The European Society for Immunodeficiencies (ESID) Registry Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity

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Abstract

Patient registries are instrumental for clinical research in rare diseases. They help to achieve a sufficient sample size for epidemiological and clinical research and to assess the feasibility of clinical trials. The European Society for Immunodeficiencies (ESID) registry currently comprises information on >25,000 patients with inborn errors of immunity (IEI). The prerequisite of a patient to be included into the ESID registry is an IEI either defined by a defect in a gene included in the disease classification of the international union of immunological societies (IUIS), or verified by applying clinical criteria. Because a relevant number of patients, including those with common variable immunodeficiency (CVID), representing the largest group of patients in the registry, remains without a genetic diagnosis, consensus on classification of these patients is mandatory. Here, we present clinical criteria for a large number of IEI that were designed in expert panels with external review. They were implemented for novel entries and verification of existing datasets from 2014, yielding a substantial refinement. For instance, 8% of adults and 27% of children with CVID (176 out of 1704 patients) were reclassified to 22 different immunodeficiencies, illustrating progress in genetics, but also the previous lack of standardized disease definitions. Importantly, apart from registry purposes, the clinical criteria are also helpful to support treatment decisions in the absence of a genetic diagnosis or in patients with variants of unknown significance.

Introduction

The diagnostic evaluation for primary immunodeficiency and immune dysregulation disorders (PID or PIDD, used synonymously), currently referred to as *inborn errors of immunity* (IEI), is typically initiated upon the manifestation of *i*, an increased severity or frequency of infections or an infection with an opportunistic microorganism, *ii,* symptoms of immune dysregulation like (multi-organ or early-onset) autoimmunity or autoinflammation, and/or, *iii,* clinical signs of immunodeficiency in a patient with syndromic features or malignancy. Other signs like a positive family history, failure to thrive, lymphopenia, hypogammaglobulinemia, or prolonged need of intravenous antibiotic treatment are among the well-recognized alarm bells prompting physicians to initiate further testing for IEI. International consensus papers on clinical diagnostic algorithms guide the diagnostic procedure, and an increasing number of these sets of warning signs has been analyzed for sensitivity and specificity[1-5].

Current technologies and the delineation of the human genome have enabled next generation sequencing diagnostics for IEI by targeted gene panels, whole exome, or genome analysis, that are becoming available in more and more countries and centers globally. Due to reduced costs as compared to historical genetic analyses and proven cost-efficiency, these novel genetic analysis tools are applied at earlier time points during hypothesis-driven diagnostic work-up[6, 7]. Further, the inclusion of severe combined or even other profound immunodeficiencies to newborn screening programs is becoming standard in many countries around the world because these diseases fulfil the medical genetics criteria for newborn screening, and screening is cost-efficient, thereby tremendously supporting early diagnosis, improving management, and increasing survival of patients with IEI[8-11]. Today, more than 340 monogenic IEI are known, and the number is increasing rapidly. The International Union of Immunological Societies (IUIS) has biennially published a classification of PIDs that classifies PIDs into 9 categories according to the underlying molecular defect[12]. In addition to this genetic tabular list of PID disorders with brief descriptions of main laboratory and clinical findings, recently, a phenotype-driven diagnostic consensus paper has been added to extend and improve the practical use of this classification[13]. The latter has also been made available as free application for mobile devices, further increasing its practical usefulness[14, 15].

Patient registries are instrumental for clinical research in rare diseases. A registry for a large, heterogenous and phenotypically overlapping group of disorders such as IEI needs stringent criteria for disease classification to allow appropriate data entry. Ideally, the registration title (*i.e.,* categorization) of every entry would be specific, undisputable, and verified. In the ESID registry, the registration title entry is the IEI diagnosis. The IEI diagnosis is considered definitive in cases in which a known monogenic pathological variant was identified that explains the phenotype, although functional testing of variants is not required for validation to date. However, despite the advances of genetic diagnostic technologies, there are still a majority of patients who lack a definitive genetic diagnosis. Therefore, clinical criteria were established by a panel of expert groups to correctly classify the majority of IEI disorders for patient inclusion into the ESID registry by disease category even if a genetic cause is unknown.

