**ARTICLE**

# Inborn errors of immunity: Manifestation, treatment, and outcome—an ESID registry 1994–2024 report on 30,628 patients

Gerhard Kindle[1,2]*, Mickaël Alligon[3]*, Michael H. Albert[4], Matthew Buckland[5,6], J. David Edgar[7], Benjamin Gathmann[1], Sujal Ghosh[8], Antonios Gkantaras[9], Alexandra Nieters[1,2], Claudio Pignata[10], Peter N. Robinson[11,12], Stephan Rusch[1,2], Catharina Schuetz[13,14], Svetlana Sharapova[15], Benjamin Shillitoe[16], Fabio Candotti[17], Andrew J. Cant[18,19], Jean-Laurent Casanova[20,21,22,23,24], Amos Etzioni[25], Alain Fischer[26,21], Isabelle Meyts[27], Luigi D. Notarangelo[28], Martine Pergent[29], C.I. Edvard Smith[30,31,32], ESID Registry Working Party, Lennart Hammarström[33]**, Bodo Grimbacher[1,34,35,36,37]**, Mikko R.J. Seppänen[38,39]**, Nizar Mahlaoui[3,40]**, Stephan Ehl[1]**, and Markus G. Seidel[41]**

**The European Society for Immunodeficiencies patient registry (ESID-R), established in 1994, is one of the world's largest databases on inborn errors of immunity (IEI). IEI are genetic disorders predisposing patients to infections, autoimmunity, inflammation, allergies, and malignancies. Treatments include antimicrobial therapy, immunoglobulin replacement, immune modulation, stem cell transplantation, and gene therapy. Data from 194 centers in 33 countries capture clinical manifestations and treatments from birth onward, with annually expected updates. This report reviews the ESID-R's structure, data content, and impact. The registry includes 30,628 patient datasets (aged 0–97.9 years; median follow-up: 7.2 years; total 825,568.2 patient-years), with 13,550 cases in 15 sub-studies. It has produced 84 peer-reviewed publications (mean citation rate: 95). Findings include real-world observations of IEI diagnoses, genetic causes, clinical manifestations, treatments, and survival**

[1]Institute for Immunodeficiency, Center for Chronic Immunodeficiency, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [2]Centre for Biobanking FREEZE, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [3]French National Reference Center for Primary Immune Deficiencies, Necker Enfants Malades University Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; [4]Department of Pediatrics, Dr. von Hauner Children's Hospital, Ludwig-Maximilians Universität München, Munich, Germany; [5]Barts Health National Health Service Trust, London, UK; [6]Molecular and Cellular Immunology Section, Immunity and Inflammation Department, Great Ormond Street Institute of Child Health, London, UK; [7]Department of Immunology, St James's Hospital, and School of Medicine, Trinity College Dublin, Dublin, Ireland; [8]Department of Pediatric Oncology, Hematology and Clinical Immunology, Medical Faculty, Center of Child and Adolescent Health, Heinrich-Heine-University and University Hospital, Duesseldorf, Germany; [9]Pediatric Immunology and Rheumatology Referral Center, 1st Department of Pediatrics, Aristotle University of Thessaloniki, Hippokration General Hospital, Thessaloniki, Greece; [10]Department of Translational Medical Sciences, Federico II University, Naples, Italy; [11]Berlin Institute of Health, Charité - Universitätsmedizin Berlin, Berlin, Germany; [12]The Jackson Laboratory for Genomic Medicine, Farmington, CT, USA; [13]Department of Pediatrics and University Center for Rare Diseases, Medizinische Fakultät Carl Gustav Carus, Technische Universität, Dresden, Germany; [14]German Center for Child and Adolescent Health, Partner Site Leipzig/Dresden, Dresden, Germany; [15]Research Department, Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Minsk Region, Belarus; [16]Paediatric Immunology and Infectious Diseases, Sheffield Children's NHS Foundation Trust, Sheffield, UK; [17]Division of Immunology and Allergy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [18]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, England; [19]Department of Paediatric Immunology and Infectious Diseases, Great North Children's Hospital, Newcastle upon Tyne, England; [20]Laboratory of Human Genetics of Infectious Diseases, INSERM U1163, Necker Hospital for Sick Children, Paris, France; [21]Imagine Institute, University Paris Cité, Paris, France; [22]St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA; [23]Howard Hughes Medical Institute, New York, NY, USA; [24]Department of Pediatrics, Necker Hospital for Sick Children, Assistance Publique-Hôpitaux de Paris, Paris, France; [25]Faculty of Medicine, Technion, Haifa, Israel; [26]Unité d'immunologie Pédiatrique, Hôpital Necker Enfants Malades, Paris, France; [27]Department of Pediatrics, Department of Microbiology, Immunology and Transplantation, ERN-RITA Core Center, University Hospitals Leuven, KU Leuven, Leuven, Belgium; [28]Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA; [29]International Patient Organisation for Primary Immunodeficiencies, Brussels, Belgium; [30]Department of Laboratory Medicine, Clinical Immunology, Karolinska Institutet, Stockholm, Sweden; [31]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; [32]Karolinska ATMP Center, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [33]Division of Immunology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden; [34]Clinic of Rheumatology and Clinical Immunology, Center for Chronic Immunodeficiency, Medical Center, Faculty of Medicine, Albert-Ludwigs-University of Freiburg, Freiburg, Germany; [35]German Center for Infection Research, Satellite Center Freiburg, Freiburg, Germany; [36]Centre for Integrative Biological Signalling Studies, Albert-Ludwigs University, Freiburg, Germany; [37]RESIST - Cluster of Excellence 2155 to Hanover Medical School, Satellite Center Freiburg, Freiburg, Germany; [38]Rare Disease Center and Pediatric Research Center, Children and Adolescents, University of Helsinki, HUS Helsinki University Hospital, ERN-RITA Core Center, RITAFIN, Helsinki, Finland; [39]Translational Immunology Research Program, University of Helsinki, Helsinki, Finland; [40]Pediatric Immuno-Hematology and Rheumatology Unit, Necker Enfants Malades University Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; [41]Division of Pediatric Hematology and Oncology, Department of Pediatric and Adolescent Medicine, Styrian Children's Cancer Research Unit for Cancer and Inborn Errors of the Blood and Immunity in Children, Medical University of Graz, Graz, Austria.

*G. Kindle and M. Alligon contributed equally to this work.   Correspondence to Michael H. Albert: michael.albert@med.uni-muenchen.de;   Markus G. Seidel: markus.seidel@medunigraz.at

**L. Hammarström, B. Grimbacher, M.R.J. Seppänen, N. Mahlaoui, S. Ehl, and M.G. Seidel jointly designed, coordinated, and supervised the study.   ESID Registry Working Party members are listed at the end of the PDF.

trends. The ESID-R fosters global collaboration, advancing IEI research and patient care. This report highlights the key role of the multinational ESID-R, led by an independent medical society, in evidence-based discovery.

## Introduction

Inborn errors of immunity (IEI) are genetic disorders affecting immunity. They almost invariably increase the susceptibility to infections and may cause autoimmunity, inflammation, allergy, and predispose individuals to malignancy ([1], [2], [3], [4], [5], [6]). IEI can manifest at any age and are characterized by a spectrum of symptoms related to impaired or uncontrolled immune responses. These often have a serious impact on the health and quality of life of those affected. Many IEI are rare diseases, including ultra-rare and hyper-rare forms (i.e., frequently <<1/ 2,000 persons affected). Thus, an international strategy was needed to collect a meaningful number of datapoints for cross-sectional analyses and longitudinal clinical observations of natural courses of specific IEI.

The European Society for Immunodeficiencies registry (ESID-R) was founded in 1994 by ESID, a nonprofit medical specialist society, creating a central database for primary immunodeficiencies. These are currently referred to as IEI or primary immune disorders (PID), differentiating them from secondary immune disorders ([7]). The ESID-R mainly serves to contain, store, and enable the analysis of IEI/PID data to improve the understanding of these diseases and their underlying immunobiology. Historically, the ESID-R was operated for the first 10 years as a hard copy-based database, and data were submitted by fax to the first chairs of the ESID-R, Lennart Hammarström and Mohammad Abedi, in Huddinge, Sweden. From 2000 to 2004, Bodo Grimbacher with coworkers in Freiburg, Germany, developed and implemented the first web-based version of the ESID-R ([8], [9]). In 2014, another major revision was carried out, headed by Stephan Ehl, Freiburg. The two key drivers of this second redesign were the goal to allow registry participation at three different levels according to center resources and the need to improve data quality so that a high level of confidence in the accuracy of the data could be inferred for clinical application and publication. In addition to inbuilt quality checks, the migration of existing data to the third version of the ESID-R and the entry of new patient data since then required a manual validation process of all included patients lacking a genetic diagnosis to meet the simultaneously developed clinical-working criteria for IEI/PID diagnoses, compiled and published by a group of experts ([10]). In late 2024, ESID decided to move the ESID-R technical and physical foundation from the Medical Center of the University of Freiburg to a commercial clinical trials operator (Castor-edc, Netherlands) to improve data, system, and access security. Maintaining the three-level study structure and the mandatory diagnosis validation process, this currently new, fourth version of the ESID-R is expected to facilitate the generation of data modules by research groups, allowing decentralized sub-study (electronic case report form) programming, independent data exports for center or sub-study analyses, automated center dashboards, and add-on features such as patient reporting.

Here, we present major findings from clinical observations of 30,628 patients, based on the current ESID-R dataset. These findings indicate epidemiologically relevant disease distributions and the calculated prevalence of diagnoses in registered patients, their clinical manifestations, diagnostic delays, treatment, disease course, and survival probabilities across all IEI/ PID categories. Furthermore, we describe the organizational and technical evolution of the ESID-R, its relationship with the international registry landscape, and its role as a research (sub-)study platform. These data are of the utmost relevance to anyone affected by immune disorders or involved in patient care, management and therapy, and drug and policy development for patients with IEI/PID around the world.

## Results

On the end date chosen for inclusion in March 2024, the ESID-R contained data for 30,628 IEI/PID patients from 194 participating centers in 33 European and other, mostly neighboring, countries. There was a steady increase in the registration of patients over time (Fig. S1 A), apart from a temporary decline in patient numbers and, to a lesser extent, in center numbers (Fig. S1 B) shortly after 2014, due to structural platform changes in 2014. These required centers to verify their patients to improve the accuracy of existing data. This allowed us to derive patient distribution by country and the minimal prevalence of PID/IEI (Table S1 and Fig. S2).

### Patient characteristics

Fig. 1 shows the clinical manifestations that led to IEI/PID diagnosis. Ages at onset, clinical, and genetic diagnosis are shown in Fig. S1 C. A steady decline in new diagnoses was observed with age, although a small second peak and plateau were seen in adulthood, and a trend for earlier identification of genetic diagnoses was observed. The delay from the onset of symptoms to clinical diagnosis and between clinical and genetic diagnosis is shown by year of clinical or genetic diagnosis, i.e., the endpoint of each delay, over the last 20 years in Fig. S1 D. As reported previously ([11]), the majority of 80.3% of patients have infections on their way to diagnosis, but only in 61.8% as sole recorded manifestation of IEI, followed by features of immune dysregulation in 11.1% and syndromic manifestations in 7.3% as sole clinical presentation at diagnosis ($n$ = 15,360; 2,746; 1,803, respectively; Fig. 1). Malignancies were among the first manifestations of IEI in 479 patients and the only initial manifestation in 117 patients (0.5%; Fig. 1).

Table 1 shows the main patient demographic and diagnosis categories, comorbidities such as malignancy, COVID-19, and living status (Fig. S3). Fig. S4 shows the patient numbers and their distribution according to their International Union of Immunological Societies (IUIS) classification, disease name, and genetic diagnosis (see detailed interactive version at https:// esid.org/html-pages/Suppl%20Fig%203_ESID_30k_sunburst_ PID.html). About half of all patients suffer from primary antibody deficiencies (PAD; $n$ = 15,123), followed in descending

Kindle et al.
ESID registry 30-years report: IEI manifestation, treatment, and outcome

Journal of Human Immunity    2 of 15
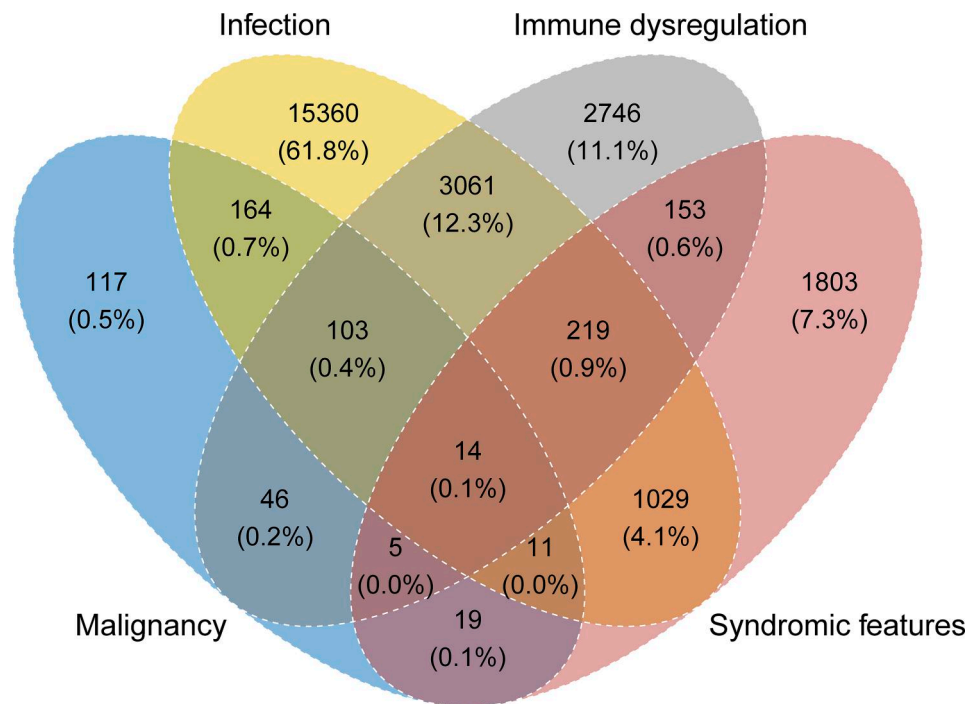https://doi.org/10.70962/jhi.20250007

Figure 1. **Main manifestations at onset of IEI or PID.** Venn diagram of main manifestations of IEI/PID with absolute patient numbers and proportions.

order by combined immunodeficiencies (CID) with syndromic features ("syndromic"; n = 4,239), phagocytic disorders ("phagocyte"; n = 2,548), CID (n = 2,531), and primary diseases of immune dysregulation (PIRD; n = 2,171; Table 1 and Fig. S4). Table 1 presents the ages at onset, clinical diagnosis, genetic confirmation, last follow-up, and the diagnostic delay. The proportion of patients reported to have suffered from malignancies was 8.9% (n = 1,783). Malignancies were reported as occurring in all subgroups of patients with IEI/PID with moderately varying frequencies, corroborating the notion that IEI/PID are cancer predisposition syndromes. The proportion of patients reported to have been affected by COVID-19 was highest in PAD (35.9%; total cohort: 29.7%). More than half of CID patients received curative therapy (52.6%), followed by those with bone marrow failure syndromes (BMF; 39.8%), PIRD, and phagocyte disorders (30.3% and 25.8%, respectively). Table S2 shows the causes of death.

**Representation of genetic IEI diagnoses**
Fig. 2 shows the absolute numbers of patients with a documented genetic diagnosis (n = 12,774, 44.5%) versus those without (n = 15,905, 55.5%, including patients not genetically tested) by IEI category. As expected, within the largest patient subgroup (PAD), the genetic diagnosis is lacking for the majority of patients (Fig. 2 A), and the clinical diagnosis of common variable immunodeficiency (CVID) is attributed, whereas patients with CID with syndromic features had the highest proportion of genetic diagnoses. The top five genes mutated per IEI category are shown in Fig. 2 B, with *IL2RG* being the most frequently reported germline genetic cause

of CID; *22q11.2* deletion syndrome, of CID with syndromic features; *BTK*, of PAD; *TNFRSF6*, of category IV, diseases of immune dysregulation; *CYBB*, of phagocyte disorders; *STAT1*, of intrinsic or innate immune disorders; *MEFV*, of autoinflammatory syndromes; C1 inhibitor, of complement deficiencies; *RTEL*, of BMF; and somatic *TNFRSF6*, of phenocopies. The top 50 genetic causes of IEI from the ESID-R are shown with patient numbers in descending order in Fig. S5.

