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RESEARCH

The Latin American Society for Immunodeficiencies Registry

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Abstract

Purpose - The Latin American Society of Immunodeficiencies (LASID) Registry was established in 2009 to collect data on Inborn Errors of Immunity (IEI) patients in the region. Although several reports have been published regarding LASID data, this is the first report of the entire dataset. Methods - The European Society of Immunodeficiencies (ESID) donated the online platform in 2008. Data was collected from participating centers from Apr 13, 2009, to Dec 31, 2022, and included demographic, clinical, and follow-up information. Results – A total of 9307 patients were included in the database. At the end of the study period, 8,805 patients were alive or lost to follow-up, and 502 were deceased. The most common type of IEI was predominantly antibody deficiency (PAD, 60.35%), and selective IgA deficiency was the most frequent diagnosis (1627 patients, 17.48%), followed by Common Variable Immune Deficiency (CVID, 1191 patients). Most patients (78.16%) were ≤ 18 years old at inclusion, and the median age at diagnosis was 4.77 years. The median time to diagnosis was 5.04 years. Antibiotics were prescribed in 32.3% of visits, followed by immunoglobulins (29.49%). Hematopoietic stem cell transplantation was performed in 5.03% of patients. Omenn syndrome was the most common disease in deceased patients, with a mortality rate of 52.63%. Conclusion – This study contributes to our understanding of IEIs in Latin America and highlights the importance of early diagnosis, appropriate treatments, and improved data collection to optimize patient outcome

Keywords Primary immunodeficiency · Inborn errors of immunity · Registry · Epidemiology · Latin America

Introduction

Single gene variants in the germline cause inborn errors of immunity (IEI), which may present clinically as increased susceptibility to infections, autoimmunity, autoinflammatory diseases, allergy, bone marrow failure, and/or malignancy. The International Union of Immunological Societies (IUIS) published in 2022 an update on the genetic causes of immune deficiency and dysregulation, describing 485 gene defects in total [1].

IEI incidence varies widely from approximately 1 in 250 for the more common forms to 1 in 1,000,000 for rare types. The actual frequency of IEI is unknown, and some estimates range from 1:10,000 to as many as 1:1,200[2]. While considered rare diseases, the combined number of individuals with an IEI presents a significant health burden [1].

The Latin American Group for Immunodeficiencies (LAGID) was established in 1993 to study the prevalence and promote awareness of primary immunodeficiencies (PIDs) in Latin American countries. The group's first report was published in 1998 and included 1,428 patients from eight countries [3]. Inborn errors of immunity (IEI) is now the preferred designation for PIDs and has been adopted by the IUIS since 2017[4] due to the increased number of recognized genes associated with immune dysregulation, also considered primary immune disorders. In 2009, the group evolved into the Latin American Society for Immunodeficiencies (LASID) and officially started an online registry [3, 5]. The LASID registry has

Beatriz Tavares Costa Carvalho is deceased. This paper is dedicated to her memory.

Extended author information available on the last page of the article

evolved from 25 centers in 7 countries in 2009[6] to 133 centers in 17 countries in 2022.

Although several reports based on the registry have been published [7–13], this is the first report of the entire data set since its inception.

Methods

The LASID registry contains information collected at the participating centers from patients diagnosed with IEI, according to the 2008 IUIS report [14] and ESID diagnostic criteria [15], which were updated regularly.

The online platform was kindly donated by the European Society for Immunodeficiencies (ESID) in 2008. All cases in our registry share a common dataset, handling non-identifying primary patient data, diagnosis, quality of life, therapy, transplantation, and laboratory information in agreement with the donated platform [16]. Each participating center collects data locally and shares it online at the central repository (LASID Registry). The now-former ESID Online Database [16] was a robust system designed for efficient data management and integration within business-to-business (B2B) frameworks, utilizing the Java 2 Enterprise Edition (J2EE) platform. It employs MySQL MaxDB for data storage and JDBC for database access, ensuring secure and reliable data handling. The system's architecture is centered around the Toolwerk EIDP, a multitier platform that facilitates XML-based interactions across various J2EE components. With its emphasis on security through SSL/TLS encryption and ease of access via standard web browsers, the ESID Online Database exemplifies a well-structured approach to enterprise-level data integration and management.

