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ORIGINAL ARTICLE

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100 years of inherited metabolic disorders in Austria—A national registry of minimal birth prevalence, diagnosis, and clinical outcome of inborn errors of metabolism in Austria between 1921 and 2021

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Abstract

Inherited metabolic disorders (IMDs) are a heterogeneous group of rare disorders characterized by disruption of metabolic pathways. To date, data on incidence and prevalence of IMDs are limited. Taking advantage of a functioning network within the Austrian metabolic group, our registry research aimed

Abbreviations: ICD 11, International Classification of Diseases 11; IMD, inherited metabolic disorders; PKU, phenylketonuria; SSIEM, Society for the Study of Inborn Errors of Metabolism.

Gabriele Ramoser and Federica Caferri are contributed equally; Sabine Scholl-Bürgi and Daniela Karall shared senior authorship.

The members of "Austrian IMD Registry Group" are given in Appendix.

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to update the data of the "Registry for Inherited Metabolic Disorders" started between 1985 and 1995 with retrospectively retrieved data on patients with IMDs according to the Society for the Study of Inborn Errors of Metabolism International Classification of Diseases 11 (SSIEM ICD11) catalogue. Included in this retrospective register were 2631 patients with an IMD according to the SSIEM ICD11 Classification, who were treated in Austria. Thus, a prevalence of 1.8/10 000 for 2020 and a median minimal birth prevalence of 16.9/100 000 (range 0.7/100 000-113/100 000) were calculated for the period 1921 to February 2021. We detected a male predominance (m:f = 1.2:1) and a mean age of currently alive patients of 17.6 years (range 5.16 months-100 years). Most common diagnoses were phenylketonuria (17.7%), classical galactosaemia (6.6%), and biotinidase deficiency (4.2%). The most common diagnosis categories were disorders of amino acid and peptide metabolism (819/2631; 31.1%), disorders of energy metabolism (396/2631; 15.1%), and lysosomal disorders (395/2631; 15.0%). In addition to its epidemiological relevance, the "Registry for Inherited Metabolic Disorders" is an important tool for enhancing an exchange between care providers. Moreover, by pooling expertise it prospectively improves patient treatment, similar to pediatric oncology protocols. A substantial requirement for ful filling this goal is to regularly update the registry and provide nationwide coverage with inclusion of all medical specialties.

KEYWORDS

gender distribution, inborn errors of metabolism, inherited metabolic disorders, minimal birth prevalence, minimal prevalence, registry study

1 | INTRODUCTION

Since the first description of the first four inherited metabolic disorders (IMDs) by Garrod in the early 1920s,[1] knowledge about the natural history, diagnostic, and therapeutic options for these disorders has increased greatly. IMDs are a heterogeneous group of rare disorders (prevalence <1/2000) caused by disrupted metabolic pathways responsible for either breakdown, storage, or synthesis of carbohydrates, fatty acids, or proteins.[2] The global birth prevalence is estimated to be 43.4 to 58.4 per 100 000 live births.[3] Even if most IMDs follow autosomal recessive inheritance, a few are X-linked or autosomal dominantly inherited.[4]

In order to classify all IMDs, the SSIEM-ICD11 Classification with 15 main disease groups and 612 single diagnoses was developed and intended for the new ICD11, but never implemented (see Supporting Information S1 "SSIEM-ICD11 classification" and Figure 1).[5]

If detected and treated early, an increasing number of IMDs have good prognosis.[4] Although IMDs can manifest with clinical symptoms at any age, 25% of all affected patients show first clinical symptoms in the newborn period.[4,6] Thus, the implementation of newborn screening programs is important. In Austria, newborn screening for IMDs was introduced in 1966, and currently detects 25 different IMDs.[7] Casual therapies—some relatively easy (dietary treatments) and some very expensive (enzyme replacement therapies)—are available for a growing number of IMDs. One of the main fundamentals for creating a national policy for the care of such patients is knowledge about the incidence/prevalence of these disorders. While estimates have been calculated for the incidence of various IMD groups,[8-12] to our knowledge there is no compilation of the real minimal birth prevalence in a nation.

The first report of the Austrian "Registry for Inherited Metabolic Disorders" covered the period 1985 to 1995. The registry was started as an initiative of the "Austrian Metabolic Group," which is part of the Austrian Society of Paediatric and Adolescent Medicine (Österreichische Gesellschaft für Kinder- und Jugendheilkunde) and was initially administered by Susanne Fang-Kircher. Data collection between 2000 and 2013 was either not complete or absent.[13] Since 2014, the registry has been

administered by Daniela Karall and Sabine Scholl-Bürgi. With this study, we aimed to improve the registry by updating patient data. Approximately 100 years after Garrod initially described the first four IMDs it seems to be an appropriate time to undertake this effort.