The ESID online registry was founded in 2004 and fulfils the role of a central IEI patient registry in Europe and some countries from other continents. It is a platform for clinical trials and other research projects. It also represents a growing network of centers, connecting experts, immunological societies, and other stakeholders. This important role of the registry underpins the relevance of a stringent and reliable data set quality, setting the ground for quality studies in our field. Examples of published and ongoing studies using the ESID registry data are the Activated PI3-Kinase Delta Syndrome (APDS) study, the study on unclassified predominantly antibody deficiencies (UnPAD) study, the Common variable immunodeficiency (CVID) burden study, or a study on patients with Ataxia teleangiectasia[16, 17]. Numerous further papers using or highlighting the ESID registry have been published; please refer to the ESID registry publications website for an overview[18].

A substantial amount of ESID registry data can be accessed by the public at the ESID registry web page[19], whereas more specific and detailed data can be retrieved and analyzed only by ESID registry members of a documenting center upon login. Thirdly, data usage by third parties may be requested by submitting a research project proposal to the ESID registry working party or may be negotiated and is subject to a contract between the ESID and the institution/party requiring access. Data from the United Kingdom Primary Immunodeficiency

Network (UKPID) are imported on a weekly interval, so that the total amount of data computed by the reporting/analysis tool are updated weekly. Publicly available ESID registry reports include: number of patients in the registry, distribution between children and adults for every country, ESID registry patient numbers and proportions per IEI main diagnosis category and per country, yielding a map of the minimal prevalence of IEI, ESID registry data on hematopoietic stem cell transplantation and gene therapy[19]. The "*members only"* section allows more specific analyses for the patients entered by the member's documenting center and the total of patients in the registry: *e.g.*, to show and export a list of IEI categories, sub-categories, specific IEI diagnoses, and gene defects, to retrieve information on the country and sex distribution as well as the rate of coverage (difference from the expected geographical prevalence).

When the ESID registry was created, no central disease classification manual was available. The registry was then entirely restructured for quality assurance and data utility purposes in 2014. During the data transfer process from the previous to the current version, an obligatory verification step of the main title of an existing or of a novel entry, *i.e.,* the IEI diagnosis, was implemented. Thus, upon choosing a diagnosis, the online entry system automatically generates a query asking whether the defined clinical criteria for the chosen diagnosis are fulfilled. The data manual also proposes to consider a number of alternative classifications if the criteria are not completely fulfilled. The present catalogue of phenotypical criteria was designed to enable correct disease classification for patients with IEI who lack a definite genetic diagnosis at the time of registry inclusion, and, similar to the IUIS documents described above, represents continually updated work in progress.

Materials and Methods

For each of 92 clinical IEI entities to be verified or excluded in patients who lack a genetic diagnosis, a number of mandatory and suggestive clinical features was defined by international experts and collected between 2013 and 2018. Drafts of proposed criteria were elaborated by experts in the field and were subsequently peer reviewed by one or more external experts in the respective category of IEI before implementation. Contributors and reviewers of each entity are stated. A regular quality check and update of these criteria at a biennial basis is being coordinated through the ESID registry working party chair. For the illustration of diagnosis transition after implementation of the diagnosis verification process, we analyzed the reclassification of entries of common variable immunodeficiency (CVID; *n*=1704) upon, *i*, clinical criteria, or, *ii*, results of genetic testing in children and adults by drawing a Sankey diagram (The Sankey Diagram Generator, Acquire Procurement Services, Brisbane, Queensland, Australia; http://sankey-diagram-generator.acquireprocure.com/).

Results: Clinical Diagnosis Criteria for IEI and their Application

The document titled *ESID Registry – Working Definitions for Clinical Diagnosis of IEI* is available in the *Online Repository* of this article (see ***Supplementary Table 1*** in the *Online Repository*) and, in a regularly updated version, on the ESID website[20]. Recently, each diagnosis of the compilation was supplemented with OMIM (*Online Mendelian inheritance in Man*) numbers of corresponding, genetically defined, diagnosis entities if available, and the respective category (1-9) of IEI according to the IUIS classification. This catalog may be downloaded and used for individual verification of a suspected IEI diagnosis before inclusion into the ESID registry. Further, upon initiation of a novel entry with a certain registration title (*i.e.*, IEI diagnosis), a pop-up window showing the respective criteria opens and requires their confirmation. ***Figure 1*** illustrates the simple steps of including a patient into the ESID registry and verifying her/his diagnosis.