**Treatment modalities according to IEI categories**
Immunoglobulin replacement therapy (IGRT), hematopoietic stem cell transplantation (HSCT), gene therapy (GT), and splenectomy are recorded in the ESID-R and listed in Table S3. As expected, the highest number and proportion of IGRT-receiving patients is seen in the subgroup of patients with PAD (Fig. 3). The highest absolute numbers of HSCT procedures were performed in patients with CID, followed by those with PIRD and phagocytic disorders. IGRT and HSCT were documented in patients with IEI/PID in any category. GT, an evolving curative treatment option devoid of some risks associated with HSCT, such as alloreactivity, was recorded in a descending order for CID, syndromic, and phagocyte disorders (Fig. 3). Splenectomy was recorded relatively frequently in patients with phenocopies, but it was also documented for any IEI category. The use of immune-modulatory treatments, such as anti-inflammatory, cell-depleting, or pathway-directed (targeted) therapies, and the rare cases of thymus or solid organ transplantation were recorded but are not shown here, as the heterogeneity of the data exceeds the scope of this general report.

Kindle et al.
ESID registry 30-years report: IEI manifestation, treatment, and outcome

Journal of Human Immunity    3 of 15
https://doi.org/10.70962/jhi.20250007

Table 1. ESID-R patient characteristics

| Covariate | Values | Whole cohort N = 30,628 | CID (I) N = 2,531 | Syndromic (II) N = 4,239 | PAD (III) N = 15,123 | PIRD (IV) N = 2,171 | Phagocyte (V) N = 2,548 | Innate (VI) N = 823 | AIS (VII) N = 1,042 | Complement (VIII) N = 1,482 | BMF (IX) N = 85 | Phenocopies (X) N = 30 | other N = 554 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gender | M | 16,767 (54.8%) | 1,470 (58.1%) | 2,473 (58.3%) | 7,782 (51.5%) | 1,329 (61.2%) | 1,693 (66.5%) | 387 (47%) | 575 (55.2%) | 681 (46%) | 57 (67.1%) | 19 (63.3%) | 301 (54.3%) |
| | F | 13,855 (45.2%) | 1,061 (41.9%) | 1,766 (41.7%) | 7,337 (48.5%) | 841 (38.8%) | 854 (33.5%) | 436 (53%) | 467 (44.8%) | 801 (54%) | 28 (32.9%) | 11 (36.7%) | 253 (45.7%) |
| Year of birth | | 1997 (1976; 2008) | 2007 (1997; 2014) | 2005 (1995; 2012) | 1984 (1963; 2001) | 2004 (1993; 2011) | 2002 (1991; 2010) | 2003 (1991; 2011) | 2008 (1999; 2013) | 1991 (1972; 2006) | 2004 (1987; 2011) | 2001.5 (1995; 2008.5) | 1998 (1974; 2007) |
| Familial case | N | 21,854 (76.6%) | 1,725 (72.9%) | 3,002 (74.1%) | 11,949 (85.4%) | 1,266 (61.1%) | 1,468 (65.4%) | 492 (62.2%) | 771 (76.6%) | 645 (46.5%) | 57 (75%) | 28 (93.3%) | 451 (87.7%) |
| | Y | 6,681 (23.4%) | 641 (27.1%) | 1,047 (25.9%) | 2,049 (14.6%) | 805 (38.9%) | 778 (34.6%) | 299 (37.8%) | 236 (23.4%) | 742 (53.5%) | 19 (25%) | 2 (6.7%) | 63 (12.3%) |
| Consanguinity | N | 24,731 (87.2%) | 1,426 (60.8%) | 3,247 (82.1%) | 13,381 (95.5%) | 1,602 (78.8%) | 1,699 (75.6%) | 589 (77.3%) | 920 (93.2%) | 1,303 (93.1%) | 66 (84.6%) | 28 (100%) | 470 (92.7%) |
| | Y | 3,624 (12.8%) | 921 (39.2%) | 708 (17.9%) | 631 (4.5%) | 432 (21.2%) | 547 (24.4%) | 173 (22.7%) | 67 (6.8%) | 96 (6.9%) | 12 (15.4%) | 0 (0%) | 37 (7.3%) |
| Age at onset of symptoms | | 3 (0.4; 14.1) | 0.3 (0; 1.6) | 0.5 (0; 2.2) | 8 (2; 30) | 2.2 (0.3; 7.5) | 0.7 (0.1; 3) | 1.2 (0.2; 3.8) | 2.8 (0.7; 5) | 8 (3; 18) | 3 (0.3; 8.1) | 2.8 (0.6; 4.9) | 3 (0.7; 15.4) |
| Immune dysregulation at onset | N | 21,482 (77.2%) | 1,712 (77.5%) | 3,242 (84.1%) | 11,175 (80.3%) | 616 (31.6%) | 1,944 (86.2%) | 632 (84.9%) | 536 (55%) | 1,182 (88.3%) | 49 (67.1%) | 4 (13.3%) | 390 (80.7%) |
| | Y | 6,347 (22.8%) | 498 (22.5%) | 613 (15.9%) | 2,741 (19.7%) | 1,335 (68.4%) | 311 (13.8%) | 112 (15.1%) | 438 (45%) | 156 (11.7%) | 24 (32.9%) | 26 (86.7%) | 93 (19.3%) |
| Infection at onset | N | 8,133 (28.9%) | 436 (19.6%) | 2,195 (56.6%) | 1,920 (13.6%) | 1,161 (59.6%) | 590 (26%) | 108 (14.4%) | 705 (72.5%) | 827 (61.5%) | 44 (60.3%) | 19 (67.9%) | 128 (26.3%) |
| | Y | 19,961 (71.1%) | 1,786 (80.4%) | 1,680 (43.4%) | 12,202 (86.4%) | 787 (40.4%) | 1,681 (74%) | 643 (85.6%) | 267 (27.5%) | 518 (38.5%) | 29 (39.7%) | 9 (32.1%) | 359 (73.7%) |
| Malignancy at onset | N | 27,294 (98.3%) | 2,180 (98.6%) | 3,766 (97.8%) | 13,620 (98.1%) | 1,885 (97.1%) | 2,235 (99.4%) | 741 (99.7%) | 969 (99.8%) | 1,333 (99.8%) | 69 (94.5%) | 25 (89.3%) | 471 (97.7%) |
| | Y | 479 (1.7%) | 30 (1.4%) | 85 (2.2%) | 269 (1.9%) | 57 (2.9%) | 13 (0.6%) | 2 (0.3%) | 2 (0.2%) | 3 (0.2%) | 4 (5.5%) | 3 (10.7%) | 11 (2.3%) |
| Syndromic manifestations at onset | N | 24,549 (88.3%) | 2,046 (92.6%) | 1,651 (42.7%) | 13,574 (97.7%) | 1,798 (92.5%) | 2,075 (92.3%) | 683 (91.8%) | 919 (94.6%) | 1,274 (95.4%) | 40 (54.8%) | 28 (100%) | 461 (95.4%) |
| | Y | 3,253 (11.7%) | 164 (7.4%) | 2,220 (57.3%) | 320 (2.3%) | 145 (7.5%) | 174 (7.7%) | 61 (8.2%) | 52 (5.4%) | 62 (4.6%) | 33 (45.2%) | 0 (0%) | 22 (4.6%) |

Kindle et al.
ESID registry 30-years report: IEI manifestation, treatment, and outcome

Journal of Human Immunity    4 of 15
https://doi.org/10.70962/jhi.20250007

Table 1. **ESID-R patient characteristics (Continued)**

| Covariate | Values | Whole cohort N = 30,628 | CID (I) N = 2,531 | Syndromic (II) N = 4,239 | PAD (III) N = 15,123 | PIRD (IV) N = 2,171 | Phagocyte (V) N = 2,548 | Innate (VI) N = 823 | AIS (VII) N = 1,042 | Complement (VIII) N = 1,482 | BMF (IX) N = 85 | Phenocopies (X) N = 30 | other N = 554 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Other onset | N | 24,466 (87.9%) | 1,992 (90.1%) | 3,298 (85.5%) | 12,947 (93.1%) | 1,782 (91.6%) | 2,086 (92.7%) | 685 (92.1%) | 545 (55.6%) | 647 (48.1%) | 59 (80.8%) | 28 (96.6%) | 397 (81.9%) |
| | Y | 3,366 (12.1%) | 220 (9.9%) | 559 (14.5%) | 963 (6.9%) | 163 (8.4%) | 164 (7.3%) | 59 (7.9%) | 436 (44.4%) | 699 (51.9%) | 14 (19.2%) | 1 (3.4%) | 88 (18.1%) |
| No clinical symptoms | N | 27,605 (94.1%) | 2,188 (91%) | 3,770 (92.5%) | 13,875 (95.9%) | 1,926 (91.5%) | 2,238 (92.3%) | 735 (91.9%) | 966 (97.2%) | 1,326 (91.2%) | 71 (91%) | 28 (100%) | 482 (97.6%) |
| | Y | 1,725 (5.9%) | 217 (9%) | 306 (7.5%) | 595 (4.1%) | 180 (8.5%) | 187 (7.7%) | 65 (8.1%) | 28 (2.8%) | 128 (8.8%) | 7 (9%) | 0 (0%) | 12 (2.4%) |
| Age at clinical diagnosis (CD) (years) | | 8.2 (2; 30.1) | 0.7 (0.3; 4.6) | 2.4 (0.4; 6.9) | 22 (6.2; 44) | 5.1 (1; 13) | 2 (0.5; 7) | 4.2 (1.1; 14) | 5 (2.7; 11.4) | 15 (5.2; 28.8) | 5 (1.3; 13.7) | 5.2 (3; 9.8) | 7.5 (2.3; 34.1) |
| Delay between onset and CD (years) | | 1.3 (0.1; 5.1) | 0.2 (0; 1.3) | 0.8 (0; 3.9) | 2.7 (0.7; 7.5) | 0.4 (0; 3.4) | 0.5 (0.1; 2.2) | 1 (0.1; 5.6) | 1.5 (0.5; 4) | 1.1 (0.1; 7) | 0.5 (0.1; 2.1) | 0.9 (0.3; 3.9) | 1.7 (0.3; 4.7) |
| Genetics | Mutation found | 12,774 (44.5%) | 1,470 (63.1%) | 3,647 (88.8%) | 2,251 (16%) | 1,671 (80.8%) | 1,693 (71.8%) | 529 (68.1%) | 662 (65.3%) | 772 (55.6%) | 49 (71%) | 30 (100%) | 0 (0%) |
| | No mutation found | 2,852 (9.9%) | 319 (13.7%) | 79 (1.9%) | 1,850 (13.1%) | 195 (9.4%) | 106 (4.5%) | 81 (10.4%) | 71 (7%) | 27 (1.9%) | 9 (13%) | 0 (0%) | 115 (24.7%) |
| | Not tested | 11,956 (41.7%) | 403 (17.3%) | 325 (7.9%) | 9,398 (66.8%) | 125 (6%) | 478 (20.3%) | 97 (12.5%) | 250 (24.7%) | 569 (41%) | 8 (11.6%) | 0 (0%) | 303 (65%) |
| | Pending | 1,097 (3.8%) | 136 (5.8%) | 57 (1.4%) | 576 (4.1%) | 76 (3.7%) | 80 (3.4%) | 70 (9%) | 31 (3.1%) | 20 (1.4%) | 3 (4.3%) | 0 (0%) | 48 (10.3%) |
| Age at genetic diagnosis (GD) | | 5.5 (1.1; 15) | 0.9 (0.3; 6.7) | 3.2 (0.4; 9.7) | 9.4 (2.9; 25) | 8.3 (1.8; 17.3) | 4.4 (1.1; 12.7) | 10 (3.2; 20.4) | 8.4 (4; 22) | 13.2 (5; 26.9) | 8.2 (3.6; 17.4) | 9.8 (5; 14.1) | NA (NA; NA) |
| Delay between CD and GD | | 0.3 (0; 2.9) | 0.2 (0; 1.2) | 0.2 (0; 1.7) | 1.3 (0.1; 8.8) | 0.2 (0; 2.2) | 0.3 (0; 2.2) | 0.8 (0.1; 5.9) | 0.1 (0; 11) | 0.2 (0; 1.6) | 0.4 (0.1; 2.6) | 1 (0.2; 4.9) | NA (NA; NA) |
| Reason of GD | Clinical | 8,787 (88%) | 975 (87.7%) | 2,601 (90.8%) | 1,629 (89.2%) | 1,192 (82.2%) | 1,081 (90.6%) | 380 (85.4%) | 515 (88.6%) | 350 (77.8%) | 39 (92.9%) | 25 (96.2%) | 0 (0%) |
| | Family | 975 (9.8%) | 77 (6.9%) | 153 (5.3%) | 170 (9.3%) | 245 (16.9%) | 100 (8.4%) | 63 (14.2%) | 65 (11.2%) | 99 (22%) | 3 (7.1%) | 0 (0%) | 0 (0%) |
| | Neonatal | 114 (1.1%) | 41 (3.7%) | 45 (1.6%) | 20 (1.1%) | 2 (0.1%) | 3 (0.3%) | 0 (0%) | 1 (0.2%) | 1 (0.2%) | 0 (0%) | 1 (3.8%) | 0 (0%) |
| | Prenatal | 112 (1.1%) | 19 (1.7%) | 64 (2.2%) | 7 (0.4%) | 11 (0.8%) | 9 (0.8%) | 2 (0.4%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

Table 1. **ESID-R patient characteristics** (Continued)