Conceived as a central reporting system and national database, the Austrian registry of IMDs not only plays an epidemiological role by recording minimal birth prevalence, minimal prevalence, and national distribution of patients with IMDs, but also aims to facilitate an exchange

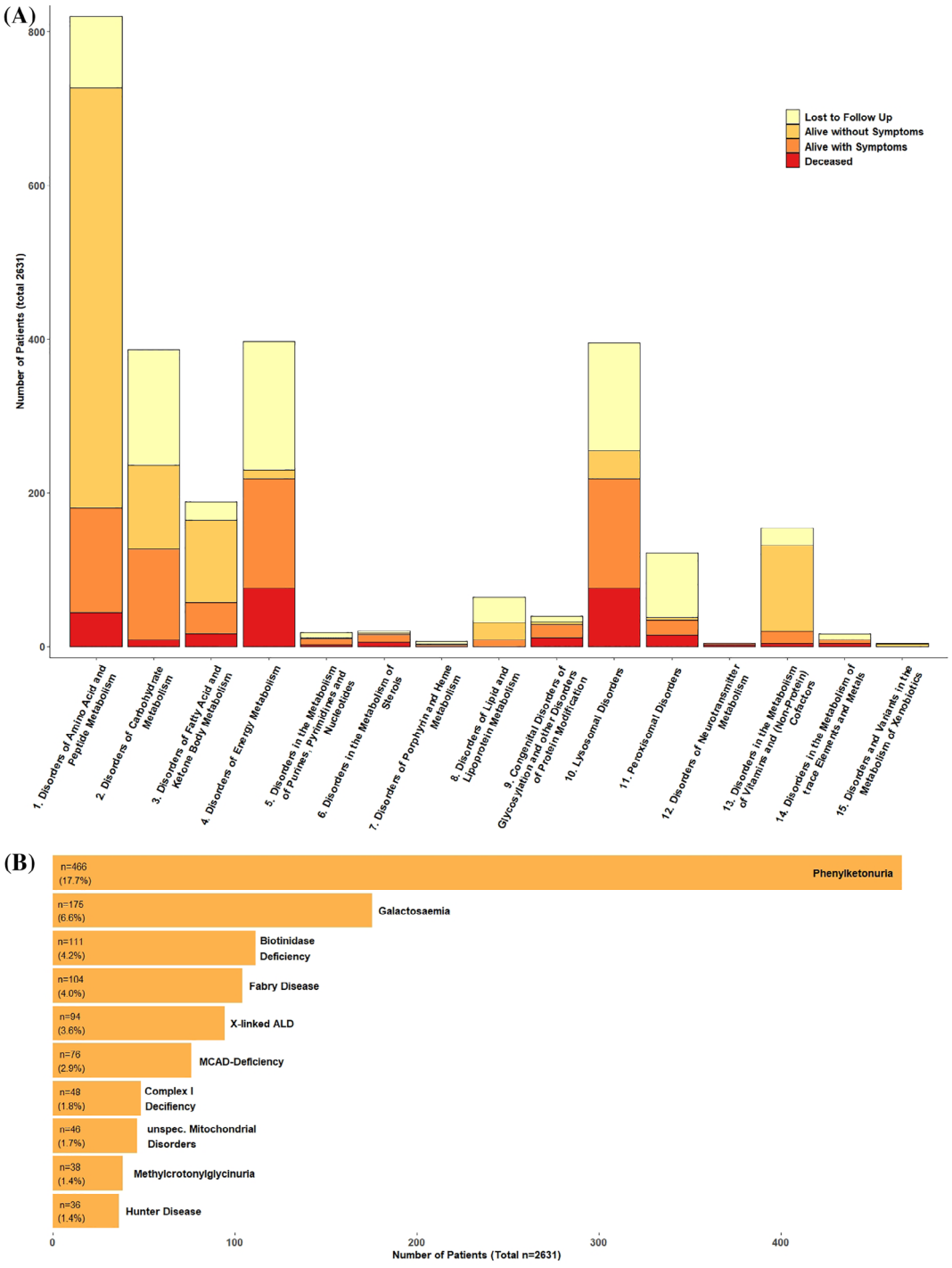

FIGURE 1 (A) Frequency and outcome of IMDs in Austria according to the 15 main categories of the ICD 11 SSIEM Classification. The *x*-axis depicts category number, *y*-axis number of affected patients in the outcome categories: unknown, alive—asymptomatic, alive—symptomatic, deceased. (B) The ten most frequent diagnoses for the 2631 study patients with IMDs in Austria according to the ICD 11 SSIEM Classification. For more detailed information, see Supporting Information S2 "Characteristics of the 10 most common IMDs in Austria"

between medical specialists, that is, of new diagnostic and therapeutic options, between treatment centers. Furthermore, it can be used as an important tool to keep track of patients and their clinical status, facilitate long-term analysis, or adjust the diagnosis. In addition, a national database can help establish contact between patients and their families in order for them to exchange their experiences and therefore be a substantial help in coping with the disease. For these aspects, the registry structure warrants safekeeping of patient's data and privacy.