To analyze the benefit and demonstrate the effect of the implementation of a mandatory verification process, we evaluated the records of CVID in children (<18 years of age) and in adults before and after application of the diagnostic criteria in 2014. The clinical diagnostic criteria of *CVID* and, for comparison, of *Unclassified antibody deficiency*, and of *Combined immunodeficiency (CID)* are shown in ***Table 1***. Of 1704 patients with the original diagnosis of CVID who were present in the registry when the verification process was implemented, 176 (10.3%) were reclassified into different diagnoses. Twenty-four were reclassified on the basis of a detected monogenic defect not listed under CVID (13.6%), and 152 (86.4%) because they did not fulfill the consensus clinical CVID criteria (***Figure 2***, and ***Supplementary Table 2*** in the *Online Repository*). Vice versa, 62 patients with other humoral immunodeficiencies (*i.e., Other hypogammaglobulinemia*, *Isolated IgG subclass deficiency*, *Agammaglobulinemia*, or *Other humoral or unclassified immunodeficiency*) were reclassified to CVID during the verification process (***Figure 2***).Those who changed from CVID to other diagnoses based on mere clinical criteria were redefined as *Unclassified antibody deficiency* (n=90; 51.1%), *Isolated IgG subclass deficiency* (n=15; 8.5%), *Unclassified immunodeficiency* (n=10; 5.7%), *Combined immunodeficiency* (n=10; 5.7%), *Agammaglobulinemia* (n=3; 1.7%), or other, rare, immunodeficiencies (n=24; 13.6%; ***Figure 2***; see also ***Supplementary Table 2*** in the *Online Repository* for more details). Patients originally classified as CVID who were reclassified to another diagnosis upon detection of a known genetic mutation were, in total,

24 (13.6%), and comprised various combined immunodeficiencies (n=13; 7.4%), *Agammaglobulinemia* (n=5; 2.8%), or various other genetic diagnoses (n=6; 3.4%) (***Figures 2 and 3***; and ***Supplementary Table 2*** in the *Online Repository*). For a comparison of the changes in diagnosis between children and adults we performed this analysis separately, showing that a substantially larger proportion of children than of adults previously entered under CVID changed their diagnosis (27.3% *vs.* 7.7%). Interestingly, the proportion of genetic *versus* clinical redefinition during the routine diagnosis verification process was double in adults (19 of 114 adult patients, 16.6% genetic redefinition) as compared to children (5 out of 62 children, 8.1% genetic redefinition). However, the final distribution of diagnostic entities after reclassification was similar between children and adults (***Figure 3***; and ***Supplementary Table 2*** in the *Online Repository*).

Discussion

The present document describes the development and current version of the *ESID Registry Working definitions for clinical diagnosis of PID/IEI* as of December 2018, and comprises the entire spectrum of primary immunodeficiencies covered by the ESID registry to date. As it uses clinical disease definitions rather than separate genetic defects, this list may appear shorter than those provided in the IUIS documents. The document was designed to enable correct classification of patients without known genetic cause of their disease within the ESID registry both for novel patient inclusions and for a mandatory verification process of existing entries starting from 2014. Furthermore, these "ESID registry *Clinical diagnosis criteria*" are useful in clinical practice when making a working diagnosis of IEI in a patient who either lacks a genetic diagnosis or has a variant of unknown significance.

To demonstrate the effect of the introduction of a mandatory verification process of a clinical diagnosis entered into the ESID database, we chose CVID as an example, because of its high frequency among entries in the ESID registry (to date, 4,773 of 25,023 patients [19%]) and its large proportion of patients lacking a defined genetic defect (4,593 of 4,773 [96%] were merely clinically defined). The reclassification of a substantial proportion of patients with CVID, namely 27.3% of children and adolescents, and 7.7% of adults formerly entered under CVID into 22 other diagnoses reflects that a much higher resolution of the main item, *i.e.*, the IEI diagnosis, was achieved by implementing this obligatory step (***Figure 1***, step 2). Previously, patient classification solely depended on the assessment and choice of the physician or documentarist who entered the patient. The biggest target group of patients who changed their diagnosis from CVID to another were those later listed under *Unclassified antibody deficiencies*, probably due to the fact that the criteria of the latter entity practically represent a subset but not all of those needed for CVID (***Table 1***). That more than 1 out of 4 children originally entered under CVID were reclassified indicates that the diagnosis of CVID is still being used too often in children, and, is important insofar as the identification of other diagnoses such as CID might imply a completely different therapeutic concept, *e.g.*, stem cell transplantation or targeted treatment. These observations suggest the requirement of a consensus definition of CVID in childhood, for which the present criteria might be a valid backbone.