| Covariate | Values | Whole cohort N = 30,628 | CID (I) N = 2,531 | Syndromic (II) N = 4,239 | PAD (III) N = 15,123 | PIRD (IV) N = 2,171 | Phagocyte (V) N = 2,548 | Innate (VI) N = 823 | AIS (VII) N = 1,042 | Complement (VIII) N = 1,482 | BMF (IX) N = 85 | Phenocopies (X) N = 30 | other N = 554 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sequencing method of GD | Gene sequencing | 7,693 (83.3%) | 848 (80.1%) | 2,122 (82%) | 1,421 (83.5%) | 1,154 (85.3%) | 970 (87.7%) | 323 (77.5%) | 459 (85.5%) | 347 (84.6%) | 26 (70.3%) | 23 (95.8%) | 0 (0%) |
| | Nongenetic definitive test | 441 (4.8%) | 35 (3.3%) | 284 (11%) | 11 (0.6%) | 12 (0.9%) | 59 (5.3%) | 3 (0.7%) | 0 (0%) | 36 (8.8%) | 1 (2.7%) | 0 (0%) | 0 (0%) |
| | Whole exome/genome sequencing | 1,100 (11.9%) | 176 (16.6%) | 183 (7.1%) | 270 (15.9%) | 187 (13.8%) | 77 (7%) | 91 (21.8%) | 78 (14.5%) | 27 (6.6%) | 10 (27%) | 1 (4.2%) | 0 (0%) |
| Malignancy at any time | N | 18,176 (91.1%) | 1,578 (93.4%) | 2,491 (88.9%) | 8,759 (89.4%) | 1,595 (91.4%) | 1,609 (95.6%) | 569 (94.7%) | 604 (98.1%) | 632 (97.7%) | 66 (90.4%) | 16 (72.7%) | 257 (89.9%) |
| | Y | 1,783 (8.9%) | 112 (6.6%) | 312 (11.1%) | 1,034 (10.6%) | 150 (8.6%) | 74 (4.4%) | 32 (5.3%) | 12 (1.9%) | 15 (2.3%) | 7 (9.6%) | 6 (27.3%) | 29 (10.1%) |
| Covid-19 | N | 5,380 (70.3%) | 456 (81%) | 801 (76.1%) | 2,613 (64.1%) | 434 (74.2%) | 363 (81%) | 130 (77.4%) | 260 (74.9%) | 177 (76.3%) | 15 (78.9%) | 6 (75%) | 125 (79.6%) |
| | Y | 2,273 (29.7%) | 107 (19%) | 251 (23.9%) | 1,461 (35.9%) | 151 (25.8%) | 85 (19%) | 38 (22.6%) | 87 (25.1%) | 55 (23.7%) | 4 (21.1%) | 2 (25%) | 32 (20.4%) |
| Living status | Alive | 20,680 (67.5%) | 1,419 (56.1%) | 2,580 (60.9%) | 10,740 (71%) | 1,519 (70%) | 1,534 (60.2%) | 546 (66.3%) | 729 (70%) | 1,127 (76%) | 52 (61.2%) | 22 (73.3%) | 412 (74.4%) |
| | Deceased | 3,216 (10.5%) | 615 (24.3%) | 676 (15.9%) | 1,117 (7.4%) | 356 (16.4%) | 269 (10.6%) | 87 (10.6%) | 23 (2.2%) | 18 (1.2%) | 22 (25.9%) | 3 (10%) | 30 (5.4%) |
| | Lost to follow-up | 6,732 (22%) | 497 (19.6%) | 983 (23.2%) | 3,266 (21.6%) | 296 (13.6%) | 745 (29.2%) | 190 (23.1%) | 290 (27.8%) | 337 (22.7%) | 11 (12.9%) | 5 (16.7%) | 112 (20.2%) |
| Age at last follow-up/death | | 20.2 (9.4; 42.6) | 8.7 (2; 18.7) | 12.5 (6.3; 19.9) | 35.4 (16.9; 55.9) | 14.8 (6.5; 24.2) | 13.7 (5.8; 23.6) | 15 (7; 27.3) | 11.2 (6; 20.9) | 27.3 (13.6; 46.4) | 14.6 (6.3; 23.7) | 18.2 (12; 22.8) | 19 (8.4; 44.1) |
| Living status (stops at CT) | Alive at last follow-up | 24,222 (81.1%) | 928 (37.1%) | 3,144 (76.5%) | 13,522 (92%) | 1,313 (61%) | 1,680 (67%) | 695 (86.1%) | 956 (95.1%) | 1,463 (99.1%) | 41 (49.4%) | 25 (83.3%) | 455 (90.6%) |
| | Deceased | 2,226 (7.5%) | 258 (10.3%) | 496 (12.1%) | 966 (6.6%) | 186 (8.6%) | 181 (7.2%) | 74 (9.2%) | 17 (1.7%) | 11 (0.7%) | 9 (10.8%) | 3 (10%) | 25 (5%) |
| | Curative therapy | 3,431 (11.5%) | 1,315 (52.6%) | 470 (11.4%) | 216 (1.5%) | 653 (30.3%) | 648 (25.8%) | 38 (4.7%) | 32 (3.2%) | 2 (0.1%) | 33 (39.8%) | 2 (6.7%) | 22 (4.4%) |
| Age at last follow-up (stops at CT) | | 19.4 (8; 42.6) | 1.3 (0.5; 11) | 11.4 (5.2; 19.3) | 35.5 (16.8; 55.9) | 12.1 (3.2; 22.7) | 11.6 (4; 21.8) | 14.6 (6.6; 27) | 11.1 (5.9; 20.7) | 27.4 (13.6; 46.5) | 10 (5; 20.5) | 18.2 (11; 22.8) | 19 (7.8; 44.1) |
| Follow-up duration (years) | | 7.2 (2.6; 14) | 4.6 (0.8; 12) | 8 (2.9; 14) | 7.9 (3.4; 14.5) | 5.6 (1.7; 11.6) | 7.7 (2; 17.2) | 6.6 (1.7; 13.1) | 4 (1.6; 7.9) | 7.7 (2.1; 16.9) | 6.7 (3.4; 10.6) | 11.2 (5.2; 17.1) | 5.2 (1.5; 11) |

Quantitative covariates: median (Q1; Q3); qualitative covariates: effective (percentage); the order of subgroups from left to right follows the IEI categories I–X of the 2022 IUS classification available on the end date chosen for inclusion; values Y for "yes/present" for real positive values, N for "no" is shown to reflect the size of the correct comparison group, excluding "unknown" replies; percentages represent the fraction of

## Survival probabilities of patients with IEI

We hypothesized that the survival probabilities of patients in the 10 IUIS categories of IEI differed due to their varying predispositions to life-threatening infections, malignancies, autoimmunity, or other manifestations and complications associated with their underlying conditions. Although the data granularity in the entire ESID-R with respect to patient follow-up intervals is not comparable with that in disease-specific prospective cohort studies, we could plot the reversed cumulative incidence function, due to the presence of competing risks, based on the relatively large patient numbers in each IEI category (Fig. 4; see Fig. S6 for the same curves with confidence intervals). Of note, natural biases such as underreporting of patients who died from IEI before diagnosis or of patients with a mild phenotype exist, and numbers at risk increased over the first few years of the observation period (0–97.9 years of age) due to the later time points of inclusion or diagnosis. We detected a steep early decline in survival in many IE categories while curves plateaued, (1) methodologically, in some where definitive treatments exist, or (2) in genotypes with variable penetrance (e.g., CID and PIRD). Additionally, while patients with PAD showed a continuous decline in survival probability from a young age across all age groups, the decline in the survival of patients with phagocyte and innate immune disorders showed an initial drop. This finding suggests that a proportion of patients are at very high risk during their first 5 years of life. Diagnoses of early deceased patients with PIRD ($n$ = 70 under 5 years of age) were mostly due to disorders with a high risk of hemophagocytic lymphohistiocytosis (81.4%); premature deaths in "innate" IEI were frequently due to IRAK4 or MyD88 deficiencies (Table S4). Patients with IEI/PID with syndromic features had a triphasic survival probability. After observing an initial decline in the first 4 years of life, we detected a second pronounced decline in survival probability in the patients' second and third decades of life, most likely due to the increased risk of malignancies in many patients in this subgroup (>25%, see Table S2), and a third, relatively steep decline in patients in their sixth to seventh decades.

## The ESID-R in the international data source landscape

Other continental or cross-regional IEI/PID registries of varying temporal and geographical depth include the global Jeffrey Modell Foundation Centers Network (>94,000 patients), the United States Immunodeficiency Network registry in the USA (>5,000), the Latin American Society for Immunodeficiencies registry in Latin America (>9,000), the ASCIA (Australasian Society for Clinical Immunology & Allergy) Register (>1,500), currently being redeveloped as part of the Australasian network, Japanese Society for Immunodeficiency and Autoinflammatory Diseases (>1,200) in Japan as part of the Asia-Pacific (Asia-Pacific Society for Immunodeficiencies) network, the Canadian registry (Canadian IEI National Registry) founded in 2024, and the registries of the Primary Immune Deficiency Treatment Consortium (PIDTC) of North America; in addition, many national registries exist inside or outside of ESID (12). Those reported in Europe are shown in Fig. S7 and Table S5. Furthermore, the ESID-R is listed as official data source in catalogues of the
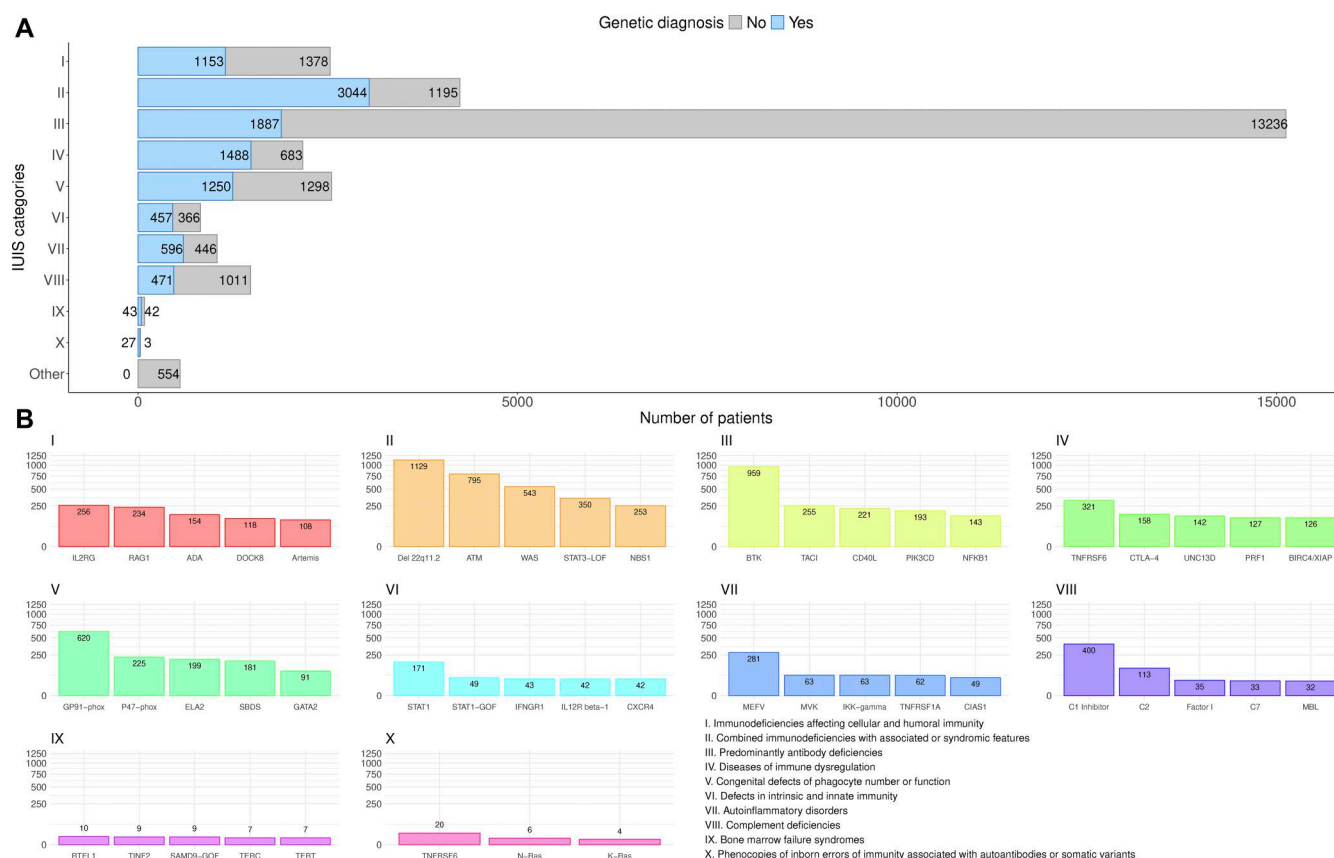
Figure 2. **Representation of genetic diagnoses of known IEI/PID in the ESID-R. (A, upper panel)** The number and proportion of patients with a genetic versus those without a genetic diagnosis is shown in descending order. **(B, lower panel)** The top 5 genetic defects or deletions registered in the ESID-R per all 10 IUIS categories of IEI are presented; the nomenclature in registry diagnosis and gene fields was not regularly updated/changed, showing, e.g., GP91-phox instead of *CYBB* and p47-phox instead of *NCF1*.

European Medical Agency and of European Rare Disease Registry Infrastructure, the European Union (EU) rare disease platform, which are metadata repositories to increase visibility and facilitate the use of rare disease patients' data.

### Scientific impact of the ESID-R and sub-studies

Up to the end date chosen for data inclusion in this manuscript, 84 peer-reviewed publications resulted from projects deriving data directly from the ESID-R (Fig. 5 and ESID website [13]). We evaluated this scientific output by categorizing and counting the publications and their citations as follows: disease-specific natural history studies (*n* = 25; 3,658 citations), country-specific epidemiological studies (*n* = 19; 2,575 citations), six reviews (422 citations), two on technical aspects (104 citations), and 15 of our own registry-conducted studies (e.g., on first manifestations or on working definitions for the clinical diagnosis of IEI/PID, 1,221 citations), plus 17 studies that could have been assigned to multiple or overlapping categories (Fig. 5), resulting in a mean citation rate of 95 per publication.

### Discussion

The ESID-R is a large and growing real-world database enabling powerful analyses that have continuously generated epidemiological and disease-specific observational results since 1994. It contributes to knowledge and improvements in patient care in IEI in Europe and beyond. The present analysis illustrates the current distribution of (1) IEI diagnoses recorded in contributing centers and countries; (2) major treatment modalities between all IEI categories; (3), ages at onset, at clinical, and at genetic diagnosis; and (4) survival probabilities. Our results underline the recommendation to potentially implement newborn screening (NBS) for certain additional IEI other than severe CID (SCID). The 7,980 citations of 84 peer-reviewed ESID-R–based publications as of early 2024 demonstrate the success of the ESID-R as a platform for research sub-studies and their substantial scientific impact. Hence, the ESID-R provides a clear example of how data collection and collaboration can benefit patients with rare diseases.

### Survival probabilities, early diagnosis, and NBS

NBS for SCID by measuring T cell receptor with or without kappa-deleting recombination excision circles in dried blood spots has been implemented in many countries around the world (14, 15, 16). A substantial survival benefit for patients diagnosed and treated by early HSCT was demonstrated and recently confirmed in a longitudinal study of the PIDTC (17). The steep early decline in survival we observed in patients with disorders
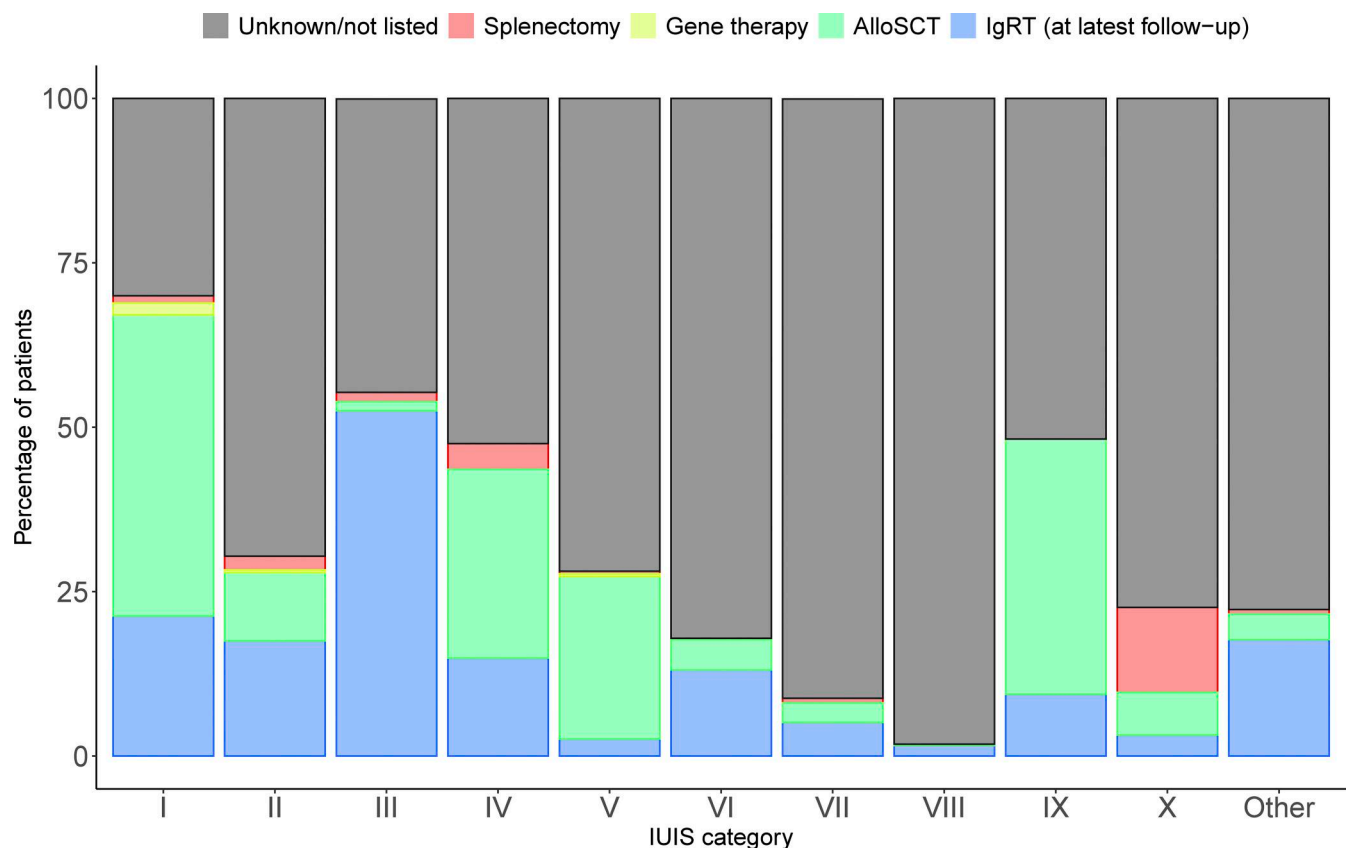
**Figure 3. Major treatment modalities of patients with IEI/PID as recorded in the ESID-R.** Relative proportions of major treatments such as IGRT (data on route, interval, and dose were recorded but are not shown), allogeneic HSCT (AlloSCT), autologous GT, and splenectomy. Only a proportion of centers recorded data on immune-modifying treatment (not shown), and the ESID-R does not capture data on antimicrobial therapy. "Unknown/not listed" and IGRT refer to the latest follow-up time point.

of immune regulation and innate IEI may argue for an extension of NBS to other immediately life-threatening IEI (e.g., familial hemophagocytic lymphohistiocytosis [FHL], XLP1, MyD88/IRAK4 deficiencies, and IPEX syndromes). To extend the spectrum of early IEI–NBS, current techniques may be supplemented by RNA sequencing or germline genetic testing, such as targeted sequencing panels and whole exome or genome sequencing. Feasibility studies of such extended NBS are ongoing in regional or national programs (18). However, the vast ethical and social implications of any omics-based addition like baby genome screening will require careful consideration of the risks and benefits (19).

