percentile of 500 days are less frequent. Of note, we did not find any evidence supporting the notion that overall median diagnostic delay for symptomatic individuals with IMDs actually decreased during this time period.

Discussion

This systematic, registry-based study investigates the diagnostic process across a broad spectrum of IMDs in a large multinational cohort. The mode of diagnosis emerged as a key determinant of the diagnostic process, with individuals identified through NBS typically being diagnosed within the first days of life and often remaining asymptomatic. However, despite the continuous expansion of NBS panels to include an increasing number of IMDs, most participants in this study were diagnosed only after the onset of symptoms and a subsequent targeted diagnostic work up. In this group a diagnostic delay of 1 year or more affected almost half of all participants, confirming results of studies on rare diseases in general[7,13] and demonstrating that we are still far from achieving the ambitious goals of rare disease organizations to provide a diagnosis in less than 12 or even 6 months to all individuals.[18,19]

Most individuals were diagnosed after the first contact with a specialized center, indicating that a considerable proportion of the total diagnostic delay in individuals with IMDs occurs before the first contact with a specialized metabolic center. This highlights early phases of the diagnostic journey—particularly the time between symptom onset and appropriate referral—as a critical bottleneck. These observations are supported by previous studies, showing that (1) individuals with rare diseases often consult multiple health care providers before receiving a correct

Table 1 Key figures on diagnostic delay among individuals diagnosed after symptom onset for International Classification of Inherited Metabolic Disorders (ICIMD) disease groups and individual IMDs (with data available for at least 10 individuals per disease)

ICIMD Disease Group	Disease	*n*	Median Diagnostic Delay (Days)	Q1	Q3	Diagnostic Delay ≥ 1 Year (Percentage)
	All	1670	270	6	1095	47.6
Cofactor and mineral metabolism		108	30	0	262	78.7
	Methylmalonic aciduria and homocystinuria. cblC type	23	23	5	61	17.4
	5,10-methylenetetrahydrofolate reductase deficiency	11	0	0	4	9.1
Complex Molecule and Organelle Metabolism		437	589	120	1735	35.9
	OPA1 deficiency	13	2555	1460	5475	100
	Beta-hexosaminidase subunit alpha deficiency	16	2920	734	6205	81.3
	N-acetylgalactosamine 6-sulfatase deficiency	15	730	365	730	80
	Heparan N-sulfatase deficiency	12	913	356	1325	75
	Beta-galactosidase-1 deficiency	11	950	243	1259	72.7
	Iduronate 2-sulfatase deficiency	21	370	120	730	71.4
	Acid sphingomyelinase deficiency	11	402	138	1095	63.6
	Niemann-Pick disease type C1	30	905	68	2099	63.3
	Alpha-galactosidase A deficiency	36	730	0	1916	61.1
	Glucocerebrosidase deficiency	53	365	0	1460	58.5
	Alpha-glucosidase deficiency	44	365	0	1825	52.3
	Alpha-iduronidase deficiency	29	360	60	1095	48.3
	PMM2-CDG	32	273	60	564	40.6
Intermediary Metabolism: Energy		207	560	120	2555	36.7
	Mitochondrial tRNA(Leu) 1 deficiency	32	3467	1095	8030	84.4
	NADH dehydrogenase core subunit 5 deficiency	10	365	365	873	80
	Creatine transporter deficiency	14	365	194	1598	64.3
	Pyruvate dehydrogenase E1 alpha deficiency	14	318	13	143	50
Intermediary Metabolism: Nutrients		684	60	0	723	64.6
	Cystathionine beta-synthase deficiency	40	773	365	3103	82.5
	Glucose transporter 1 deficiency	23	1460	367	3355	73.9
	Homogentisic acid oxidase deficiency	10	915	203	2343	70
	Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency	12	795	315	1529	66.7
	Hepatic phosphorylase kinase α 2 subunit deficiency	31	365	108	1340	54.8
	Carnitine palmitoyltransferase 2 deficiency	11	323	0	1095	45.5
	Very long-chain acyl CoA dehydrogenase deficiency	11	14	1	729	45.5
	Glutaryl-CoA dehydrogenase deficiency	25	30	0	1095	40
	Phenylalanine hydroxylase deficiency	13	175	14	420	38.5
	Medium-chain acyl CoA dehydrogenase deficiency	13	1	0	730	38.5
	Aldolase B deficiency	29	210	0	550	34.5
	Amylo-1.6-glucosidase (debrancher) deficiency	24	180	23	394	29.2

(continued)