That a large proportion of patients who were later classified as *Combined immunodeficiency* or as *Agammaglobulinemia* instead of CVID is due to the identification of a genetic cause is no surprise. However, it is interesting that a much larger proportion of adults than of children with CVID underwent successful genetic diagnostics and were reclassified. However, because the ESID registry did not record negative genetic testing for patients classified and registered before verification, it is not possible to distinguish whether this difference is due to a higher proportion of adult patients as compared to children with a clinical phenotype of CVID who underwent successful genetic testing, or whether a larger proportion of children had already undergone genetic testing prior to classification and had been classified as monogenic IEI other than CVID. Likely, this difference will disappear with increased application of next generation sequencing panel, exome, or genome diagnostics in all age groups driven by the availability of targeted treatment approaches.

An increasing number of patients with clinical features of IEI undergoes next generation sequencing diagnostics, but detected variants do not always represent variants known to explain the respective disease phenotype. The latest catalog of genes known to be potentially mutated in IEI and available for selection in the ESID registry for a patient entry, termed "*ESID Online Registry – List of Diseases and Genes*" can be downloaded from the ESID website[21]. If a known genotype can be associated with multiple phenotypes and is thus listed under various disease entities, as, for instance, the case in a RAG1 mutation, then the clinical diagnosis as defined by the documenting physician is required for the selection of the patient's registration title, *i.e.* the IEI diagnosis (*e.g.*, SCID, Omenn syndrome, atypical SCID, etc.), but the application of clinical criteria is not needed. Until now, the ESID registry data section on genetic information does not collect information on variants of unknown significance (VUS), heterozygous variants that may be disease-causing, copy number variations, and it does not capture digenic or polygenic effects except for a free text entry possibility for "additional genes". Further, with the only exception of *STAT3*, the differences between gain- or loss-of-function mutations, dominant negative effects, or haploinsufficiency are not distinguished. In the light of the challenges and needs arising from next generation sequencing, a future version of the registry tab on genetic data should ideally collect information on the exact position of a mutation, the possibility of multiple gene defects, likely pathogenic variants, the functional effect of a detected mutation (if

known or tested, and how), VUS, and combine them with more refined phenotypic details. Undoubtedly, these additions will require a substantial amount of programming work and resources, increasing the cost of information technology and maintenance on one hand, and more time per patient and dedication to accuracy of the documentarist, bearing the risk of a decrease in data completeness, quality, and stringency on the other hand.

Additionally, in a subgroup of patients in whom a known genetic underpinning of IEI is identified, the phenotype differs from the expected, genotype-associated, clinical picture. Some of these patients might have dual or multiple genotypes, leading to a mixed phenotype. In another subgroup of patients the disease course might be progressive, leading to a shift from one, *e.g.*, CVID to CID or another IEI category. Today, unfortunately, such genotypical or phenotypical variations that represent potentially valuable additions to previous knowledge are not recorded within the ESID registry. If a patients' phenotype changes from one IEI diagnosis to another, and the gene defect is also listed under the new category, he can be reclassified to the new diagnosis. This new PID-diagnosis and the complete history of previous documented diagnoses is recorded and shown in the user interface. Further shortcomings are, *e.g.,* that the system does not supervise the registration of patients with mutations that are not disease-causing, which is left to the interpretation of the documenting person; and, the current system fails to account for patients who present with atypical phenotypes, if no disease-causing mutation has been identified. For now, the prime requisite for inclusion of a new patient into the ESID registry is the correct definition of an IEI diagnosis and its confirmation by the documentarist or physician. Currently, this step is not monitored or curated on a general basis. However, in specific sub-projects (see level 2 and level 3, below), data monitoring is the responsibility of the respective study project committee and might be carried out for quality assurance on a study-specific basis. In its current form, the first level of an entry in the ESID registry with a defined IEI registration title (*e.g.,* "CVID") does not collect a vast number of additional patient- and disease-specific items other than type of presenting symptom (*e.g.,* infection, immune dysregulation, syndromic features, malignancy), diagnostic delay, way to and method of diagnosis, and main treatment modality (*e.g.,* immunoglobulin replacement, stem cell transplantation, gene therapy), because experience has shown a tendency that the quality of data sets decreases with increasing size. However, optional additional levels of entries (level