### Methodological and organizational limitations

Physicians and other documentarists regularly collect data for the ESID-R on a voluntary basis, with data quality and quantity (i.e., data depth and accuracy) varying substantially between centers and across countries. Depending on resources dedicated to data documentation, an underestimation of the prevalence of IEI/PID, assumed to be widely similar across Europe, of around 30% was demonstrated (20). While all centers can participate in the ESID-R and scientific sub-studies for free, minimum infrastructure is required. With the rare exception of per-patient fees in pharma-sponsored level-3 studies, ESID does not financially

reimburse for data entry. The participants mainly benefit from the international academic collaboration and representation, which increases their awareness for disease phenotypes and current clinical research questions. Also, each center may obtain their own (local and regional) epidemiological data within a legally and ethically approved and financially sustainable technical framework (see survey results in the supplemental material). Furthermore, ESID has no means of monitoring the data quality other than by inbuilt checks for logic and completeness at the time point of data entry. So far, automated transfers of data from electronic health records (eHR) into the ESID-R, which have the potential to overcome many of the aforementioned obstacles and to enhance both the quality and quantity of recorded data, have not been attempted due to regulatory obstacles and the heterogeneity of eHRs in the 194 participating centers. All of the above, along with the fact that some monogenic IEIs have only been described recently while others have been recognized for decades, introduces a systemic ascertainment bias into the dataset when comparing, e.g., numbers of diagnoses and time of survival. For example, X-linked agammaglobulinemia (caused by mutations in *BTK*) (21) is probably not eight times more prevalent than, e.g., the autosomal-dominant CTLA4-(haplo)insufficiency (22, 23) or NFKB1-(haplo)insufficiency (24). In summary, we build on the trust of participants and the success of this huge cooperative effort
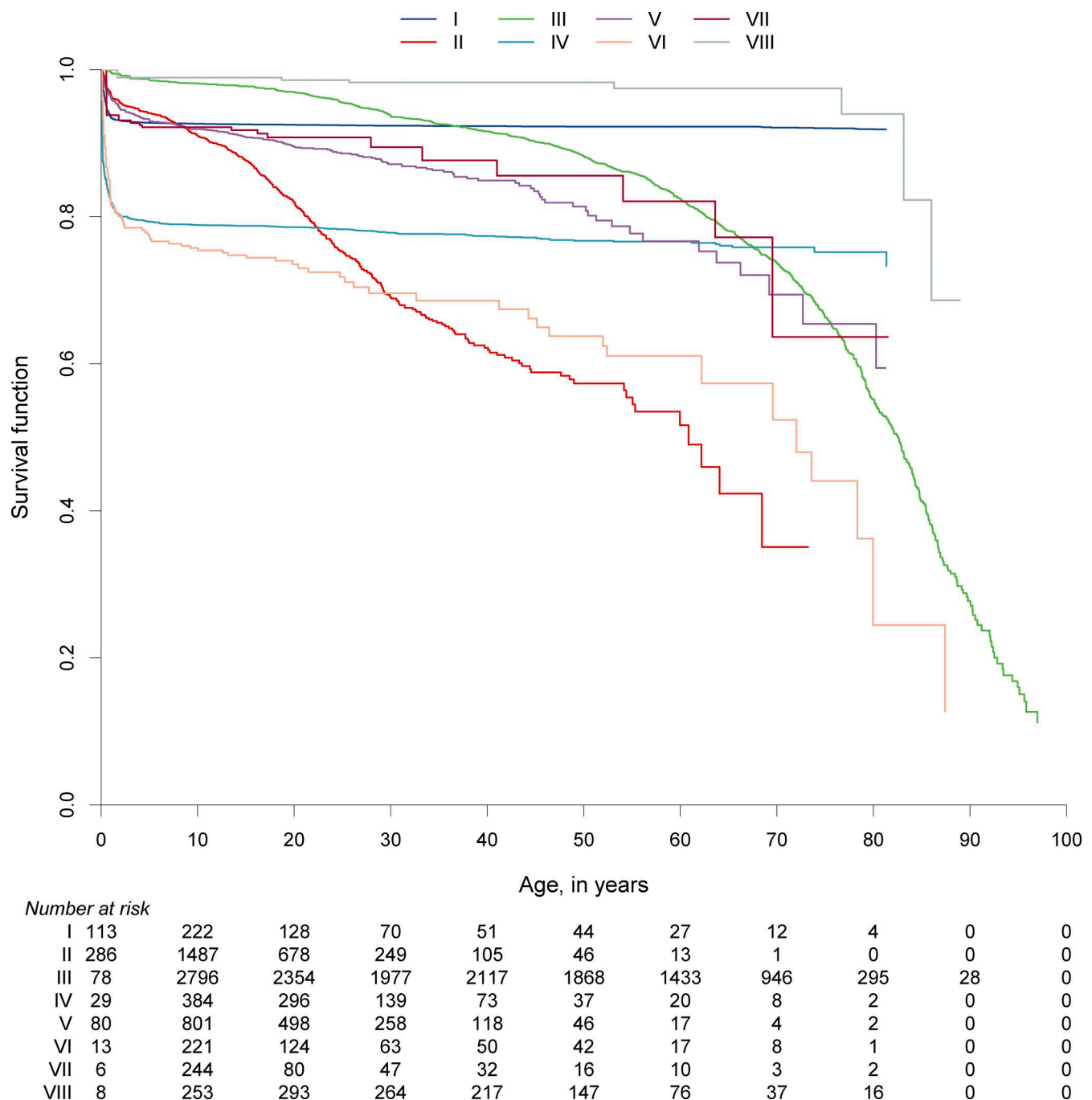
Survival function vs. Age, in years

Legend: I, II, III, IV, V, VI, VII, VIII

**Number at risk**

| | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 113 | 222 | 128 | 70 | 51 | 44 | 27 | 12 | 4 | 0 | 0 |
| II | 286 | 1487 | 678 | 249 | 105 | 46 | 13 | 1 | 0 | 0 | 0 |
| III | 78 | 2796 | 2354 | 1977 | 2117 | 1868 | 1433 | 946 | 295 | 28 | 0 |
| IV | 29 | 384 | 296 | 139 | 73 | 37 | 20 | 8 | 2 | 0 | 0 |
| V | 80 | 801 | 498 | 258 | 118 | 46 | 17 | 4 | 2 | 0 | 0 |
| VI | 13 | 221 | 124 | 63 | 50 | 42 | 17 | 8 | 1 | 0 | 0 |
| VII | 6 | 244 | 80 | 47 | 32 | 16 | 10 | 3 | 2 | 0 | 0 |
| VIII | 8 | 253 | 293 | 264 | 217 | 147 | 76 | 37 | 16 | 0 | 0 |

**Figure 4.** **Survival probabilities of main categories of IEI/PID and the living status at last news.** Inverse cumulative incidence curves as described and referenced in the Supplemental material. Start = age at diagnosis, stop = age at last news, and event = living status (0 = censored, 1 = deceased first, and 2 = curative therapy first). There were 21,206 patients censored; 1,960 patients who deceased first; and 2,901 patients who had a curative therapy first (not showing deaths after curative therapy); roman numbers refer to the IUIS categories for IEI/PID as listed in Fig. 2 B.

to continue the ESID-R in its fourth technical version starting from late 2024, serving as an up-to-date, simple, and free platform for inherently motivated international scientific clinical research collaboration.

**Challenges of reporting genetic data**
Collecting data from the heterogenous patient population of individuals with IEI/PID and storing these in a registry presents many challenges. Scientists estimate that current routine next-generation sequencing technologies can reveal a molecular cause in ~30–35% of IEI cases (18). It is noteworthy that information classifying detected variants by applying American College of Medical Genetics criteria or performing functional validation is not collected in the ESID-R. Phenotype information derived from the ESID-R might support the efforts of the ClinGen Immunology Gene and Variant Curation Expert Panels (25). The incorporation
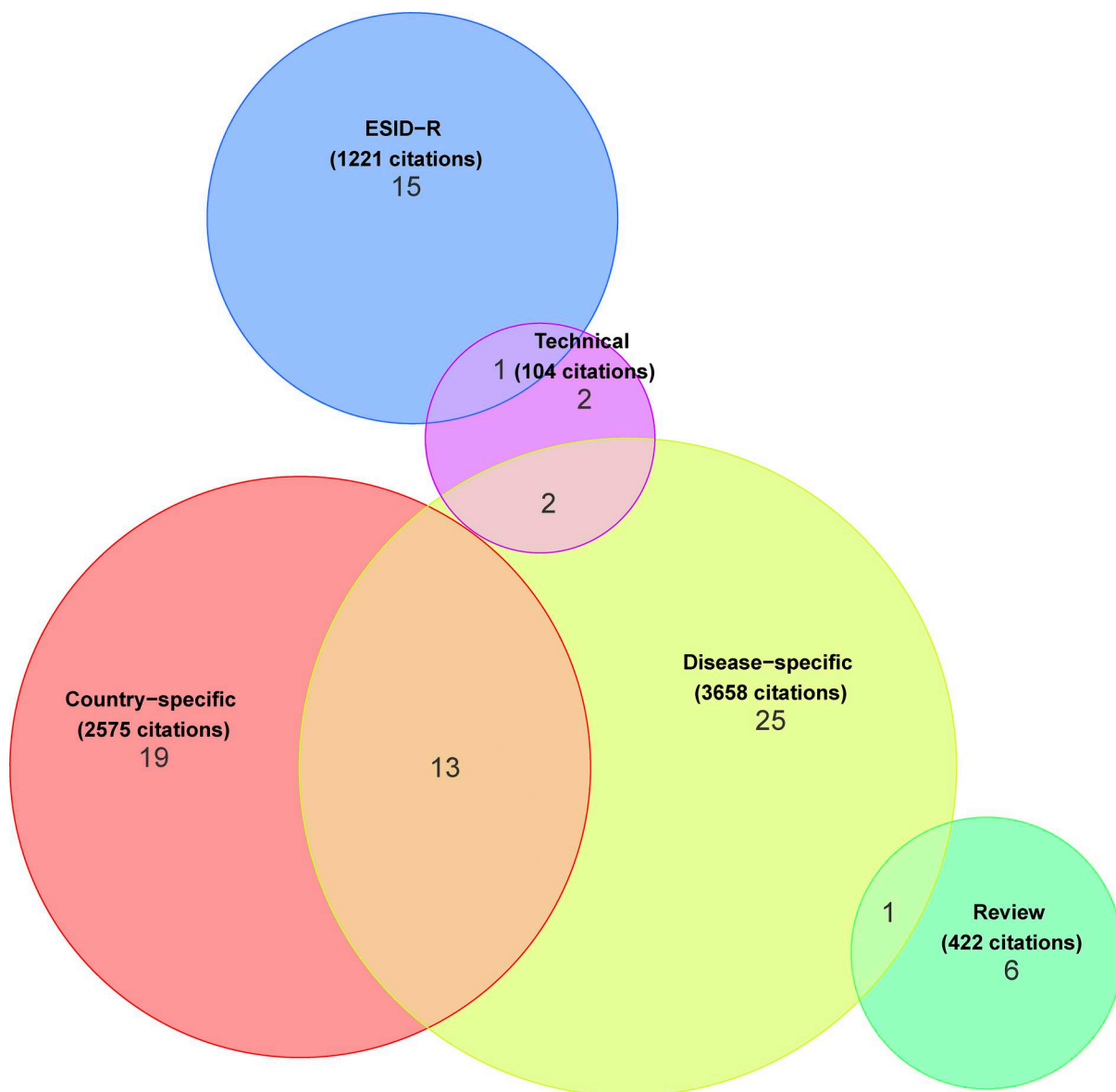
**Figure 5. Number, categories, and citation counts of ESID-R–based publications.** A total of 7,980 citations of 84 peer-reviewed ESID-R–based publications until early 2024 were recorded. See also the website for regular updates of ESID-R–related publications at https://esid.org/working-parties/registry-working-party/registry-publications/.

of genetic data beyond known pathogenic mutations, ideally linked to precisely defined phenotypes according to the human phenotype ontology (HPO) (26), represents a biologically interesting future challenge. This includes the verification of variants of unknown significance, intronic changes, somatic mutations and mosaicism, epigenetic factors, variable penetrance, and other less-studied factors such as noncoding modifier alleles and monoallelic expression (27).

**Link to other registries, synergies, overlapping efforts**
From a scientific perspective, it has become increasingly important to compare outcomes for IEI/PID patients with and without cellular therapy (HSCT or GT). The registry of the European Society for Blood and Marrow Transplantation (EBMT) currently registers definitive cellular therapies in about 700 patients with

IEI per year (28), many of whom are also registered in the ESID-R. Hence, to optimize future research, datasets from the ESID and the EBMT registries for the same patients should be combined. Better alignment of the registries and their data fields is urgently needed to facilitate such studies, and we expect the new technical platform to facilitate data exports and imports alike across providers. Furthermore, the IUIS classification has gradually incorporated more diseases from overlapping specialties (e.g., hematology-oncology, rheumatology, and gastroenterology), many of which are (also) covered by other medical societies and patient registries. Thus, although data from many of these patients are stored in the ESID-R, their proportion in the ESID-R does not reflect the real-world distribution. The registry of the European Reference Network for Rare Immunological and Autoimmune Diseases, an EU sponsored network of healthcare providers from reference

centers for PID/IEI, rheumatology, autoinflammatory, and autoimmune diseases, aims to collect common data elements from patients across these disease areas. This initiative may help to avoid redundancy. Finally, using independent (meta-)identifiers such as the European SPIDER-ID (29) in all registries would help scientists to disentangle the registry landscape.

### Future: Artificial intelligence (AI) in registry work for data analysis and interpretation

Advanced software tools and AI (e.g., large language models, natural language processing, and machine learning) will certainly transform clinical decision-making and other crucial processes in medicine, including the field of IEI (30, 31) Automated eHR-scanning and data-harvesting processes, ideally for specific terms in accordance with HPO, medical reports, and disease classification codes (e.g., ICD-11 or ORPHA codes), but also for free text may be used to identify currently undiagnosed IEI/PID patients. These individuals might benefit from early screening by preventing complications. Accordingly, as a first step, data from an IEI/PID registry like the ESID-R that includes data from patients with an established diagnosis could be used to train AI models and to predict a monogenic IEI or at least the most likely affected pathway in patients who lack a genetic diagnosis. Consequently, patients may undergo screening for disease-specific risks and receive appropriate therapy early in their course. In addition to AI-assisted automated data extraction from eHRs to feed patient registries with structured information, complementing the ESID-R with AI-based tools has the potential to transform this data-collection platform to an electronic IEI/PID patient management assistant in the future.

### Conclusions and perspectives

The rarity and complexity of many IEI grants them an orphan status regarding pharmaceutical research and development. The feasibility of clinical research, including drug trials and post-authorization efficacy and safety studies, thus depends on large networks of academic institutions and medical specialist societies. As one of the largest registries, containing extensive longitudinal datasets and having a pan-European reach, the ESID-R is likely to remain one of the most relevant scientific registries for patients with IEI.

## Materials and methods

### Technical background and operating mode of the ESID-R

The study protocol, the patient informed consent template and the center data transfer agreement plus amendments thereof were approved by the Institutional Review Board (IRB) and the data protection officer at the Medical University of Freiburg, Germany (Albert-Ludwigs-University). A substantial amendment was approved by the Medical University of Graz, Austria (24–334 ex 11/12, IRB00002556) and implemented in 2024. Details of the operational structure and technical background are found in the supplemental material.