2 | METHODS

2.1 | Inclusion criteria

All patients with an IMD according to the SSIEM-ICD11 Classification (see Supporting Information S1 "SSIEM-ICD11 classification" and Figure 1), who received treatment or were diagnosed in Austria, were included in this retrospective survey. We excluded patients whose minimal dataset consisting of birth date and diagnosis was not complete.

2.2 | Data collection

To obtain the maximal number of patients and achieve a national coverage that is as comprehensive and complete as possible, all 169 Austrian departments for Pediatrics, Neurology, and Internal Medicine were regularly every 6 to 12 months invited to register every patient with an IMD, who was or is currently being treated at their center. In 2020, 66/169 centers responded and of those 29 centers were involved in treatment of patients with IMDs including the four major pediatrics centers Medical University Hospital of Vienna, Salzburg University Hospital of the Paracelsus Medical Private University, Medical University Hospital of Graz, and Medical University Hospital of Innsbruck. The last reporting period began in March 2020 and ended in February 2021. Patients from earlier reporting periods also were included in the registry, but if not updated in 2020, the outcome was changed to "lost to follow up."

The dataset was pseudonymized and included birth date, gender, ethnicity, consanguinity, diagnosis, date of diagnosis, diagnostic setting, and clinical outcome. Minimal dataset consisted of birth date and diagnosis.

Diagnostic setting covers the categories: (a) newborn screening, (b) selective screening, and (c) family screening. Clinical outcome was divided into the following four categories: (a) alive—without symptoms, (b) alive—with symptoms, (c) dead, (d) lost to follow-up.

Gender distribution was evaluated. X-linked mode of inheritance[14] was evaluated separately.

Finally, as an example, phenylketonuria was evaluated for minimal prevalence, minimal birth prevalence, age at diagnosis and outcome.

2.3 | Calculation of minimal birth prevalence and prevalence for 2020

Using the birth date of every included patient, the minimal birth prevalence per year from 1921 to 2020 was calculated by dividing the total of all patients born with inherited errors of metabolism per year by all live births per year. Data source for the number of live births per year was Statistics Austria.[15]

To evaluate the minimal prevalence of IMDs in Austria for 2020, the sum of all patients who are still alive was divided by the Austrian population in 2020. Data source for the population in Austria in 2020 was Statistics Austria.[15]

2.4 | Statistical analysis

For analysis of data the opensource R software environment for statistical analysis (R version 4.0.2 [June 22, 2020]) and RStudio (Version 1.4.615) was used (R Core Team, 2020). For the creation of figures the R package "ggplot2" was used (Wickham, 2016).

3 | RESULTS

3.1 | Establishing a nation-wide registry for IMDs

This retrospective registry study included 2631 patients with IMDs. Of the 2774 initially reported patients 143 did not meet the inclusion criteria and were excluded. Currently, 1627/2631 (61.8%) are alive. Thus, by using the Austrian population statistics for 2020, a minimal prevalence of 1.8/10 000 patients with IMDs for 2020 was calculated.[15]

3.2 | Diagnoses and respective outcome

We detected 247 different diagnoses according to the SSIEM-ICD11 classification. The three most common categories were disorders of amino acid and peptide metabolism (819/2631; 31.1%), disorders of energy metabolism (396/2631; 15.1%) and lysosomal disorders (395/2631; 15%) (see Figure 1). Of all the study patients 17.7% had phenylketonuria (466/2631), 6.6% had a classical galactosaemia