Data was collected from Nov 17, 2009, to Dec 31, 2022.

Statistical Analysis

Descriptive statistics reporting mean, SD, median, and interquartile range were performed using GraphPad Prism version 10.0.0 (153) for Windows, GraphPad Software, Boston, Massachusetts, USA.

Results

From Apr 23, 2008, to Dec 31, 2022, 9307 IEI patients were registered in the database. See Fig. 1 for the cumulative and annual number of IEI registered patients. Argentina, Brazil, Mexico, and Colombia were the most significant contributors. Figure 2 demonstrates other countries' inputs. Online Resource 1 shows the number of registered patients per center.

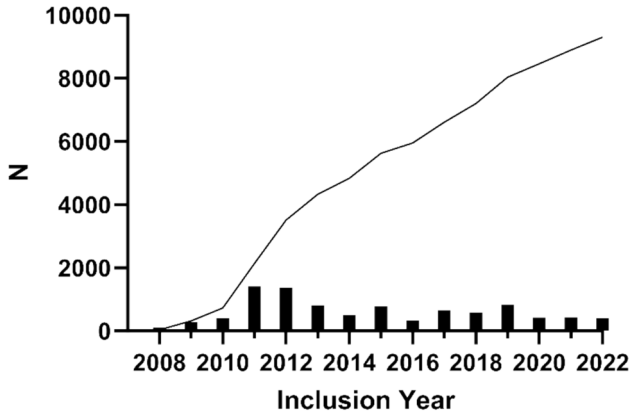

Fig. 1 Number of registered IEI patients per year and cumulative numbers

At the end of the analysis, 8,805 patients were alive or lost to follow-up, and 502 were deceased. The male-to-female ratio was 1.5:1, with 5544 male (59.57%), 3751 female (40.30%), and 12 (0.13%) patients with no gender information. The mean age at inclusion was 13.88 (± 13.91) years. See Table 1 for more information regarding clinically significant age data. Most patients (78.16%) were ≤ 18 years old at inclusion, and 833 (55.98%) were younger than 10 years old. See Fig. 3 for age categories at inclusion. Most patients had no family history of IEIs (71.33%), while 15.54% had at least one relative with an IEI. There was no information regarding family history for 13.13% of cases. Consanguinity in the family was reported in 4.53% of cases.

Predominantly antibody deficiencies (PADs) were the most common type of IEI (60.35%) described in the database (Fig. 4), while selective IgA deficiency was the most common of 164 diagnoses found in the cohort. When selective IgA deficiencies were not included, PADs accounted for 42.87% of all cases. The 20 most common diagnoses comprised 82.72% of the total cases and are described in Table 2.

See Online Resource 2 for the 50 most common diagnoses in each country.

Antimicrobials were the most frequently prescribed drugs during follow-up (32.30%), followed by immunoglobulins (29.49%). and corticosteroids (11.90%). Table 3 shows additional information about treatments. Online Resource 3 shows details about administration routes for immunoglobulins and corticosteroids. Only 104 patients (0.81% of total treatments) discontinued medications due to adverse reactions. Immunoglobulins and corticosteroids were responsible for 40.38% and 35.58% of discontinuations due to adverse reactions. Online Resource 4 shows other causes for treatment interruption and related drugs.

Hematopoietic stem cell transplantation (HSCT) was performed in 469 patients (5.03%) during the follow-up

Fig. 2 Number of IEI registered cases per country. Color density is related to the number of registered cases

Table 1 Age at clinical meaningful events

Age (Years)	*N**	Mean (± SD)	Median (IQR)
At last follow-up	9180	18.2 (14.16)	14.51 (1.81–10.28)
At death	495	10.2 (14.84)	3.24 (0.85–14.10)
At diagnosis	7402	9.47 (14.03)	4.77 (1.81–10.28)
At the onset of symptoms	4788	5.02 (10.05)	1.04 (0.27–4.22)
Time to diagnosis (in years)	4665	4.05 (6.16)	5.04 (1.95–65.26)
Follow-up duration (in years)	7420	8.36 (6.85)	6.99 (3.40–11.33)

*Patients with relevant data.SD. Standard deviation. IQR, interquartile range

period; bone marrow and cord blood were the most common donated tissues (97.50%). For more details about these procedures, see Online Resource 5 and Online Resource 6.