### Data and statistical analyses

The study population included all patients with IEI/PID recorded in the ESID-R on March 19, 2024. Patients considered as discharged (n = 538), patients with secondary immunodeficiency who were documented as part of one national subregistry only (n = 417), or without definitive IEI diagnosis (n = 306) were excluded from the study, leaving 30,628 patients. IEI were classified using the latest classification of the IUIS (6), with abbreviations of the category names using, e.g., "PIRD," typically referred to as primary immune regulatory diseases, as synonym for "Diseases of immune dysregulation" (category IV; i.e., including FHL). The statistical analyses were conducted using R (version 4.3.2). Continuous and categorical variables were reported using the medians and interquartile ranges, raw effectives, and percentages, respectively. Survival probabilities were estimated by applying the cumulative incidence function. Overall survival was defined as the time between birth and death from any cause. Curative therapies, such as allogeneic HSCT and GT, were considered as competing events. Survival was analyzed using the R package survival version 3.8–3 as described previously (32). As only patients with an eligible diagnosis are included, they are not considered to be at risk of dying before they are diagnosed (32). The prevalence was calculated based on the European population in 2019 (R package rnaturalearth version 1.0.1).

### Role of the funding source

The present and former funding entities of ESID (i.e., Plasma Protein Therapeutics Association Europe [Baxter, Biotest, Grifols, Kedrion, and Octapharma], Novartis, UCB Pharma, Celltech, GlaxoSmithKline Pharma, Pharming, Takeda [and corporate predecessors], and Chiesi) had no role in the study design, study conduct, data collection, data management, data analysis, data interpretation, or writing of this report.

### Online supplemental material

In the supplement of this manuscript additional content is available relating to the evolution of the ESID-R and its content as well as supplementary figures as referenced in the text. Fig. S1 shows the history of patient inclusion into the ESID registry. Fig. S2 shows the visualization of ESID-R patient inclusion per population per country (minimal IEI/PID prevalence map). Fig. S3 shows the living status of patients at the age of last news in the ESID-R. Fig. S4 shows the IEI/PID distribution in an interactive, nested pie chart, showing details such as patient numbers with specific IEI/PID diagnoses at mouse-over and click to zoom. Fig. S5 shows the top 50 genetic diagnoses of IEI/PID patients in the ESID-R. Fig. S6 shows survival estimates separately for each IUIS category of IEI with confidence intervals. Fig. S7 shows countries in and around Europe with national patient registries used in addition to the ESID-R. Table S1 shows the contributing countries, sorted by the calculated prevalence per 100,000 inhabitants. Table S2 shows the underlying and main causes of death. Table S3 shows the therapy. Table S4 shows the sub-analysis of IEI/PID diagnoses in patients who died before the age of 5 years in two subcategories of IEI/PID. Table S5 shows the institutions of participants of the 2024 ESID-R survey on the international IEI/PID registry landscape.

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# Supplemental material
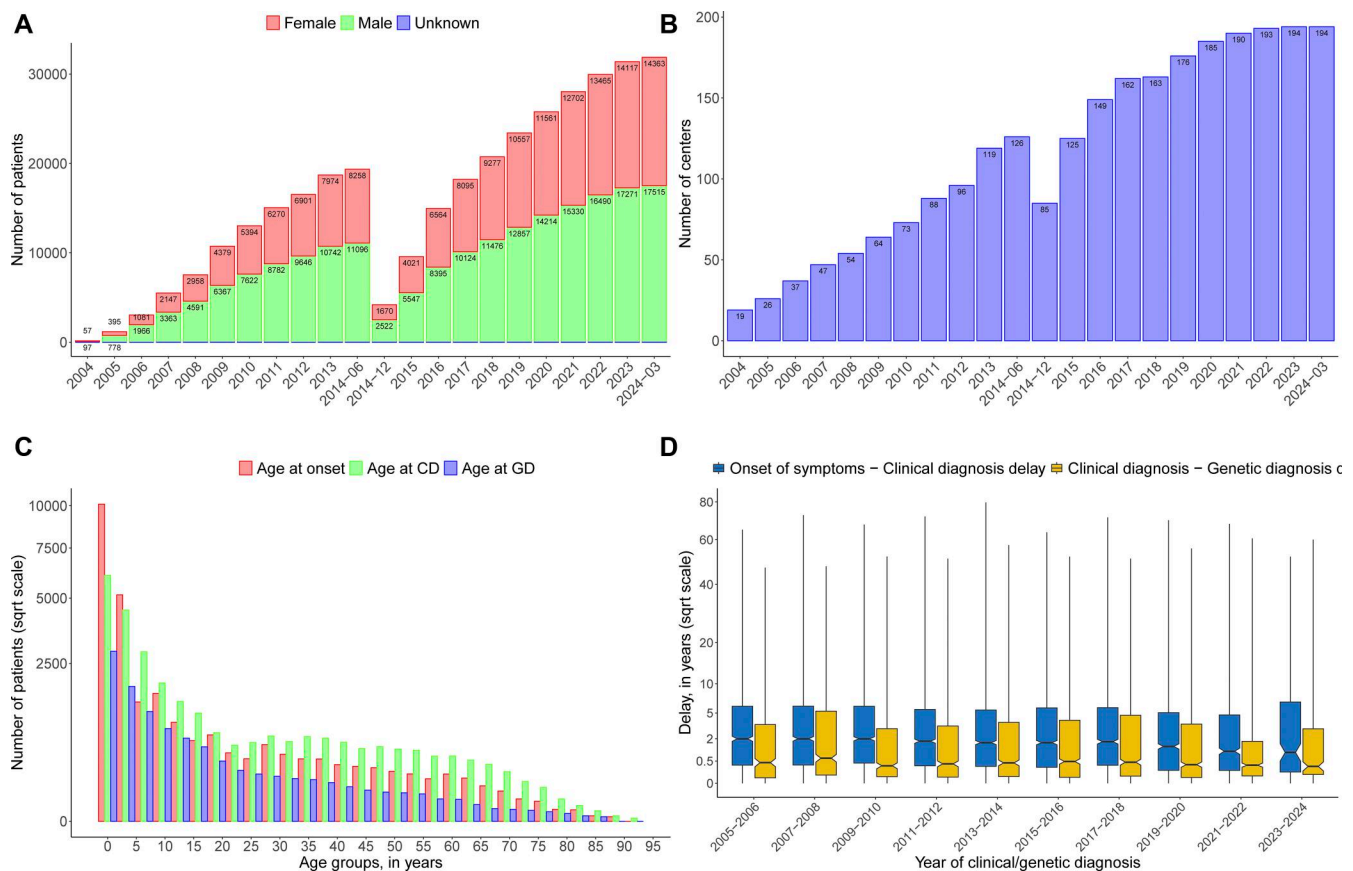


Figure S1. **The history of patient inclusion into the ESID registry over the last 20 years. (A, upper left panel)** Cumulative number of patients registered in the ESID-R. The total number shown here is 31,889 patients (male $n$ = 17,515; female $n$ = 14,363; unknown $n$ = 11), before exclusion of those discharged ($n$ = 538), those with secondary immunodeficiency ($n$ = 417), and those without a definitive diagnosis of IEI/PID ($n$ = 306). Data are shown for the online registry only. Data from the very first version (hardcopy) were not transferred to the first online registry but newly entered. According to "The Source" (https://esid.org/wp-content/uploads/2024/03/ESID_TheSource_2003.pdf), the total number in 2003 was 9,707 patients. **(B, upper right)** Cumulative number of ESID-R participating centers. **(C, lower left)** Age at onset of IEI or PID. Age groups of age at disease onset, clinical diagnosis (CD) of IEI/PID, and of genetic diagnosis (GD) are shown. **(D, lower right)** Diagnostic delay (in years from first manifestation to clinical diagnosis and from clinical diagnosis to genetic diagnosis) of patients diagnosed over the last 20 years in the ESID-R. The x axis shows the year of clinical/genetic diagnosis in 2-year intervals. The blue boxes represent the delay between onset of symptoms and clinical diagnosis (blue) and between clinical and genetic diagnosis (orange); the y axis shows the delay in years: median with 95% confidence interval (notch size of boxes), interquartile range (boxes), and range (min-max, whiskers).

# Prevalence map of PID
## for 100,000 inhabitants (based on 2019 population)
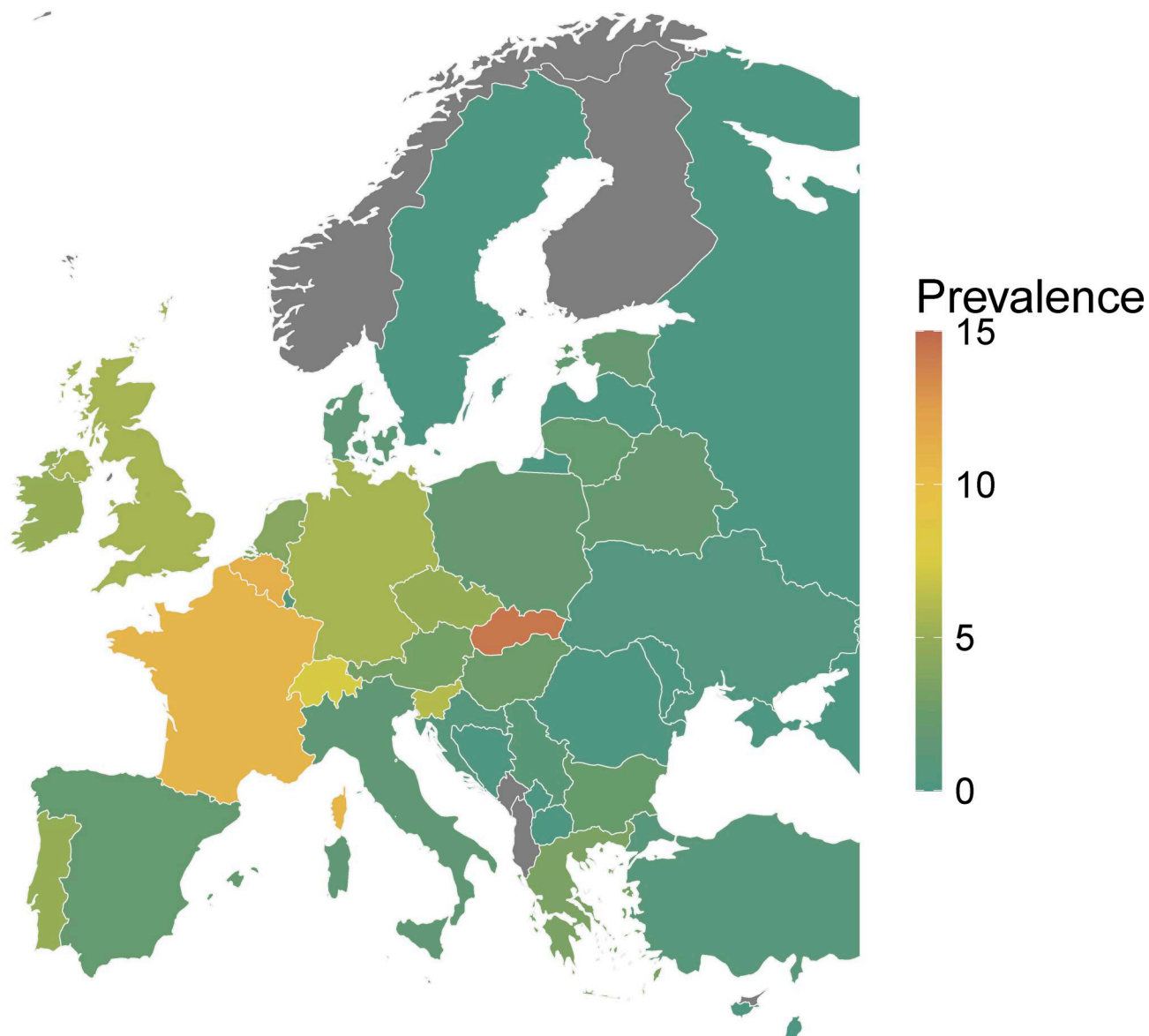
Data: rnaturalearth − ne_countries

Figure S2. **IEI/PID minimal prevalence map according to ESID-R patient numbers and the 2019 population (same data as in** Table S1**).**
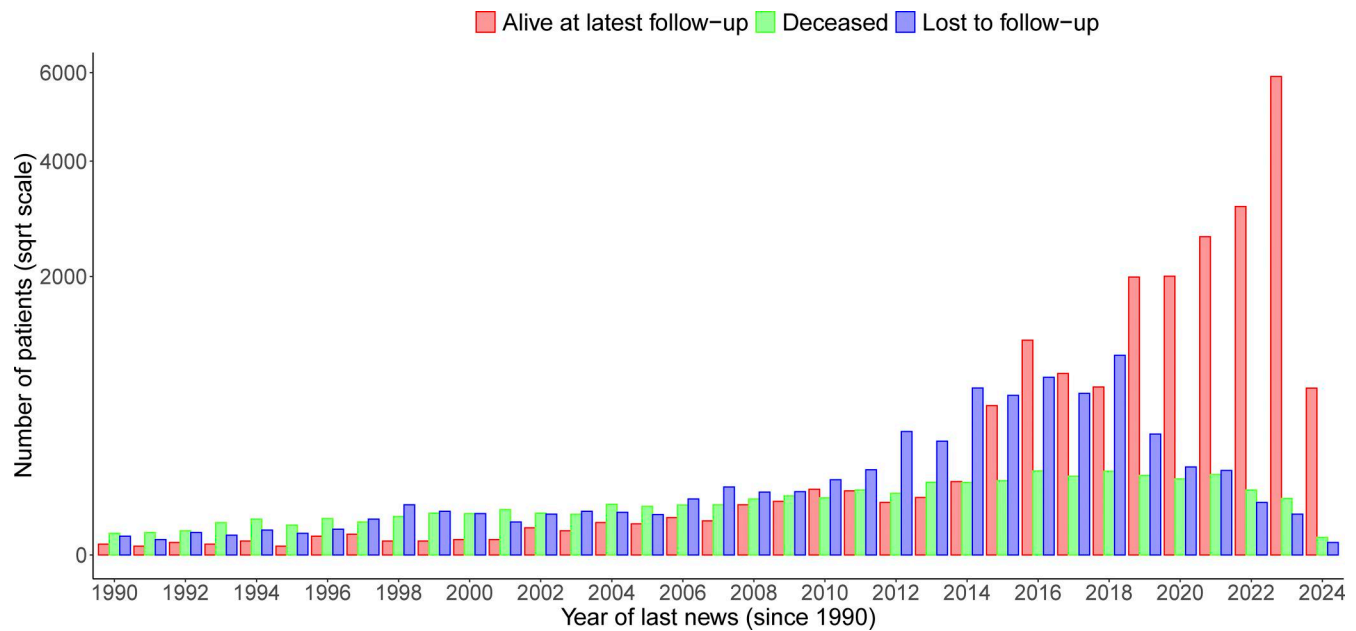
Figure S3. **Living status of patients at the year of last news in the ESID-R captured until March 2024.** "Last news" is the date when the patient was last seen or his/her condition was reported (by telephone or medical report). It is not the documentation date. Together, these data reflect the overall follow-up rate and living status of patients up to the time point of data closure in March 2024.
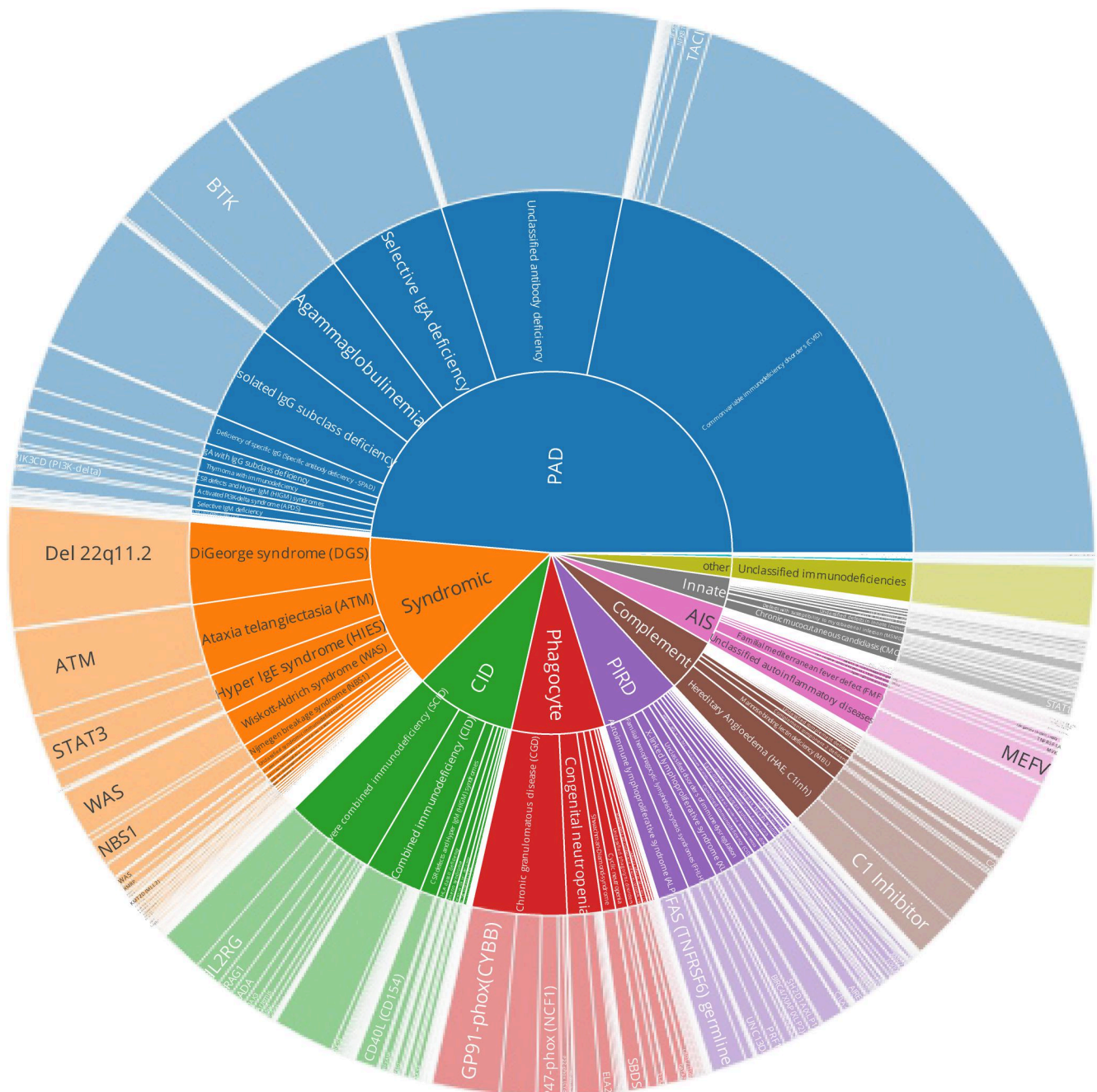
Figure S4. **IEI/PID distribution, nested pie chart for IUIS category, diagnosis, and gene.** This is merely a sketch; please see the interactive version of the figure with all data labels and patient numbers shown on mouse over and click to zoom at https://esid.org/html-pages/Suppl%20Fig%203_ESID_30k_sunburst_PID.html.