Table 1 Continued

ICIMD Disease Group	Disease	*n*	Median Diagnostic Delay (Days)	Q1	Q3	Diagnostic Delay ≥ 1 Year (Percentage)
	Branched-chain ketoacid dehydrogenase E1 beta deficiency	11	1	0	198	27.3
	Ornithine transcarbamylase deficiency	54	0	0	158	22.2
	Methionine synthase deficiency	11	90	35	305	18.2
	Argininosuccinate lyase deficiency	12	3	0	61	16.7
	Glucose-6-phosphate transporter deficiency	17	90	60	125	11.8
	Propionic acidemia due to propionyl-CoA carboxylase subunit beta deficiency	18	5	1	120	11.1
	Glucose-6-phosphatase deficiency	29	30	0	60	10.3
	Galactose-1-phosphate uridyltransferase deficiency	33	7	2	12	9.1
	Trifunctional protein subunit alpha deficiency	16	0	0	30	6.3
	Fumarylacetoacetase deficiency	17	15	0	60	5.9
	Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency	14	1	0	3	0
	Argininosuccinate synthetase deficiency	10	2	0	35	0
Lipid Metabolism and Transport		148	285	30	1095	51.4
	X-linked adrenoleukodystrophy and adrenomyeloneuropathy	14	913	365	1734	85.6
	Mevalonate kinase deficiency (severe)	10	423	225	2215	60
	Smith-Lemli-Opitz syndrome	89	150	28	730	38.2
Metabolic Cell Signaling		41	670	30	2555	36.6
	ATP-sensitive potassium channel regulatory subunit deficiency	16	44.5	1	411	31.3
Metabolism of Heterocyclic Compounds		43	180	0	1460	53.5
	Porphobilinogen deaminase deficiency	18	183	0	913	50
Intermediary Metabolism: Others		2	765	383	1148	50

diagnosis, (2) general practitioners and pediatricians often lack profound knowledge about rare diseases, and (3) timely referrals are impeded by geographic or structural disparities in access to specialized care.[8,16,24,25]

As expected, the diagnostic delay varied greatly between different IMDs and ICIMD disease groups. Cystathionine beta-synthase deficiency, for example, also known as classic homocystinuria, was one of the diseases with the largest median diagnostic delay in this data set, confirming results from a previous study.[26] Because of the availability of treatment options and the potential damage of a delayed therapy start, it was already previously described as a priority rare disease for the development of solutions reducing the diagnostic delay.[17] Of note, and in contrast to many other diseases with a large diagnostic delay in our data set, Cystathionine beta-synthase deficiency has diagnostic biomarkers that are easy to determine in blood: homocysteine and methionine.[27] This underscores that broad availability of biomarkers alone is insufficient to ensure timely diagnoses for affected individuals.

In general, diseases with the highest diagnostic delays in our data set tend to present later in life with nonspecific symptoms and a gradual, often insidious progression. In contrast, diseases with the lowest rates of diagnostic delay in this study, such as methylmalonic aciduria because of methylmalonyl-CoA mutase deficiency and fumarylacetoacetase deficiency (Tyrosinemia type I), present early in life with severe and potentially life-threatening symptoms

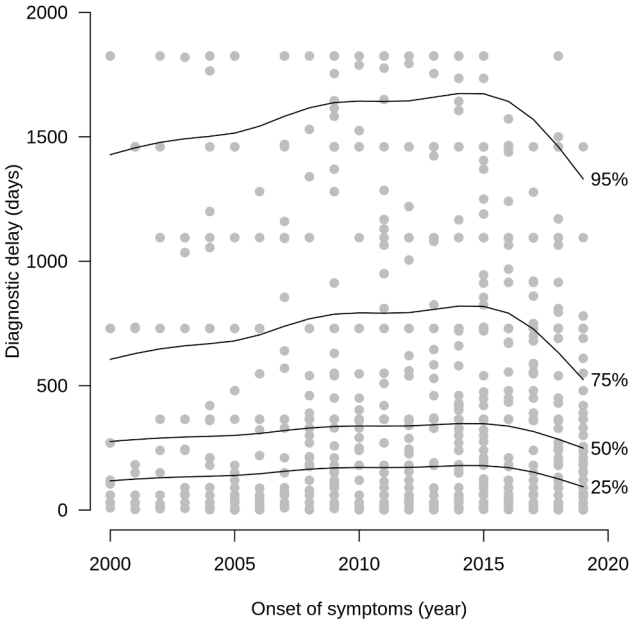

Figure 3 Diagnostic delay according to year of symptom onset among individuals with IMDs diagnosed after symptom onset. Each circle represents an individual case; solid lines indicate the 25th, 50th, 75th, and 95th percentiles from quantile regression. To reduce bias from right censoring, only patients with a maximum possible diagnostic delay of 5 years and symptom onset between 2000 and 2019 were included ($n = 1027$). Across the study period, no consistent trend toward shorter or longer diagnostic delay was observed, except that beginning with year 2016, diagnostic delays above the 75th percentile of 500 days are less frequent. IMDs, inherited metabolic diseases.

and a biochemical derangement that can be rapidly identified by basic metabolic work up. Taken together, these observations may explain a significant portion of the variability in the diagnostic delay across IMDs.