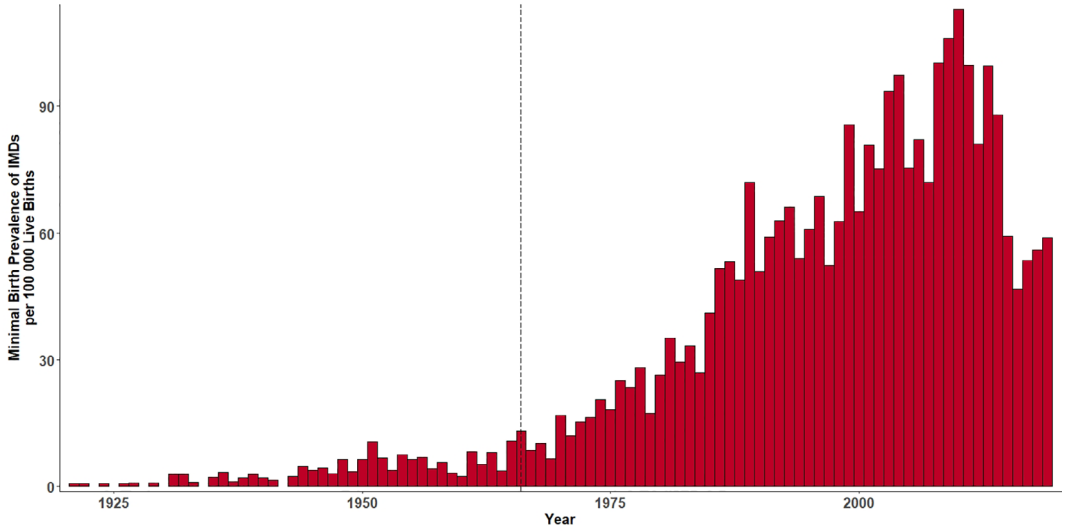

FIGURE 2 Minimal yearly birth prevalence of IMDs per 100 000 live births in Austria between 1921 and 2021. The dotted line marks the introduction of newborn screening in Austria. Data on live births per year were retrieved from Statistics Austria.[15] The *x*-axis indicates the year, *y*-axis number of patients with IMD born in the respective year. For more detailed information, see Supporting Information "Birth prevalence of the 10 most common IMD's in Austria"

(175/2631), and 4.2% had a biotinidase deficiency (111/2631) (see Figure 2, Table 1, and Supporting Information). Data on diagnosis setting were available for 1988/2631 (75.6%) patients. For 48.9% of all study patients (972/1988) newborn screening, for 43.7% (868/1988) selective screening and for 7.4% (148/1988) family screening detected their diagnosis (see Table 1 and Supporting Information S2 "Characteristics of the 10 most common IMDs in Austria").

Information on clinical outcome was available for 1890/2631 (71.8%) patients; 86.1% (1627/1890) are alive, 35.3% (667/1890) with and 50.8% (960/1890) without symptoms. Unfortunately, 10% (263/ 2631) have died (see Figure 1 and Table 1).

3.3 | Minimal birth prevalence and age of patients

Despite the fact that not all patients with IMDs have been included in the registry, we estimated a median minimal birth prevalence of IMDs in Austria of 16.9/100 000 from 1921 to 2021. The lowest birth prevalence was 0.7/100 000 in 1921 and the highest birth prevalence was 113/100 000 in 2010 (see Figure 3 and Supporting Information S3 "Birth prevalence of the ten most common IMDs in Austria between 1921 and 2021").

In the group of the 1627 patients currently still alive, median age is 17.6 (range 5.16 months-100 years). The 100-year-old is a male patient with diagnosis of Fabry disease (see Table 1 and supplemental material).

Most patients (48.6% [791/1627]) were adults (>18 years, range 18-100); 41.6% (677/1627) were between 6 and 18 years of age; 9.2% (150/1627) were between 1 and 5; and 0.6% (9/1627) were between 0 and 12 months of age (see Fig.).

Of the 2631 study patients, 263 (10.0%) are deceased. For 170/263 (64.6%) patients, information about the date of death is available. Median age at death was 2.12 (range 0-84.3) years.

The date of diagnosis is known for 81.9% (2154/2631) of the cohort. Median age at diagnosis was 1.92 months (range 32 weeks of pregnancy-74.2 years). The 74.2-year-old patient had a mitochondrial disorder. The first diagnosis of an IMD in Austria was Gaucher disease, diagnosed in 1948. Two patients were diagnosed prenatally (alkaptonuria, transcobalamin II deficiency). Most patients (59.9% [1290/2155]) were diagnosed within the first year of life, namely between 1 and 5 years of age in 13.9% (300/2155), between 6 and 18 years in 14.3% (308/2155), and over 18 years in 11.9% (256/2155) (see Figure 3).