The twenty most common causes of death, corresponding to 82.27% of all events, are presented in Table 4and 5 Omenn Syndrome had the highest mortality rate (52.63%), with a mean age of death at 0.53 years old. Children accounted for most registered deaths, with a mean age of 10.2 (± 14.84) and a median of 3.24 (0.85–14.10) years (Table 1). Over half (58.78%) of the deaths occurred before age two, and SCID was the most frequently associated cause of death (34.45%) in this age group.

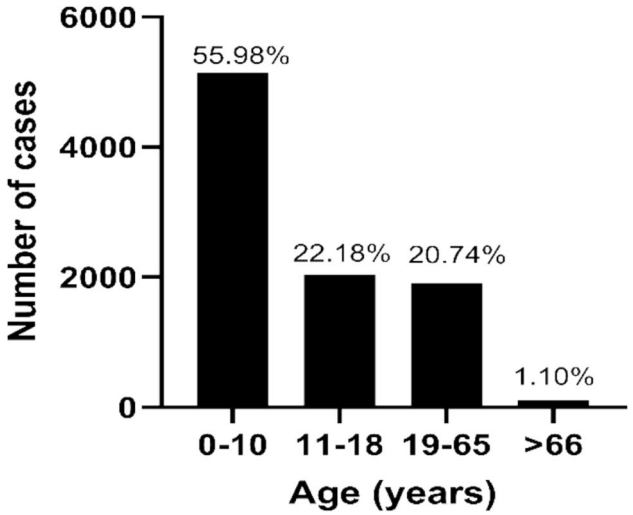

Fig. 3 Age categories at IEI patients inclusion

Discussion

Well-designed and well-maintained registries that track inborn errors of immunity (IEI) and immune dysregulation syndromes have been instrumental in advancing our understanding of these complex diseases. These registries provide a wealth of data, enabling researchers to gain insights into the various nuances of diseases, including the variability in their presentation and responses to interventions. As a result, IEI registries have facilitated the development of more informed and effective treatments, ultimately improving patient outcomes [17]. These registries also connect experts aiming to improve patient care, locate patients with rare diseases for research studies, and increase global awareness of these rare diseases. The significant role played by these registries in the progress made in combating these conditions cannot be overstated.

Seven other reports were published based on the LASID registry. The first report of the registry data [7] was published in 2012 in abstract form and described the increased number of cases (304 to 2878) and contributing centers (23 t 47) since its creation in 2009. Antibody deficiencies were the most common diagnosis (59.7%), followed by specific well-defined syndromes (17.3%), T-cell defects (10.31%), and phagocyte disorders (9.3%). The next study [8], published in 2012, detailed several LASID initiatives and described patient numbers (4900) and contributing centers (87). PADs continued to be the most common diagnosis (52%), followed by well-defined syndromes (19%). Cabral et al. [9] published a report on Hyper-IgM syndrome in 37 patients, with the majority having germline CD40-L mutations and pneumonia as the most frequent clinical manifestations. Results from fifty patients with Hyper-IgM syndrome [13], including those