## patients per gene (top 50)



| Gene | Patients |
|------|----------|
| Del 22q11.2 | 1129 |
| BTK | 959 |
| ATM | 795 |
| GP91-phox(CYBB) | 620 |
| WAS | 543 |
| C1 Inhibitor | 400 |
| STAT3-LOF | 353 |
| FAS (TNFRSF6) germline | 321 |
| MEFV | 281 |
| IL2RG | 256 |
| TACI | 255 |
| NBS1 | 253 |
| RAG1 | 234 |
| P47-phox (NCF1) | 225 |
| CD40L (CD154) | 221 |
| ELA2 | 199 |
| PIK3CD (PI3K-delta) | 193 |
| SBDS | 181 |
| STAT1 | 171 |
| CTLA-4 | 158 |
| ADA | 154 |
| NFKB1 | 143 |
| UNC13D | 142 |
| PRF1 | 127 |
| BIRC4/XIAP (XLP2) | 126 |
| DOCK8 | 118 |
| SH2D1A (XLP1) | 114 |
| C2 | 113 |
| AIRE | 113 |
| Artemis | 108 |
| LRBA | 101 |
| JAK3 | 94 |
| GATA2 | 91 |
| RAG2 | 87 |
| RFXANK | 76 |
| NFKB2 | 76 |
| FOXP3 | 71 |
| RMRP | 70 |
| PIK3R1 | 70 |
| P22-phox (CYBA) | 70 |
| STAT3-GOF | 66 |
| MVK | 63 |
| LAD1 / ITGB2 | 63 |
| IKK-gamma (NEMO, IKBKG) | 63 |
| TNFRSF1A | 62 |
| KMT2D (MLL2) | 58 |
| RAB27A | 56 |
| IL7Ralpha | 52 |
| AID | 52 |
| CIAS1 (NLRP3) | 49 |

**Figure S5. Top 50 genetic diagnoses of IEI/PID patients recorded in the ESID-R.** The top 50 genes mutated in ESID-R patients with monogenic IEI/PID are shown with respective patient numbers in descending order.
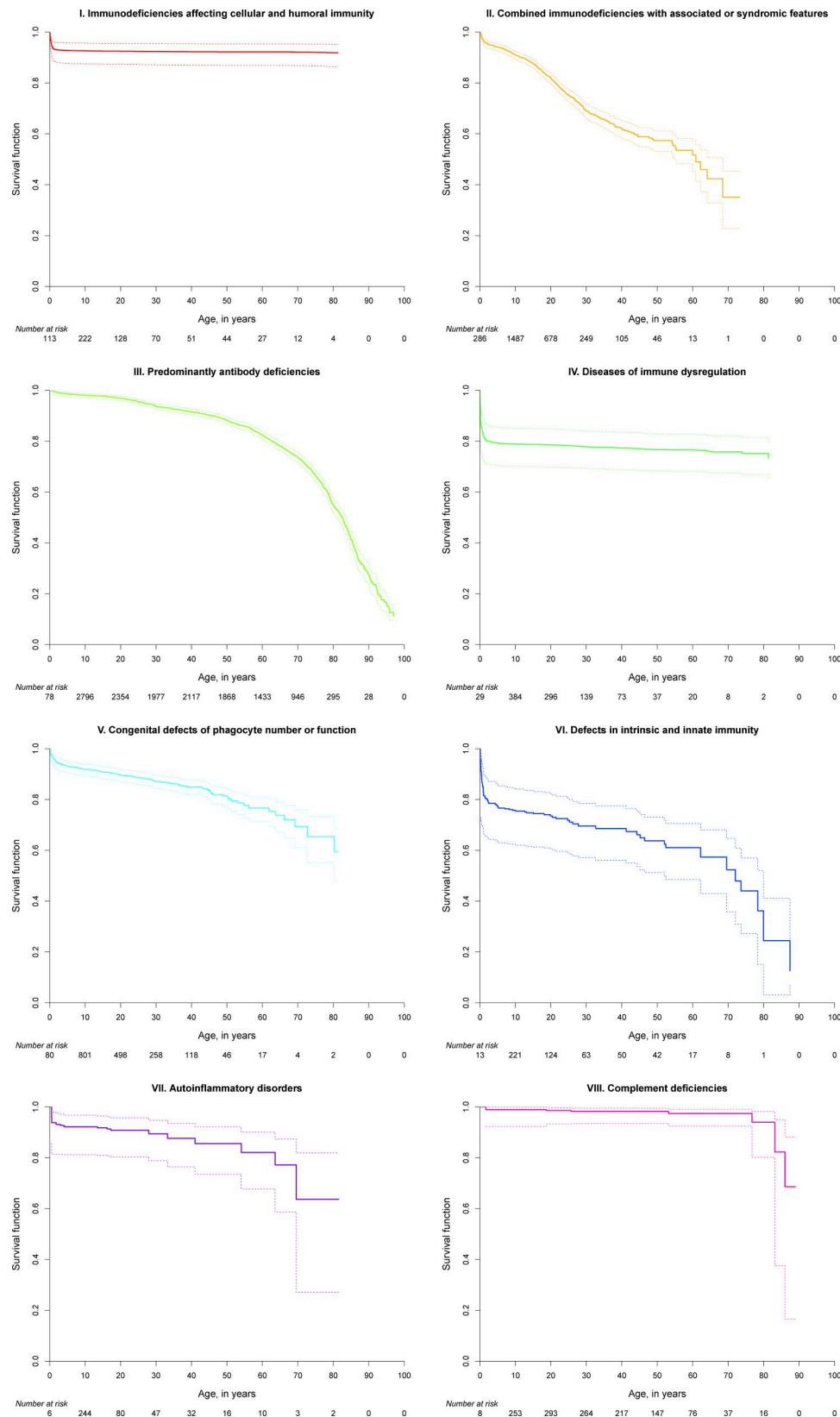
**Figure S6.** **Survival probabilities of main IUIS categories of IEI/PID and the living status at last news with confidence intervals.** Inverse cumulative incidence curves and confidence intervals as described and referenced above. Start = age at diagnosis, stop = age at last news, and event = living status (0 = censored, 1 = deceased first, 2 = curative therapy first). There were 21,206 patients censored; 1,960 patients who deceased first; and 2,901 patients who had a curative therapy first (not showing deaths after curative therapy); roman numbers refer to the IUIS categories for IEI/PID as listed in Fig. 2 B. Numbers at risk present patients in the ESID-R from their age at diagnosis onward until definitive/curative treatment or death.
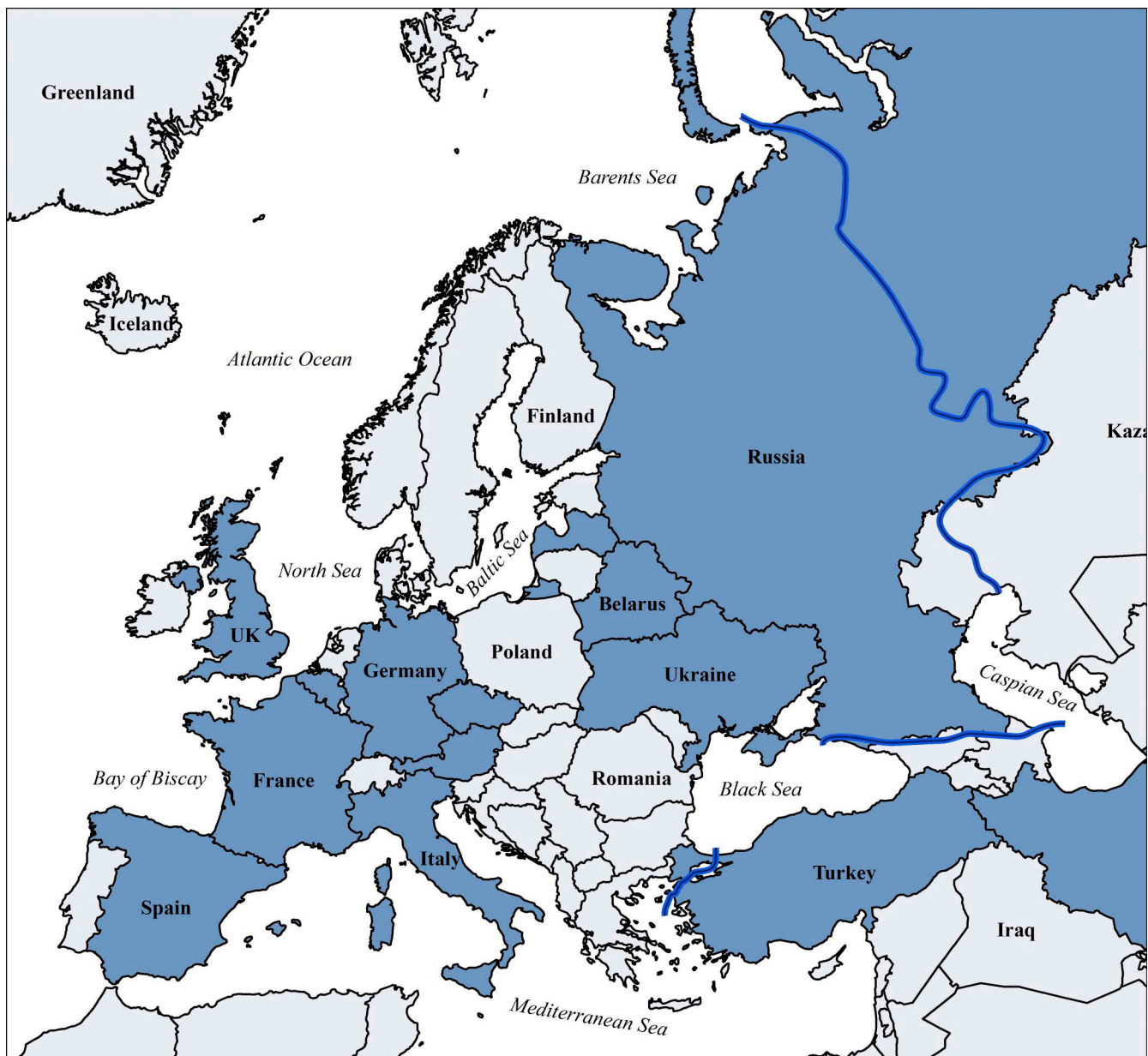
Figure S7. **Countries with national patient registries or national sub-registries within the ESID-R according to the 2024 ESID survey (all participating IEI/PID centers worldwide are listed in** Table S5**).** Blue line: approximate boundary of geographical Europe.

### Historical evolution of the ESID-R, objectives, structure, and content

The transition from the first hard-copy-based to the first online version of the ESID-R was headed by Bodo Grimbacher, Freiburg, Germany, with the help of Barbara Frisch and Viviane Knerr, as well as programmers Dominik Veit and Stephan Rusch, in 2000–2004. The biggest hurdles faced during this first restructuration were ethical considerations, data protection, and obtaining industry funding. The second overhaul was conducted by Stephan Ehl, Freiburg, and programmers Benjamin Gathmann and Stephan Rusch in 2014 and focused on content restructuration. The ESID-R steering group, led by the elected chairperson of the ESID-R Working Party, oversees all aspects of the evolution of the registry, including the design, operations, financing, and setup of dedicated studies.
Specific objectives of the ESID-R include.

(1) Collection of epidemiological data: The registry contains basic information on patients with IEI, including their medical history, diagnosis, genetics, treatment, and disease progression. Data on the prevalence of these rare diseases and the associated health burden are important for political decision-makers.
(2) Analysis and research: By analyzing the collected data on these rare diseases through multicenter collaboration, researchers can gain new insights into the pathophysiology and treatment of primary immunodeficiencies.
(3) Support of clinical studies and trials: Registry data can serve as the basis for clinical studies or trials aimed at developing new therapies, improving the treatment of patients affected by those diseases, and for post-marketing surveillance studies of new drugs and medicinal products.
(4) Improving patient care: Through the analyses and publication of registry data, the registry helps improve IEI patient care by providing physicians and healthcare providers/decision-makers with access to up-to-date information and practices.

Both versions of the ESID-R operating from 2004–2014 and 2014–2024 had the following key features (33):

(1) Database architecture: The ESID-R utilizes a sophisticated database architecture to manage the vast amount of data collected from patients. This database is designed to be scalable, ensuring it can handle the increasing volume of patient records and research findings over time.
(2) Data security: Ensuring the security and privacy of patient data is paramount. The ESID-R implements stringent security measures to protect sensitive information, including encryption protocols and access controls.
(3) Web-based platform: The ESID-R is accessed through a web-based platform, allowing authorized users to input and access data remotely. This platform is user-friendly and intuitive, facilitating seamless data entry and retrieval processes. Only an up-to-date web browser and stable internet connection are required to access the system. No additional on-site software needs to be installed/maintained at the documentation centers.
(4) Framework and technologies: The ESID-R is built using a combination of programming languages, frameworks, and technologies suited to its specific requirements. Common technologies include SQL databases for data storage, web development frameworks for the user interface, and data analysis tools for reporting and research purposes.