3.4 | Gender differences

Data on gender were available from 99.7% of all study patients (2624/2631). With 1452 male (55.3%) and 1172 female (44.7%) patients, there was a male predominance (ratio m:f = 1.24:1). For further analysis, the 295/2631 patients (196 male, 99 female) with an X-linked inherited diagnosis were excluded. Even then, male predominance persisted with 1256/2329 male (53.9%) and 1073/2329

TABLE 1 Characteristics of the study cohort

	All IMDs		Phenylketonuria	
	Number	Percent %	Number	Percent %
Total number of patients	2631	100	466/2631	17.7
Patients alive (2020)	1627/2631	61.8	434/466	93.1
Minimal prevalence (2020)	1.82/10 000	—	0.09/10 000	—
Birth prevalence (median)	16.9/100 000	—	8.9/100 000	—
Patient age (median)	17.6	—	19.8	—
Age at diagnosis (median)	1.92 months	—	11 days	—
Gender	2624/2631	99.7	466/466	100
m:f ratio	1.2:1	—	1.2:1	—
Male	1452/2624	55.3	252/466	54.1
Female	1172/2624	44.7	214/466	45.9
Unknown	7/2631	0.27	0/466	0
Diagnosis setting	1988/2631	75.6	421/433	97.2
Newborn screening	972/1988	48.9	433/466	92.9
Selective screening	868/1988	43.7	10/466	2.2
Family screening	148/1988	7.4	2/466	0.4
Unknown	643/2631	24.4	21/466	4.5
Outcome	1890/2631	71.8	435/466	93.4
Alive—with symptoms	667/1890	35.3	15/435	3.5
Alive—without symptoms	960/1890	50.8	419/435	96.3
Deceased	263/1890	13.9	1/435	0.2
Lost to follow-up	741/2631	28.2	31/466	6.7

Note: For more detailed information see Supporting Information S2 "Characteristics of the 10 most common IMDs in Austria."

female (46.1%) patients (ratio m:f = 1.17:1) (see Table 1, Figure 4 and Supporting Information S4 "Gender distribution of the 15 main categories of the SSIEM-ICD11-classification").

3.5 | Medical centers and ethnicities

Information on ethnicity was available for 1877/2631 of the study patients, comprising 77 different ethnicities. The five most common ones were Austria (1214/1877; 64.7%), Turkey (250/1877; 13.3%), Italy (56/1877, 3%), Serbia (36/1877; 1.9%), and Germany (36/1877; 1.9%).

Data on consanguinity were available for 219/2631 of the study patients, namely positive for 95/219 and negative for 124/219.

All nine Austrian states are involved in providing therapy to patients with IMDs. Of the 2631 study patients, 43.1% (1135/2631) were cared for in Vienna, 23.1% (609/2631) in Tyrol, 13.9% (367/2631) in Styria, 11.6% (304/2631) in Salzburg, 2.9% (77/2631) in Upper Austria, 2.7% (72/2631) in Vorarlberg, 1.4% (38/2631) in Lower Austria, 1% (27/2631) in Carinthia, and 0.08% (2/2631) in Burgenland.

Data on medical specialty/discipline are available for 2555/2631 of the study patients. Most patients (86.0% [2197/2555]) with IMDs received treatment or were diagnosed at departments of pediatrics, 8.2% (210/2555) neurology, 4.9% (124/2555) internal medicine, and 0.9% (24/2555) at departments of other medical specialties (eg, dermatology; see Figure 5).

Median age of patients currently alive and cared by pediatricians (n = 1378) is 16.19 years; 594/1378 (43%) patients were older than 18 years and 784/1378 were younger than 18 years.

3.6 | Phenylketonuria (PKU)

In the Austrian IMD register, 17% of all patients are reported to have phenylketonuria (classical PKU, hyperphenylalaninemia, or atypical PKU) (466/2631). The global PKU prevalence is estimated to be 1:23 930