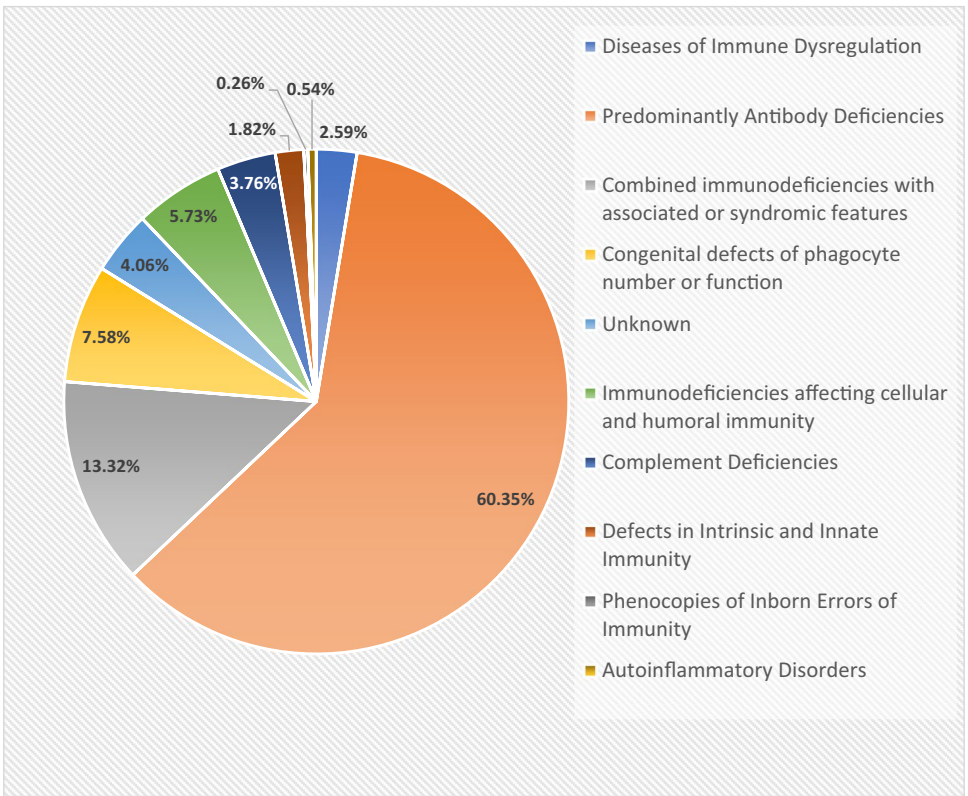

Fig. 4 Proportional prevalence of IEI types

Table 2 The 20 most common IEI diagnoses in the LASID registry

Disease name	*N*
Selective IgA deficiency	1627
Common variable immune deficiency with no gene defect specified (CVID)	1151
Transient hypogammaglobulinemia of infancy	620
Specific antibody deficiency with normal Ig levels and normal B cells	593
Other hypogammaglobulinemias	498
BTK deficiency. X-linked agammaglobulinemia (XLA)	453
Ataxia-telangiectasia	381
DiGeorge/velocardiofacial syndrome Chromosome 22q11.2 deletion Syndrome (22q11.2DS)	374
Unclassified immunodeficiencies	267
AD-HIES - STAT3 deficiency (Job Syndrome)	210
Hereditary angioedema	207
Agammaglobulinemia with unknown gene defect	203
Wiskott-Aldrich syndrome (WAS)	191
CGD with unknown gene defect	182
X-linked chronic granulomatous disease (CGD), gp91phox	169
IgG subclass deficiency with IgA deficiency	148
T-B- SCID with unknown gene defect	98
Other T-cell disorders	93
Secondary hypogammaglobulinemia	93
Cyclic neutropenia with unknown gene defect	87

Table 3 Frequency of medication group prescription to IEI patients during follow-up visits

Medication group	*N*	%
Antimicrobials*	4124	32.30
Immunoglobulins	3765	29.49
Corticosteroids	1520	11.90
Antihistamines	462	3.62
Antileukotrienes	410	3.21
Biologicals	387	3.03
Antiandrogens	107	0.84
Antifibrinolytics	64	0.50
C1 inhibitors	48	0.38
B2R antagonist	33	0.26
Fresh Frozen Plasma	5	0.04
None	21	0.16
Unknown	54	0.42
Other	1769	13.85

*Includes antibiotics. antivirals. antifungals. antiparasitic and antituberculosis drugs

previously described, were reported in 2022, presenting 6 novel CD40-L mutations. Clinical characteristics were similar to those already described. Another study [11], presented in abstract form, described a novel Btk gene *de novo* mutation. Finally, 71 patients from Latin America with chronic granulomatous disease were described [12] first as an abstract at the 2012 at the ESID conference. The full report [10] was published later describing the clinical and genotypic characteristics of these patients.

This article presents valuable information on a large-scale retrospective analysis of patients with inborn errors of immunity (IEI) enrolled in the LASID Registry from Apr 23, 2008, to Dec 31, 2022. The database included 9.307 patients, with Argentina, Brazil, Mexico, and Colombia being the largest contributors. Even though advances in genetic technology have contributed significantly to diagnosing IEI, genetic testing is unavailable in many countries, particularly in the developing world. It is, therefore, surprising that only 267 (2.86%) patients in the database were categorized as having "unclassified immunodeficiencies" (Table 2). The true prevalence of IEI in Latin American countries is unknown, but it has been assumed to be around 1 in 2000 individuals [18].