### The three-level content structure

The old version of the online ESID-R (2004–2014) was closed for documentation on June 25, 2014. During the first main revision of the online registry in 2014, a three-level structure was implemented. Level 1 addresses the task of the registry as a simple epidemiological tool. To achieve patient registration by as many centers as possible, the dataset is kept short and simple such that caregivers who know the patient well can fill in the data without consulting the patient chart in much detail. It contains basic epidemiological information, information about main categories of symptoms at initial presentation, and information about some key therapies (immunoglobulins, HSCT, and GT). The yearly update is restricted to survival and implementation of major therapies. The level 1 registration also serves to identify patients for additional in-depth studies, including interventional trials. Level 2 was designed for long-term studies on certain diseases or disease groups without a predefined end. Level 2 datasets allow registration of a limited number of clinical manifestations and lab values that are provided on a yearly basis. It was particularly designed to capture longitudinal data in disease groups, for which the molecular basis has not been fully resolved (such as CVID or specific antibody deficiencies). Again, the datasets are kept simple to limit the burden of registration. Level 3 was designed for studies on particular genetically defined diseases based on a study protocol with a defined endpoint. The level 3 dataset can contain very detailed information, including grading of symptoms, more sophisticated lab values, detailed treatment information, and quality of life data. Registration intervals are at least yearly. Level 3 studies usually offer financial support for the documenting centers.

The level 2 and 3 projects or "sub-studies" are designed by independent research groups. To apply for implementation of a study in the ESID-R, a statistical evaluation plan, a time and budget forecast, need to be defined in a standardized study proposal, which is assessed for feasibility and to avoid redundancy or competing interests by the registry steering committee and the elected chairperson in regular meetings. There should also be a financial contribution from the principal investigator or research institution to (at least partly) cover the costs associated with the setup, coordination, data maintenance, and analyses of these registry sub-studies (details on ESID website, fee structure). When signing the informed consent, patients may choose to have their anonymized data be included either in sub-studies of academic research groups or of pharmaceutical industry–sponsored consortia, or none of them.

Kindle et al.
ESID registry 30-years report: IEI manifestation, treatment, and outcome

**Journal of Human Immunity**  S8
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## Supplemental methods

The ESID-R operates based on a technical infrastructure designed to securely receive, store, and enable the analysis of data related to IEI. These data cover, for example, various aspects of the disease, including genetic mutations, clinical symptoms, laboratory test results, imaging findings, and treatment outcomes. Patients with IEI are registered in the web-based database when their disease data are submitted by an authorized physician or healthcare professional or documenting personnel. Centers or sites where patients are cared for are typically university clinics/hospitals and have a data transfer and general data protection regulation-compliant handling agreement and a local IRB approval in place. The data are de-identified and kept strictly confidential to protect patient privacy.

During the evolution of the registry, it was possible to enter diseases (e.g., LRBA) in multiple categories depending on the development of reported phenotypes and assignment within the IUIS classification. Only with the last update in 2024 a "genetic hierarchy" for categorizing diseases was introduced.

Different measures are applied to avoid duplicates. Firstly, for centers that use the "personalized version" of the registry, where identifying data is kept on a separate server, the pseudonymization tool (Mainzelliste) creates a notification that this (or a similar) patient seems to have been registered before. The system thereby encourages the documenting person to investigate further before proceeding with the creation of a new patient documentation. This option is not available for centers that enter pseudonyms directly. Secondly, persons who sign the consent (patients or parents, next of kin) are always asked whether they have signed a similar consent before. These measures reduce the likelihood of double registrations in the first place. Thirdly, for patients who are transferred from pediatric to adult centers or who move from one region or country to another, usually the caring hospital is aware of the site where the follow-up is done in the future, and, if this is an ESID-R documenting center, the patient data can be reassigned to the new center internally, and follow-up for the adult or relocated patient can be continued in the same documentation under the new center's name.

The Kaplan–Meier curves were generated as described (32). The Kaplan–Meier is done using the start and stop notation to take care of the left truncation effect. Start = age at diagnosis, stop = age at last news, and event = living status (0 = censored, 1 = deceased first, 2 = curative therapy first). There were 21,206 patients censored; 1,960 patients who deceased first; and 2,901 patients who had a curative therapy first.

## Supplemental results and discussion

NBS and longitudinal patient documentation in the ESID-R. The ESID-R data structure does not (yet) allow an analysis of improved diagnostic delay and survival in patients diagnosed with SCID in the ESID-R in the NBS era (Fig. S1 C). Firstly, NBS for SCID has been performed sequentially over the last decade, but is still not generally available; and secondly, collecting the intended annual follow-up information may cause a system-inherent delay, including underreporting of SCID patients following definitive therapy (or death), before their data are stored in the ESID-R. The ESID-R Working Party continues to face significant challenges while aiming to integrate data collected over a patient's entire disease course into a single registry, as this ranges from NBS or clinical diagnosis, through different clinical events, such as a form of definitive therapy, and/or chronic treatment, and/or their optional participation in observational sub-studies and on to a cure or until death. The living status at last news from patient is shown in Fig. S3.

The ESID-R in the international landscape of registries for patients with rare immunological diseases. To depict the current situation of the global IEI registry landscape and participants' motivations, we searched PubMed, communicated with representatives of sister societies around the globe, and performed an online survey in 2024. Of 533 publications retrieved by searching for primary immunodeficiency patient registry and exclusion of disease-specific or other secondary sub-studies, the remaining publications showed that a vast majority of IEI/PID registries are national epidemiological databases with a limited temporal and geographical scope regarding longitudinal patient data (32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51). They, naturally, contain a substantially smaller number of patient datasets than the continental ESID-R, which also includes data from patients of some neighboring countries. As such, they are valuable and necessary platforms for the connection of healthcare providers and clinical experts, as well as for health politicians and economists. A relatively recently published overview of the global registry landscape and the burden of IEI/PID from 80 countries evaluated the distribution of IEI/PID diagnoses and other factors, such as the diagnostic delay or immunoglobulin treatment in relation to the countries' resources and societal factors, such as the rate of consanguinity (12). These data show that the key drivers to implement and maintain an IEI/PID patient registry range from health policy, warranting access to expert care and modern treatments, over patient advocacy, to clinical, biological, and pharmaceutical research and development. Importantly, International Patient Organisation for Primary Immunodeficiencies, the global patient organization for IEI, has identified the existence of registries as one of the six key principles of care as part of its PID LIFE Index, a tool to measure the quality of IEI/PID healthcare in a country (52). To analyze the policy of patient inclusion and obtain feedback from documenting physicians or study nurses, we designed a survey distributed through ESID in 2024. A total of 43 physicians from 29 different European and non-European countries participated in this survey (Table S5). 70% of respondents (30/43) said they would exclusively register their patients into the ESID-R; 30% of the survey respondents (13/43) said they would also enter patient data into one of the following disease-specific (other than general IEI/PID) registries: Eurofever, Severe Chronic Neutropenia International Registry, Juvenile Inflammatory Rheumatism Cohort, and the registry of the EBMT/Center for International Blood and Marrow

Kindle et al.
ESID registry 30-years report: IEI manifestation, treatment, and outcome

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Transplant Research. Motivations for entering data into the ESID-R included collaborative research (88%), networking (84%), taking part in academic or pharmaceutical studies (84% and 72%), and improvements in patient care (72%) and for IEI education purposes. Reasons given for not entering patient data into the ESID-R were lack of personnel (84%), legal challenges regarding data transfer (37%), no obvious local benefit (23%), and concerns about small countries being underrepresented (14%). Survey participants stated that they would like a simplified version of the patient consent form, easy interoperability between national registries and the ESID-R, and grant incentives for entering patient data, especially if these were needed at a higher level of granularity.

HPO in IEI/PID and potential benefit of integrating HPO into the ESID-R. The HPO comprehensively organizes and defines the phenotypic features of human disease, supporting genomic and phenotypic analyses through semantic similarity and machine learning algorithms (31). Currently, the HPO terminology for IEI/PID still needs to be further developed with help of the community of clinical immunologists and researchers focusing on IEI/PID, i.e., new HPO terms for relevant phenotypic features to be added, and existing HPO terms to be revised, such that the definitions and hierarchical placement in the HPO reflect current knowledge (26). The HPO can be used with the Global Alliance for Genomics and Health Phenopacket Schema to represent not only phenotypic features but also measurements, biopsies, and treatments over the entire time course of a disease (53). Collections of phenopackets may support translational research in immunology by providing standardized input data for software programs designed to identify genotype–phenotype correlations and characterize disease subtypes (54) (*Preprint*). Integrating the HPO terminology into the ESID-R would inspire studies within or across IUIS categories, especially in monogenic entities. To make full use of the HPO, better systems for simple but comprehensive and accurate data entry are needed.

**Provided online are Table S1, Table S2, Table S3, Table S4, and Table S5. Table S1 shows the contributing countries, sorted by the calculated prevalence per 100,000 inhabitants. Table S2 shows the underlying and main causes of death. Table S3 shows the therapy. Table S4 shows the sub-analysis of IEI/PID diagnoses in patients who died before the age of 5 years in two subcategories of IEI/PID. Table S5 shows the institutions of participants of the 2024 ESID-R survey on the international IEI/PID registry landscape.**

# Appendix

ESID-R Working Party members: Dalia Abd Elaziz, Sohilla Lofty M. Abdelkader, Avigaelle Abitbol, Hassan Abolhassani, Lalash Abrahim, Mohamed Abuzakouk, Pietro Andrea Accardo, Nabila Achir Moussouni, Veronica Afonso, Philipp Agyeman, Martina Ahlmann, Alessandro Aiuti, Abla Akl, Güzide Aksu, Kim Albers, Meda Diana Alecsandru, Olga Aleinikova, Svetlana Aleshkevich, Radwa Salah Eldeen Youssif Alkady, Luis Allende, Zoe Allwood, Manrique de Lara Laia Alsina, Daniela Ambrosch-Barsoumian, Lisa Ameshofer, Kenza Amour, Evrim Anadol, Ariharan Ananthachagaran, Chantal Andriamanga, Julia Andris, Karin Andritschke, Federica Angelini, Tobias Ankermann, Katrin Apel, Siamak Arami, Ömür Ardeniz, Peter Arkwright, Karina Arnold, Rudolf Ascherl, Najla Assam, Nurit Assia-Batzir, Faranaz Atschekzei, Sybille Aumann, Volker Aumann, Magnus Aurivillius, Bernd Ausserer, Tadej Avcin, Sezin Aydemir, Emel Aygören-Pürsün, Cagdas Ayvaz Deniz, Chiara Azzari, Lo Babacar, Perrine Bach, Sophie Bachmann, Peter Bader, Shahrzad Bakhtiar, Renate Bancé, Catherine Bangs, Katerina Barfusz, Safa Baris, B. Barlan Isil, Michaela Bartsch, Lucia Augusta Baselli, Laura Batlle-Maso, Elena Bertolini, Helge Baumann, Ulrich Baumann, Veronika Baumeister, Helen Baxendale, Suzanne Bazen, Beatrice Beaurain, Julien Beauté, Mounia Bechar-Makhloufi, Norbert Beck, Brigitta Becker, Christian Becker, Uta Behrends, Renata Beider, Rita Beier, Amel Belkacem, Luisa Belke, Sven Bellert, Bernd H. Belohradsky, Lilia Ben Slama, Aouatef Ben-Bouzid, Vincent Benoît, Thamila Berdous-Sahed, Jan Bergils, Anna Berglöf, Peter Bergman, Katarzyna Bernat-Sitarz, Jolanta Bernatoniene, Ewa Bernatowska, Benedikt Bernbeck, Claire Bethune, Kai Beuckmann, Malini Bhole, Anika-Kerstin Biegner, Stefan Bielack, Kirsten Bienemann, Arndt Bigl, Amélie Bigorgne, Marc Bijl, Nadine Binder, Michaela Bitzenhofer-Grüber, Geraldine Blanchard Rohner, Dagmar Blank, Claudia Blattmann, Julia Blau, Audra Blaziene, Stefan Blazina, Markéta Bloomfield, Roswitha Blume, Barbara Boardman, Sebastian Bode, Jaap-Jan Boelens, Christoph Boesecke, Delfien Bogaert, Johannes Bogner, Nadezda Bohynikova, Claire Booth, Victoria Bordon, Arndt Borkhardt, Melanie Börries, Michael Borte, Stephan Borte, Lukas Bossaller, Madeleine Bossard, Jeannet Botros, Soraya Boucherit, Jeannette Boutros, Oksana Boyarchuk, Onur Boyman, Kaan Boztug, Sara Branco Pereira da Silva, Thomas Braschler, Sophie Bravo, Robbert Bredius, Philip Bright, Carolina Brito de Azevedo Amaral, Nicholas Brodszki, Grit Brodt, Allan Brolund, Pauline Brosselin, Bastian Brummel, Sonja Brun-Schmid, Jürgen Brunner, Roswitha Bruns, Christina Buchta, Dietke Buck, Aileen Bücker, Martina Bührlen, Stefan Burdach, Siobhan Burns, Janet Burton, Luis Caminal, Caterina Cancrini, Clementina Canessa, Nathan Cantoni, Brindusa Capilna, Fabiola Caracseghi, Isabel Caragol, Javier Carbone, Maria Carrabba, Latanya Chamberlain, Anita Chandra, Christophe Chantrain, Helen Chapel, Julie Chassot, Ronnie Chee, Matteo Chinello, Charu Chopra, Zita Chovancova, Martin Christmann, Krystyna Chrzanowska, Peter Ciznar, Karlien Claes, Carl Friedrich Classen, Martin Classen, Alexis-Virgil Cochino, Alison M. Condliffe, Selim Corbacioglu, Ana Isabel Cordeiro, Donatienne Cordier Wynar, Claire Core, Laurence Costes, Tanya Coulter, Virginie Courteille, Maria Cristina, Maria Cucuruz, Nel Dabrowska Leonik, Mandy Dähling, Mary Louise Daly, Claudia-Sabrina Daniel, Maria Giovanna Danieli, James Darroch, Graham Davies, Frans de Baets, Christiane De Boeck, Javier De Gracia Roldan, Narimene de Nadai, Iris de Schutter, Nathalie De Vergnes, Esther de Vries, Josine de Witte, Theo Debert, Corina Defila, Judith Deimel, Diane Delaplace, Rosa Maria Dellepiane, Nelli Dellert, Laura Delliera, Anita Delor, Ulrike Demel, John Dempster, M.M. den Os, Rosmarie Dengg, Sora Asfaw Desisa, Alexandra Desta, Drahomira Detkova, Maite Dewerchin, Romina Dieli Crimi, Dagmar Dilloo, Florentia Dimitriou, Sarah Svenja Dinges, Jasmin Dinser, Nabila Dipani, Johannes Dirks, Anna-Maria Dittrich, Lylia Djermane, Yagmur Dogru, Figen Dogu Esin, Angelika Dombrowski, Julia Dominguez Escobar, Michaela Döring, Camilla Heldbjerg Drabe, Susann Drerup, Barbara Drexel, G.J.A. Driessen, Gregor Dückers, Yasmine Dudoit, Andrea Duppenthaler, Georg Ebetsberger-Dachs, Mate Barnabas Ecser, Maartje Eekman, Rosanna Ehrat, Eva Eisl, Olov Ekwall, Rabab El Hawary, Sabine M. El-Helou, Aisha El-Marsafy, Sarina Elbe, Suzanne Elcombe, Alia Eldash, Youssif Alkady Radwa Salah Eldeen, P.M. Ellerbroek, Roland Elling, Jane Elliott, Angelika Engelhardt, Diana Ernst, Fügen Ersoy, Stefanie Esper, Isabel Esteves, Andrew Exley, Martin Faber, Giovanna Fabio, Gaby Fahrni, Laura Eva Faletti, Laura Eva Faletti, Claire-Michele Farber, João Farela Neves, Emilia Faria, Henriette Farkas, Evangelia Farmaki, Maria Faßhauer, Anders Fasth, Gerd Fätkenheuer, Stefanie Faustmann, Gisela Fecker, Conleth Feighery, Cornelia Feiterna-Sperling, Perez Eduardo Fernandez-Cruz, Cordeiro Ferreira Concalo, Alice Ferster, Tobias Feuchtinger, Oliver Feyen, Daniela Finke, Sigrid Fitter, Stefan Flaschberger, Lucia Fleckenstein, Dirk Föll, Adriano Fontana, Concetta Forino, Elisabeth Förster-Waldl, Nora Franchet, Dagmar Freitag, Urs P. Frey, Hannah Margarete Frick, Elisabeth Friedel, Wilhelm Friedrich, Barbara Frisch, Lukas Frischknecht, Stephanie Fritzemeyer, Alenka Gagro, Manfred Gahr, Nermeen Mouftah Galal, Eleonora Gambineri, Agnes Gamper, Franziska Gams, Astrid Ganzow, Nicolas Garcelon, Tomaz Garcez, Marina Garcia Prat, Ann Gardulf, Janine Garibay, Birgit Garwer, Jonathan Gathmann, Corinna Gebauer, Linda Geberzahn, Tilman Geikowski, Ulf Geisen, Christiane Gemander, Andrew R. Gennery, Marie Gerisch, Michael Gernert, Katrin Gerrer, Stev Gerschmann, Carolin Giannini, Juana Gil Herrera, Noemi Gimenez Sanz, Matthias Girndt, Ramona Girrbach, Hermann Girschick, Ioannis Gkougkourelas, Dominika Gładysz, Susanne Gnatowski, Elisabeth Gnodtke, Vera Goda, Sarah Goddard, Daniela Goebel, Jean-Christophe Goffard, Sigune Goldacker, Eva Maria Gollowitsch, Manuella Gomes, Mark Gompels, Míriam González, Luis Ignacio Gonzalez Granado, Pavels Gordins, Katharina Gößling, Lisa Göschl, Lucy Gossens, Ewelina Gowin, Lea Graafen, Leo Graca, Brigita Gradauskiene (Sitkauskiene), Dagmar Graf, Norbert Graf, Elliot Grange, H. Anne Grashoff, Johann Greil, Sofia Grigoriadou, Helen Gronlund, Ute Groß-Wieltsch, Teresa Guerra, Kissy Guevara-Hoyer, Mor Seny Gueye, Noemie Guibert, Birgit Gülnur, Tayfun Güngör, Marina Guseva, David Guzman, Marcel Haag, Gabriele Haase, Henriette Haenicke, Filomeen Haerynck, Ines Hafsa, David Hagin, Emine Haliti, Michael Hallek, Gonca Hancioglu, Rupert Handgretinger, Leif G. Hanitsch, Susanne Hansen, Tetyana Hariyan, Thomas Harrer,