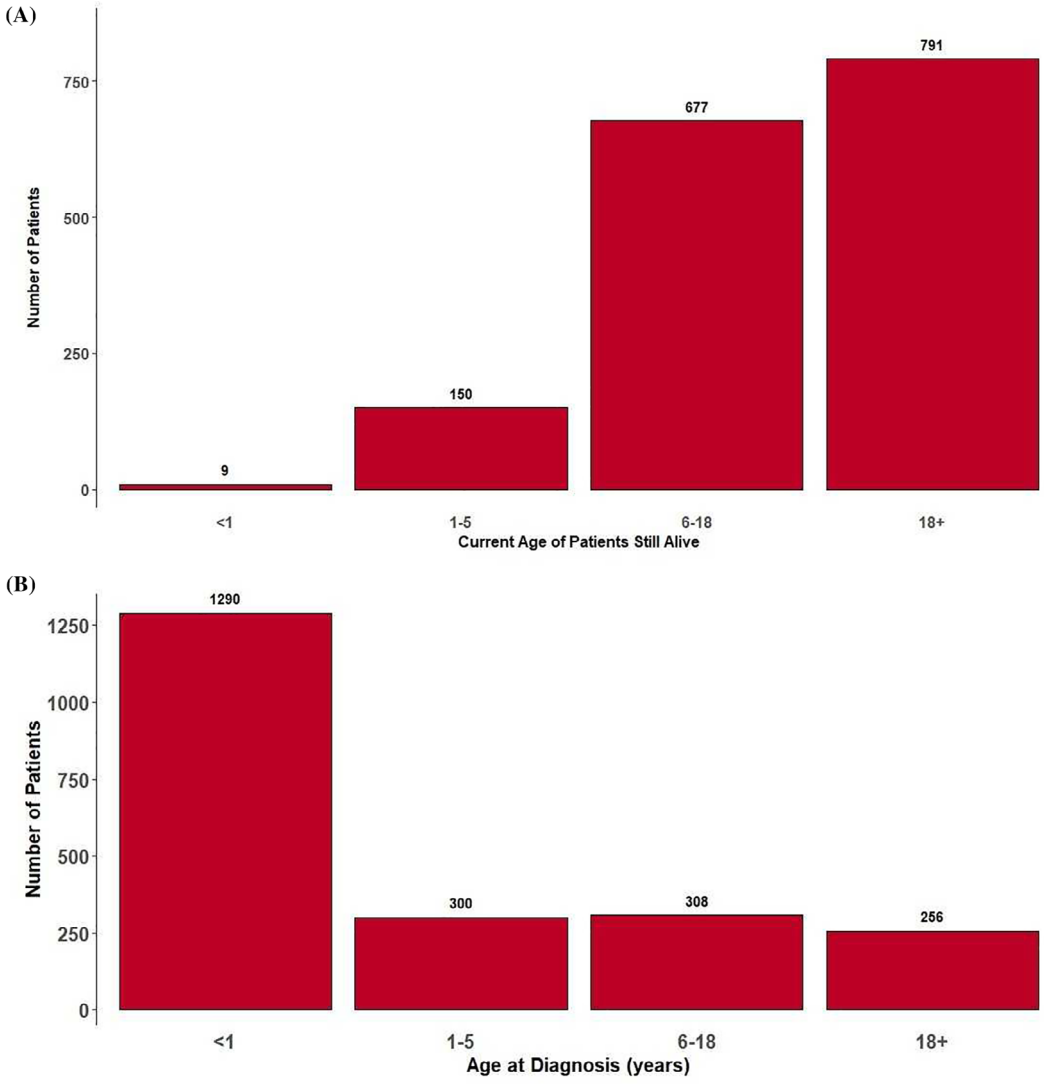

FIGURE 3 (A) Age structure of all patients still alive in Austria in 2020 (1627/2631). Most patients (48.6% [791/1627]) were adults (>18 years, range 18-100); 41.6% (677/1627) were between 6 and 18 years; 9.2% (150/1627) were between 1 and 5; and 0.6% (9/1627) were between 0 and 12 months. (B) Age structure at date of diagnosis (2155/2631). Date of diagnosis is known for 81.9% (2155/2631) of the cohort. Median age at diagnosis was 1.92 months (range 32th week of pregnancy—74.2 years). Two patients were diagnosed prenatally (alkaptonuria, transcobalamin II deficiency). Most patients (59.9% [1290/2155]) were diagnosed in the first year of life, namely between 1 and 5 years of age in 13.9% (300/2155), between 6 and 18 years in 14.3% (308/2155), and over 18 years in 11.9% (257/2155)

newborns.[16] In Europe, prevalence of PKU varies from 1:4000 (Italy) to 1:112 000 (Finland).[16] The first patient with phenylketonuria in our cohort was born in 1964. In our study the median minimal birth prevalence for phenylketonuria since 1964 was 8.9/100 000 (range 0-27.5/100 000) live births—the minimal prevalence for PKU in 2020 was 0.48/10000. Of the 466 patients with PKU, median age was 19.8 years (range 0.44-56.4 years). Median age at diagnosis was 11 days. Most (97.3% [433/466]) of the patients with PKU were diagnosed through newborn screening. For phenylketonuria, sex distribution was male-predominant with 252 (54.1%) male and 214 female (45.9%) patients. Outcome was available for 435 patients. Of them, 15/435 (3.5%) live with, 419/435 (96.3%) without symptoms, and 1/435 (0.2%) patient has deceased (see Table 1 and Supporting Information "Characteristics of the 10 most common IMDs in Austria").