PADs continue to be the most common diagnosis (60.35% and 42.87%, with and without IgA deficiencies. respectively), as shown by the first LASID report [8] (52% of PADs). PADs are also reported as the most common type of disease in registries around the world [19]. As some other IEIs also present antibody deficiencies (e.g., SCID, Wiskott-Aldrich syndrome, and others), these conditions represent the most frequent problem in these patients. In addition, immunoglobulin levels dosage is the most accessible test in every country, facilitating the diagnosis and follow-up of antibody deficiency.

Selective IgA (sIgA) deficiency was the most commonly reported diagnosis in the database, with a mean

Table 4 Ten most common causes of death among IEI patients, age at diagnosis, mortality rate, and diagnostic delay for each disease

Disease name	*N* (total)*	Mean age at diagnosis	Mean diagnostic delay (years)	Deaths (*N*)	Mortality rate (%)	Mean age at death (years)
Common variable immune deficiency with no gene defect specified (CVID)	1151	24.17	8.53	54	4.69	36.32
Ataxia-telangiectasia	381	5.56	3.34	53	13.91	15.80
T-B- SCID with unknown gene defect	98	1.24	0.50	40	40.82	1.55
X-linked chronic granulomatous disease (CGD). gp91phox	169	3.30	2.05	32	18.93	6.37
Wiskott-Aldrich syndrome (WAS)	191	2.04	1.88	25	13.09	4.41
CGD with unknown gene defect	182	5.25	2.90	25	13.74	4.41
T-B + SCID with unknown gene defect	82	1.72	0.94	24	29.27	1.29
BTK deficiency. X-linked agammaglobulinemia (XLA)	453	5.26	3.38	19	4.19	12.38
Other T-cell disorders	93	10.94	4.03	19	20.43	5.34
Î³c deficiency (common gamma chain SCID, CD132 deficiency)	42	1.17	0.52	19	45.24	1.45
CHS with unknown gene defect	38	1.12	0.94	14	36.84	2.91
Griscelli syndrome, type 2	32	1.65	1.31	14	43.75	1.89
Unknown deficiency	111	8.44	3.75	14	12.61	12.16
Specific antibody deficiency with normal Ig levels and normal B cells	593	8.90	5.17	11	1.85	9.77
Unclassified immunodeficiencies	267	7.11	3.50	11	4.12	2.36
DiGeorge/velocardiofacial syndrome Chromosome 22q11.2 deletion Syndrome (22q11.2DS)	374	2.81	2.37	10	2.67	0.55
Omenn syndrome	19	0.66	0.53	10	52.63	0.53
Adenosine deaminase (ADA) deficiency	21	1.39	0.90	7	33.33	0.74
AD-HIES - STAT3 deficiency (Job Syndrome)	210	6.59	5.03	6	2.86	12.87
Agammaglobulinemia with unknown gene defect	203	6.49	3.29	6	2.96	13.64

*Not all patients present relevant data

Table 5 Mortality rate according to IUIS classification of IEI

Disease type	*N*	Mortality (%)
Diseases of Immune Dysregulation	241	20,3
Predominantly Antibody Deficiencies	5616	3,9
Combined immunodeficiencies with associated or syndromic features	1239	5,5
Congenital defects of phagocyte number or function	705	8,7
Unknown	378	5,0
Immunodeficiencies affecting cellular and humoral immunity	533	7,1
Complement Deficiencies	350	7,4
Defects in Intrinsic and Innate Immunity	169	6,5
Phenocopies of Inborn Errors of Immunity	24	0,0
Autoinflammatory Disorders	50	14,0

age at diagnosis of 8.23 years. The disease was associated with a very low mortality rate, 1 in 1627 patients (0.06%). Although some sIgA deficiency patients may present with varied clinical symptoms resembling other antibody deficiencies, over half are probably asymptomatic [20].