Pia Hassunah, Maria Hatzistilianou, Fabian Hauck, Thomas Hauser, Margje H. Haverkamp, Grant Hayman, Paul Heath, Christian Hedrich, Maximilian Heeg, Michael Heike, Martin Heimbrodt, Sabine Heine, Ulrich Heininger, Christian Heinrich, Valerie Heinz, Andreas Heitger, Matthew Helbert, Arthur Helbling, Camilla Heldbjerg Drabe, Antje Hellige, Julya Hempel, Karen Henderson, Jörg Henes, Philipp Henneke, Christian Hennig, Karin Henrichs, Martin Herbst, Walter Hermann, Manuel Hernandez, Anja Hernández, Edyta Heropolitanska, Edyta Heropolitanska-Pliszka, Richard Herriot, Friedrich Herrmann, Archana Herwadkar, Christoph Hess, Ursula Hess, Sebastian Hesse, Sonja Higgins, Anna Hilfanova, Sophie Hilpert, Chantal Hintze, Eva Hlavackova, Eva Hlaváčková, Isabel Hodl, Adna Hodzic, Miriam Hoernes, Christina Hoffmann, Andreas Holbro, Christiane Höllinger, Lisa Holtsch, Ursula Holzer, Dirk Holzinger, Manfred Hönig, Andrea Hönscheid, Julia Horn, Gerd Horneff, Claire Hoyoux, Nataliya Hristova, Kai Hübel, Angela Hübner, Christian Huemer, Aarnoud Huissoon, Brigitte Hülsmann, Patrick Hundsdörfer, Hans-Iko Huppertz, Kristina Huß, Sadia Hussain, Julien Husson, Tanja Hüttner-Foehlisch, Hanna Ijspeert, Aydan Ikinciogullari, Kökçü İlknur, Ninela Irga, Alexandra Jablonka, Karina Jahnz-Rozyk, Marcus Jakob, Donate Jakoby-Gaide, Peter Jandus, Annette Jansson, Melanie Jaquet, Helene Jardefors, Edyta Jargulinska, Barbara Jauk, Milos Jesenak, Katharina Jilka, Stephen Jolles, Alison Jones, Regina Jones, Birgit Jonkman-Berk, Göran Jönsson, Hilary J. Joyce, Pricillia Juliana, Michael Kabesch, Leo Kager, Christian Kahlert, Petra Kaiser-Labusch, Ioannis Kakkas, Dirk Kamitz, Maria Kanariou, Lothar Kanz, Elif Karakoc-Aydiner, Boris Karanovic, Mutlu Kartal-Kaess, Elisabeth Käser, Terese L. Katzenstein, Hana Kayserova, Peter Kelleher, Tessa Kerre, Sara Sebnem Kilic, Martina Kirchner, Simone Kiwit, Ayca Kiykim, Jessica Klasen, Maja Klaudel-Dreszler, Ariane Klein, Christoph Klein, Andreas Klein-Franke, Ilona Kleine, Stefan Kleinert, Christian Klemann, Marion Klima, Adam Klocperk, Robin Kobbe, Dilara Fatma Kocacik Uygun, Melanie Koch, Yvonne Kochler, Naschla Kohistani, Marina Kojic, Antonio Kolios, Uwe Kölsch, Sylwia Koltan, Irina Kondratenko, Christoph Königs, Julia Konoplyannikova, Peter Kopac, Jana Kopp, Dieter Körholz, Julia Körholz, Pauline Korte, Larysa Kostyuchenko, Ina Kötter, Sven Kracker, Pavlina Králícková, Christof Kramm, Philipp Kramme, Máté Krausz, Wolfhart Kreuz, Johanna Krista, Gergely Kriván, Gabriele Kropshofer, Renate Krüger, Olga Krystufkova, Maria Ktistaki, Jörn-Sven Kühl, Alexander Kühn, Taco W. Kuijpers, Wietse Kuis, Silke Kullmann, Andreas Kulozik, Dinakantha Kumararatne, Ria Kümmler, Andrea Kündgen, Magdalena Kurenko – Deptuch, Cosima Kuss Paula, Necil Kütükcüler, Cécile Lafoix-Mignot, Beate Lamers, Peter Lanbeck, Paul Landais, Sybille Landwehr-Kenzel, Vanessa Langemeyer, Thorsten Langer, Petra Lankisch, Nadia Lanz, Manrique de Lara, Eusebia Lara-Villacanas, Lisa Laubenthal, Hans-Jürgen Laws, Loic Le Mignot, Ronan Leahy, Jae-Yun Lee, Andrea Lehmann, Kai Lehmberg, Patricia Lehner, Hans Leibfrit, Leoni Leistner, Petra Lesch, Simon Leutner, Manolis Liatsis, Linda Libai Véghová, Johanna Liebel, Johannes G. Liese, Kotryna Linauskiene, Richard Linde, Martina Linßner, Conrad Ferdinand Lippert, Jiri Litzman, Pilar Llobet, Babacar Lo, Tariq Lodin, Jindrich Lokaj, David Longhino, Hilary Longhurst, Susana Lopes da Silva, Catharina Lorenzen, Vassilios Lougaris, Doris Löw, Annelie Lubatschofski, Mary Lucas, Verena Lutz-Wiegers, Sabine Maaß, Maria Elena Maccari, Anna Macura-Biegun, Vanessa Maerz, Paraskevi Maggina, Hannah Mahrenholz, Sarah Maier, Mounia Makhlouf, Anne Malfroot, Laura Malinauskiene, Wilma Mannhardt-Laakmann, Ania Manson, Felicia Mantkowski, Petra Manzey, Carolina Marasco, Nufar Marcus-Mandelblit, Wolfgang Marg, Gasper Markelj, Laszlo Marodi, José Goncalo Marques, Laura Marques, Karin Marschall, Natalia Martínez, Rafael Martinez de la Ossa Saenz-Lopez, Inmaculada Martinez-Saguer, Baldassarre Martire, Antonio Marzollo, Refiloe Masekela, Katja Masjosthusmann, Tania Nicole Masmas, Nuria Matamoros, Jutta Mattern, Pearl Mau-Asam, Elizabeth McDermott, Nichole McIntosh, Karmen Mesko Meglic, Ruben Meijer, Andrea Meinhardt, Safa Meshaal, Yasmina Messaoud, Björn Meyer, Dirk Meyer-Olson, Romain Micol, Bozena Micoloc, Gudrun Mielke, Cinzia Milito, Tomas Milota, Siraj Misbah, Carolin Mödden, Michael Mohr, Karina Mohrmann, Mostafa Moin, Luis Molinos, Jana Möller, Sarah Möller-Nehring, Henner Morbach, Viviana Moschese, Olga Moser, Despina Moshous, Radoslaw Motkowski, Jayashree Motwani, Nermeen Mouftah Galal, Carmen Müglich, Anna Mukhina, Eva Muller, Christiane Müller, Gabriele Müller, Hedi Müller, Ingo Müller, Thomas Müller, Zoe Müller, Ulf Müller-Ladner, Sarah Müller-Stöver, Esther Münstermann, Núria Murtra Garrell, Moritz Muschaweck, Miriam Mutert, Zohreh Nademi, Paru Naik, Andrea Näke, Andrea Martin Nalda, Gulnara Nasrullayeva, Nora Naumann-Bartsch, Verena Nemitz, Olaf Neth, Andreas Neubauer, Jennifer Neubert, Carla Neumann, Tim Niehues, Mara Niemuth, Chris Nieuwhof, Daniela Nolkemper, Sadia Noorani, Budde Adya Noorlander, Gundula Notheis, Sanam Amelie Nowatsh, Gaelle Obenga, Suheyla Ocak, Mehmet Oker, Peter Olbrich, Anna Olipra, Heymut Omran, Prasad Oommen, Linda Opitz, Jaroslava Orosova, Solveig Oskarsdottir, Hülya Özsahin, Malgorzata Pac, Jana Pachlopnik Schmid, Franco Pandolfi, Efimia Papadopoulou-Alataki, Theodora Papastamatiou, Anna Papatriantafillou-Schmieder, Alba Parra-Martinez, Olga Paschenko, Srdjan Pašić, Jarek Pasnik, Smita Patel, Martin Pavlík, Estela Paz Artal, Anouk Peeters, Sara Branco Pereira da Silva, Ruy Perez-Becker, Marc Perez-Guzman, Markus Perlhagen, Hans-Hartmut Peter, Marin Petrić, Michael Pfreundschuh, Pierre Philippet, Capucine Picard, Barbara Pietrucha, Leonora Pietzsch, Monica Piquer Gibert, Kerstin Pirolt, Alessandro Plebani, Daniel E. Pleguezuelo, Katrin Pollok, Helena Pommerening, Daniela Popihn, Aleksandra Poplonek, Marina Popp, Fulvio Porta, Jan Portegys, Klara Posfay-Barbe, Judith Potjewijd, Sebastian Poulheim, Seraina Prader, Petra Prämassing-Scherzer, Martina Prelog, Johan Prevot, Arthur Price, Timothy Price, Marijke Proesmans, Johan Provot, Federica Pulvirenti, Isabella Quinti, Anna Raab, Anita Rack, Stefan Raffac, Eduardo Ramos Oviedo, Philippe Randrianomenjanahary, Anja Ranohavimparany, Maria Raptaki, Roonaka Rashidzadeh, Margit Rathwallner, Shereen Reda, Nahida Redouane, Frederico S. Regateiro, Janine Reichenbach, Bianca Reimers, Cornelia Reinhardt, Dirk Reinhardt, Anne Reinprecht, Tamara Reiß, Ismail Reisli, Eleonore Renner, Nima Rezaei, Alex Richter, Darko Richter, Nikolaus Peter Rieber, Nadja Rieckehr, Marion Riedel, Heidi Riescher, Johannes Rischewski, Nicole Ristl, Henrike Ritterbusch, Tanja Ritz, Francois Rivier, Jürgen K. Rockstroh, Joachim Roesler, Himatur Rofiah, Elizabeth Rogerson, Elisabeth Rolfes, Beate Roller, Yaryna Romanyshyn, Roberto Rondelli, Fien Roosens, Angela Rösen-Wolff, Valentina Rösler, Johannes Roth, Tobias Rothoeft, Agathe Roubertie, Gesa Rübsam,

Abraham Rutgers, Paul Ryan, Gudrun Sach, Kambis Sadeghi, Ulrike Sahrbacher, Angelika Saidi, Özden Sanal Tezcan, Silvia Sanchez-Ramon, Juan Luis Santos, Ravishankar Sargur, Ihor Savchak, Sinisa Savic, Bernhard Schaaf, Marzena Schaefer, Christina Schäfe, Eva Scharbatke, Ellen Schatorje, Uwe Schauer, Carmen Scheibenbogen, Raphael Scheible, Clemens Scheinecker, Romana Schiller, Beatrice Schilling, Freimut Schilling, Steffi Schlieben, Thilo Schmalbach, Marc Thomas Schmalzing, Pirmin Schmid, Nadine Schmidt, Reinhold Ernst Schmidt, Monika Schmitz, Dominik Schneider, Dominik T. Schneider, Reinhard Schneppenheim, Cathy Scholtes, E.H. Schölvinck, Stefan Schönberger, Stefan Schreiber, Rik Schrijvers, Andrea Schroll, Simone Schruhl, Johanna Schrum, Ralf Schubert, Sebastian Schuh, Ansgar Schulz, Claudia Schulz, Ilka Schulze, Hendrik Schulze-Koops, Ulf Schulze-Sturm, Eva-Maria Schumacher, Elvira Schürmann, Gesine Schürmann, Volker Schuster, Eva Schwaneck, Klaus Schwarz, Tobias Schwarz, Carolynne Schwarze-Zander, Lothar Schweigerer, Wolfgang Schwinger, Anna Sediva, Jörg Seebach, Reinhard Seger, Florian Segerer, Barbara Selle, Suranjith Seneviratne, Hatidje Shabanaj, Anna Shcherbina, Anne Siepelmeyer, Kathrin Siepermann, Anna Simon, Arne Simon, Katja Simon-Klingenstein, Marija Simonovic, Merlin Simsen Baratault, Elena Sindram, Alla Skapenko, Maiken Skarke, Malgorzata Skomska-Pawliszak, Mary Slatter, Julie Smet, Ali Sobh, Bettina Sobik, Georgios Sogkas, Michael Sohm, Xavier Solanich-Moreno, Pere Soler Palacín, Franz Sollinger, Raz Somech, Anja Sonnenschein, Annarosa Soresina, Marijke Sornsakrin, Stavrieta Soura, Sabrina Spaccarotella, Guiseppe Spadaro, Monika Sparber-Sauer, Christof Specker, Carsten Speckmann, Lisa Speidel, Matthaios Speletas, Klaus-Daniel Stachel, Catherine Stadon, Aurélie Stanislas, Cynthia Stapornwongkul, Paulina Staus, Regina Steck, Cathal Steele, Herbert Steffin, Urs Steiner, Sandra Steinmann, Wim Stevens, Martina Stiefel, Sarah Stieger, Sophie Stiehler, Hermann Stimm, Silvia Stojanov, Matthias Stoll, Dominique Stoppa-Lyonnet, Tobias Strapatsas, Gabriele Strauß, Monika Streiter, Riet Strik-Albers, Gaby Strotmann, Héctor Suárez Casado, Jose Luis Subiza, Mikael Sundin, Birgit Süß, Fabienne Sutter, Anna Szaflarska, Monika Szemkus, Hannah Tamary, Sofia Tantou, Michael D. Tarzi, Helga Taschner, Ulf Tedgard, Carla Teixeira, RJM ten Berge, Klaus Tenbrock, Sabine Tester, Ilhan Tezcan, Sonja Thalguter, Julian Thalhammer, Katharina Thoma, Moira Thomas, Fabian Thomczyk, Vojtech Thon, Adrian Thrasher, Patricia Tierney, Nadine Tietsch, Alberto Tommasini, Beate Tönnes, Hans-Peter Tony, Maria Trachana, Carmen Trapp, Lourdes Tricas, Maria Conceicao Trindade Neves, Jordis Trischler, Hugo Ubieto, Anett Uelzen, Annette Uhlmann, Jan Ullrich, Kurt Ullrich, Ekrem Ünal, Gerhard Urbanski, Simon Urschel, Aleksandra Uszynska, Angelo Vacca, N.N. Vaganov, Daniel Vagedes, Stefanie Valicevic, Florence Vallelian, Rachel T. van Beem, Charlotte van Damme, Annick van de Ven, J. 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