4 | DISCUSSION

The registry provides an unique data collection of IMDs in Austria in an effort to improve general understanding of IMDs and patient's treatment. With 247 recorded different disorders (40.4% of the diagnoses listed in the SSIEM-ICD11 classification) our study documents the broad diversity of IMDs in terms of diagnosis, age and outcome in Austria.

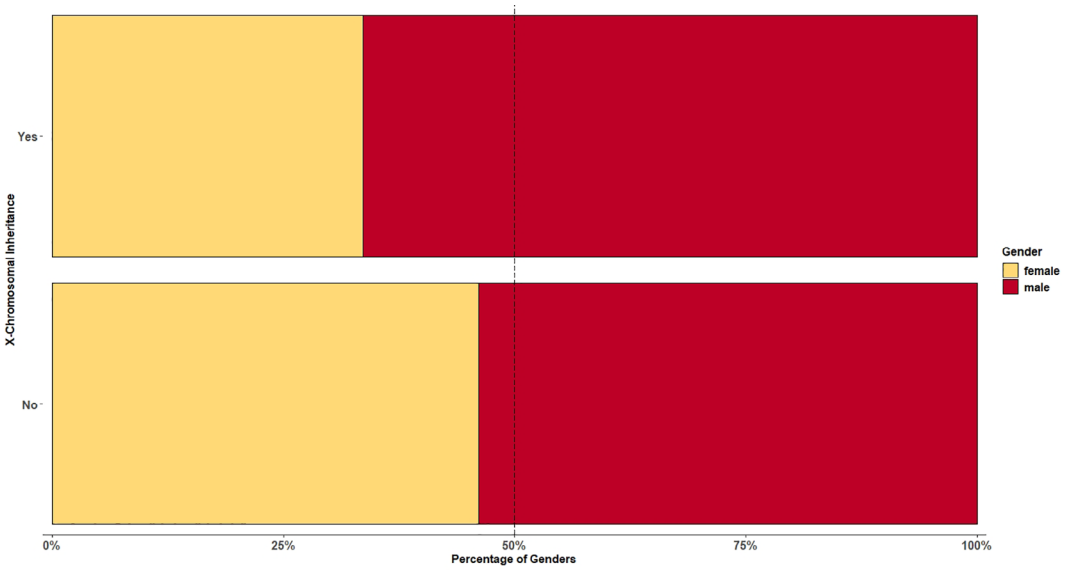

FIGURE 4 There was a male predominance in our cohort (m:f = 1.24:1).). For further analysis, the 295/2631 patients (196 male, 99 female) with an X-linked inherited diagnosis were excluded. Even then, male predominance persisted with a ratio m:f = 1.17:1. For more detailed information, see Supporting Information S4 "Gender distribution of the 15 main categories of the SSIEM-ICD11-classification"

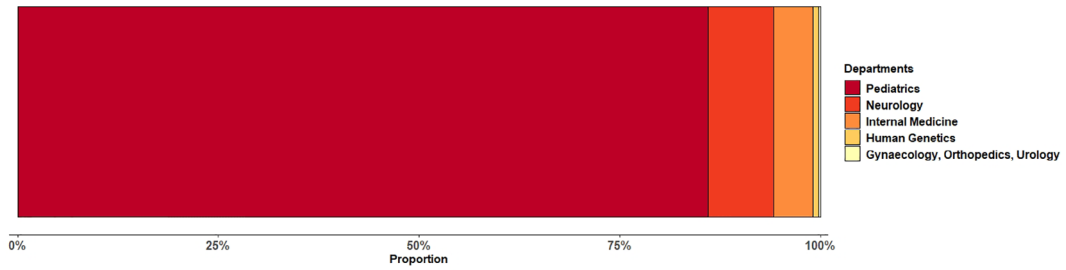

FIGURE 5 Distribution of treating disciplines. Most patients (86.0% [2197/2555]) with IMDs received treatment at departments of pediatrics, 8.2% (210/2555) neurology, 4.9% (124/2555) internal medicine, and 0.9% (24/2555) at departments of other medical specialties (eg, dermatology)

Taking advantage of the fact that Austria is a relatively small country with four historically established major pediatric centers specialized in IMDs (Medical University Hospital of Vienna, Salzburg University Hospital of the Paracelsus Medical Private University, Medical University Hospital of Graz, and Medical University Hospital of Innsbruck) and about 100 physicians involved in the care of patients with IMDs, we aimed to establish a real minimal birth prevalence for our country and to complete and update the data in the Austrian IMD Registry.[13]