Common variable immunodeficiency (CVID) was the second most common diagnosis in the database. The mean age at diagnosis was 24.19 (± 0.6) years, while the mean age of death was 36.32 (± 16.88) years (Table 4). The development of next-generation sequencing (NGS) has revealed that more patients with a phenotype of common variable immunodeficiency (CVID) have a genetic variant that causes the disorder. If a pathogenic variant is identified, such patients are no longer diagnosed with CVID but a CVID-like disorder [21]. However, this designation has not been recognized in the 2022 update of the International Union of Immunological Societies (IUIS) expert committee (EC) on Inborn Errors of Immunity (IEI) [22]. Even though

it would be reasonable to expect a decline in CVID diagnoses without gene defects in recent years, our database did not show such a trend (data not shown).

While early diagnosis has been shown to increase survival and decrease costs [23], diagnostic delays for IEIs are, unfortunately, common [24–28]. CVID patients had the most prolonged delays to reach a diagnosis (8.53 years) in our data set (Table 4). Factors such as poor awareness among non-specialist healthcare professionals, inadequate infrastructure, and a lack of screening programs may be responsible for diagnostic delays. Additionally, IEI can go unnoticed because of the broad range of non-infectious manifestations or when the focus is on treating complications instead of addressing the underlying cause. A complete diagnosis often requires expert physicians and access to specialized centers, which may be lacking in certain Latin American regions. Furthermore, inconsistencies in diagnostic criteria can also lead to delays [29].

Lack of access [30] may explain why immunoglobulins were prescribed in only 29.49% of visits, even though antibody deficiencies are the most common condition described in the registry. The cost of the medication and reimbursement policies are barriers to the widespread use of this life and cost-saving therapy [23]. Shortage of plasma products is another barrier to immunoglobulin access globally [30, 31]. Latin America contributes to just 1% of plasma collection worldwide but purchases around 4% of global stores, making them deeply dependent on North American resources as the USA is the largest contributor to plasma products supply in the world [31]. On the other hand, immunoglobulin replacement therapy is increasing in some countries in the region, as a Brazilian report shows [32]. Contrary to some countries in the developed world [25, 28, 33], the subcutaneous administration of IgG was reported for only a small proportion of patients (7.31%).

Hematopoietic stem cell transplant (HSCT) and gene therapy are the only curative treatments available to IEI patients with SCID, chronic granulomatous disease (CGD), and dysregulatory disorders [34, 35]. Other IEIs may also be treated with HSCT or gene therapy, depending on the disease characteristics and donor availability [36]. In our cohort, HSCT was performed in 5% of all patients, but not all had information about the type of donor (Online Resource Table 5). For those with existing data, related donors were available in 60% of HSCTs, and 65.85% had good outcomes. Lack of infrastructure and expertise, delayed diagnosis, and referral [37] may account for the higher-than-expected mortality for some diseases in our cohort, particularly SCID.

While the study provides valuable insights into the demographics, disease characteristics, and outcomes of IEI patients in the database, some limitations must be considered. First, the retrospective data may introduce biases and incomplete information. Additionally, the database's completeness and accuracy depend on the data entry quality from various centers. Furthermore, the study does not provide long-term follow-up data for survivors or detailed information about the specific treatments and their efficacy.

Lack of disease awareness and specialized physicians are just a few of the challenges that IEI registries around the world face to collect patients' data [19]. Low funding and inadequate diagnostic infrastructure are adversities [17] that need to be addressed even before physicians and patients can be educated about IEI symptoms and diagnosis. In this regard, LASID and other registries around the world are paramount to improve physician education [6]. Political initiatives are necessary to improve funding and infrastructure, particularly in low- and middle-income countries.

In future research, efforts should be made to improve data quality and establish standardized data collection protocols. Long-term follow-up data could offer valuable information on the management and outcomes of IEI patients over time, which can aid in refining treatment strategies and improving patient care.

This study contributes to our understanding of IEIs and highlights the importance of early diagnosis, appropriate treatments, and improved data collection to optimize patient outcomes. Further research and collaborative efforts are needed to enhance our understanding of these rare disorders and improve patient care and outcomes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10875-024-01822-6.

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Data Availability Data may be accessed upon request to the corresponding author.

Declarations

Competing Interests ASG has received research funding from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and researcher initiative grants from Takeda. She received fees for educational activities or as a consultant for Catalyst Pharmaceuticals, CSL Behring, Takeda, Kalvista, Pharvaris, Pint-Pharma, Multicare, and BioMarin. ACN declare receiving speaker's fees and participating in advisory boards for Takeda, CSL Behring, Novartis, AstraZeneca,

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