Sex-based disparities have been reported in large heterogenous cohorts of individuals with rare diseases, suggesting longer delays in female participants.[7,8,24] However, this could not be confirmed by our study evaluating an IMD cohort. When stratified by inheritance mode, diagnostic delay did not differ by sex in autosomal inherited IMDs, and no significant overall sex difference was observed in analyses restricted to X-linked disorders. Although females with certain X-linked IMDs (Fabry disease, X-linked adrenoleukodystrophy, or Ornithine transcarbamylase deficiency) are known to present later or with milder or atypical phenotypes, these biological differences might not necessarily translate into longer diagnostic delays. However, the sample size for X-linked disorders was limited and the predominantly early age at symptom onset in our cohort, with a median onset in infancy, may further limit the influence of sex-related diagnostic biases. Sex-dependent diagnostic pathways may still exist for individual disorders and warrant further investigation in larger, disease-focused cohorts.

Age at symptom onset has also been examined as a potential contributor to diagnostic delay—although findings across rare diseases remain inconsistent. Some studies suggest that earlier symptom onset may be associated with longer diagnostic delay,[8] whereas others report greater delays when symptoms begin in adulthood particularly between the ages of 30 to 44 years.[7] A recent review of IMD patients diagnosed at age 65 or older further supports the association between later onset and diagnostic delay, reporting a median diagnostic delay of 14.5 years.[28] In our cohort, older age at onset of symptoms was likewise associated with longer diagnostic delay. This finding may reflect differences in diagnostic awareness, with rare diseases, including IMDs, being more frequently considered in pediatric care settings than in adult medicine[29] and/or differences in symptom severity, with adult onset IMDs potentially presenting with milder or less specific symptoms. Furthermore, diseases with acute onset and life-threatening manifestations are unlikely to be survived for months and years without appropriate therapy. Therefore, extreme diagnostic delay in IMDs with acute pediatric onset are not to be expected.

It is often assumed that the widespread adoption of advanced diagnostic technologies—particularly next-generation sequencing (NGS)—has shortened diagnostic delays in rare diseases in recent years. This perception is supported by a study based on the Spanish national rare disease registry, which reported a gradual decrease of diagnostic delay in rare diseases since the 1960s and a marked decline after 2018.[7] However, this analysis did not correct for right censoring, potentially leading to systematic underestimation of the diagnostic delay in more recent years. In our cohort, no median reduction in diagnostic delay was observed for individuals with IMDs between 2000 and 2019, after minimizing bias from right censoring and allowing the full delay period to elapse by the end of the study window. Similar observations of persisting diagnostic delays were reported for mucopolysaccharidosis I and III and Pompe disease,[30,31] indicating that until the end of 2019 the technical improvements have not yet translated into a measurable reduction of the diagnostic odyssey in IMDs. Because NGS has become increasingly accessible in Europe since 2019, future registry updates with longer follow-up will be essential to assess the full impact of NGS implementation on diagnostic timelines in IMDs.

Although this study relies on a large data set, there are several limitations that warrant consideration. First, the U-IMD registry includes only individuals with a confirmed diagnosis, which inherently excludes individuals still in the diagnostic process. Therefore, the study may underestimate the true diagnostic delay for individuals with an IMD. Second, both age at symptom onset and age at diagnosis were collected retrospectively and may be subject to inaccuracies, particularly in participants born decades ago, for whom documentation is sparse and recall bias may influence the data. Moreover, certain early symptoms may be nonspecific or only retrospectively attributable to the IMD. Third, as

U-IMD is not a population-based registry, selection bias is possible because centers may prioritize data entry based on research interest or clinical focus, potentially skewing representation across different diseases.

Despite these limitations, this multinational, registry-based analysis of 3747 individuals across 316 different IMDs offers the most comprehensive overview to date of diagnostic trajectories in IMDs. The findings reveal that diagnostic delay remains a substantial challenge, particularly among individuals with later-onset symptoms and that this delay has not improved over the past 2 decades. These insights highlight the ongoing need for improved clinical pathways, better implementation of new diagnostic strategies such as first-line (ultra-)rapid exome or genome sequencing, increased education on rare diseases for health care providers, and broader implementation of extended NBS programs to ultimately reduce the diagnostic odyssey for individuals with IMDs.

Data Availability

The data underlying this study were obtained from clinical records of patients with inherited metabolic disorders. Because these disorders are rare and the dataset includes detailed clinical timelines related to diagnostic delay, even deidentified data may permit potential reidentification of individual patients. Accordingly, the complete data set is not publicly available. Deidentified aggregate data and data subsets can be shared upon request to the corresponding author.

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Author Contributions

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Ethics Declaration

The U-IMD registry was approved by the Heidelberg University Institutional Review Board under S-387/2018. Identifiable patient data were accessible only to authorized registry personnel in accordance with the General Data Protection Regulation (GDPR). Certain authors had access to identifiable data within their institutional responsibilities for maintaining the registry; however, all analyses for this manuscript were conducted using pseudonymized data.

Conflict of Interest

Carlo Dionisi-Vici received research founds, consulting fees, honoraria for lectures, participation to advisory board, and support for attending meetings not directly related to this study from Nutricia, Takeda, Sanofi, Piam, Mamoxi, Immedica, Ultragenix, Genespire, Moderna, IECURE, Alexion, Recordati, and Chiesi. All other authors declare no conflicts of interest.

Additional Information

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