Median minimal birth prevalence of IMDs in Austria in the last hundred years was calculated to be 16.9 per 100 000 live births (0.7-113). There were 0.7 registered cases of IMDs per 100 000 live births in 1921, and the birth prevalence increased up to 113/100 000 by 2010. Hence, by 2010 the birth prevalence in Austria is higher than the estimated global (50.9/100 000 live births) and Italian birth prevalence (26.9/100 000 live births).[3,9] The observed higher birth prevalence and increase of course has to be attributed to enhanced diagnostic methods like implementation of newborn screening programs (starting in 1966) and for example, tandem mass spectrometry (started in 2002) or new genetic methods.[6] Historically, patients were seen by their local physician. Presumably, several disorders went undiagnosed and some patients, who were diagnosed but not treatable, remained in the primary care setting. Over the years, most patients with IMDs have been diagnosed and/or treated at pediatric departments, even though 50% are adults.

From the 2631 study patients, age at diagnosis ranges from 32nd week of pregnancy to 74.2 years. The age range at diagnosis indicates that some patients with IMDs have not yet been diagnosed and therefore the minimal birth prevalence after 2010 is lower than before 2010.

Newborn screening for IMDs was introduced in Austria in 1966 and since 2002 up to 30 IMDs have been screened for. Newborn screening comprises 48.9% of diagnoses in our cohort. We assume, this could be a reason that at present 59% of all patients with IMDs in Austria are alive and asymptomatic under their therapeutic regimens as 25% of all IMDs manifest in newborn period.[16] Although most disorders are diagnosed in the first year of life, the median age of our cohort was 17.6 years. Hence half (48.6%) of the patients are adults. Nevertheless, 86% of all patients are managed at pediatric departments. Inclusion of neurologists, internists and other specialties in the training and treatment of patients with IMDs is necessary in order to ensure care of the adult group and also a timely transition of patients with IMDs diagnosed in childhood when reaching juvenile and adult age.

In line with previous literature, our study cohort shows a male predominance with a ratio m:f = 1.2:1 for IMDs, even after excluding X-linked inherited diseases.[9] Further research is needed to investigate this sex difference. Comparing with data of Austria statistic, there was a male predominance in the Austria population between 2010 and 2020.[15]

The registry makes it possible to analyze individual IMD groups and individual disorders, thus helping understand their epidemiology and clinical course (see Table 2). As an example, we chose to analyze the ten most common disorders more closely (see Supporting Information S2 "Characteristics of the 10 most common IMDs in Austria").

There are several limitations to this registry study. As data collection is retrospective it relies on reports of treating physicians. Of the total cohort of 2631 patients with IMDs, 28.2% (= 741/2631) were recorded as lost to follow-up. However, this is comparable with other registry studies.[9] Therefore, as only the minimal prevalence can be estimated, it is likely that the actual prevalence of IMDs in Austria is higher than 1.8/10 000. Further, the data set is still not complete, as we are aware that some patients are not reported to the registry because of being undiagnosed or treated abroad.

Finally, since IMDs are a heterogeneous group of mostly (very) rare disorders, every single experience and exchange between care providers is essential for improving patient care. Thus, the registry could play an essential role in providing a national and international exchange between medical centers and evaluating the care of patients over a longer period of time. It also allows patients with IMDs to come into contact with each other, exchange their experiences and learn about clinical trials being conducted.

5 | CONCLUSION

Beside its epidemiological value, the Austrian Registry for IMDs also permits an exchange between care providers and patients. A total of 247 diagnoses are recorded in our cohort and illustrate the heterogeneity of IMDs.

Also when X-linked inherited IMDs were excluded we recorded a male predominance of IMDs in our cohort (m:f = 1.2:1). Further studies are needed to investigate this distribution.

Thanks to improved treatment and early diagnosis most of our patients are now adults. Thus, in future, medical care needs to also be provided by other disciplines such as Internal Medicine and Neurology.

An essential requirement for a functioning registry is that it be updated on a regular basis by the members of the Austrian Register Group.

CONFLICT OF INTEREST

The authors have no conflicts of interests to declare.

AUTHOR CONTRIBUTIONS

Gabriele Ramoser and Federica Caferri were involved in project design, data collection and evaluation and manuscript preparation. Bernhard Radlinger performed data analysis and interpretation and manuscript preparation. Gabriele Ramoser, Federica Caferri, Bernhard Radlinger, Sabine Scholl-Bürgi, and Daniela Karall were involved in project design, data collection, discussed the data, and reviewed the manuscript.

ETHICS STATEMENT

The approval of the Ethics Committee of the Medical University of Innsbruck and Vienna for this study is available.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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