2 and level 3 studies for subsets of patients) were created within the ESID registry for the purpose of answering hypothesis-driven study questions. The present *Working definitions for clinical diagnosis of PID/IEI* provide the function of a standardized phenotypic diagnostic classification process and thereby enhance the discriminative depth and quality of individual datasets within the ESID registry without burdening participants with additional need to describe features that underlie the diagnosis after patient inclusion. In future, it may be conceivable to record the confirmatory steps of clinical criteria when they are applied during patient inclusion, for instance by recording "clicks" and translating this information into a standardized clinical code terminology, to accumulate even more individual disease-specific information. In line, the implementation of a yearly phenotype follow-up questionnaire, based on the same disease-specific clinical diagnostic criteria as at inclusion, might allow the collection of new important data on the natural disease courses, *e.g.*, in entities with progressive disease phenotypes, and to relate that to genetic data in future.

The usefulness and quality of data extracted from patient registries for rare diseases largely depends on correct data entry. It is thus of utmost importance for the ESID registry's quality assurance to review and check the disease classification of any newly added patient. With implementation of clinical criteria for 92 entities of IEI for patients who lack a monogenic underpinning of their disease, a substantial gain in refinement of the ESID registry disease cohorts was achieved as demonstrated for CVID. Moreover, apart from their use for correct classification in the ESID database, we deem these criteria highly useful for making the correct diagnosis of IEI in the clinical setting. They may also be used to guide clinical and laboratory investigations, and support or dispute IEI working diagnoses that are not genetically confirmed. An extension of the use of these comprehensive, stringent, and consensus definitions of IEI for additional purposes such as clinical studies (*e.g.,* as inclusion or exclusion criteria), for establishing an IEI diagnosis, and for teaching purposes in clinical immunology is warranted. Together, the ESID registry clinical diagnostic criteria set a standard for making a diagnosis in IEI, either in patients without genetic diagnosis, as a starting point to make a genetic diagnosis, or in support of a definitive genetic diagnosis.

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Conflict of interest statement

The authors declare no conflict of interests.

Author contributions

SE, NM, BGrimbacher, MB, IQ, JvM, and MGS contributed data sets, added and edited parts of the manuscript text; SE and NM jointly coordinated the work; GK, BGathmann, SR, and RS collected and analyzed ESID registry data and clinical criteria; LMG helped with the content and structure of the tables; MGS wrote the first draft of the paper and designed the figures.

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Legends

Table 1. Examples of the *ESID Registry – Working Definitions for Clinical Diagnosis of PID* for *Common variable immunodeficiency (CVID)*, *Unclassified (predominantly) antibody deficiencies,* and *Combined immunodeficiencies (CID)*. PID, primary immunodeficiency.

Figure 1. Simplified algorithm of a patient entry or diagnosis verification process in the ESID registry. ESID, European Society for Immunodeficiencies; IEI, inborn errors of immunity.

Figure 2. The ESID registry entries under the diagnosis of common variable immunodeficiency (CVID) before (left, *n*=1704) and after (right, *n*=1590) obligatory application of the ESID clinical criteria OR entry of a genetically confirmed diagnosis (direction from left to right). Other humoral immunodeficiencies that were later classified as CVID are shown in yellow (total *n*=62); entries with CVID that were confirmed as CVID (*n*=1528) or reclassified under a different IEI category based on clinical criteria are marked in green (n=152; 86.4% of reclassified patients from CVID) or, if based on genetic criteria, in purple (*n*=24; 13.6%), and are grouped for clarity. The thickness of lines/bars corresponds to the relative patient number. More detailed data are shown in Supplementary Table 2 in the *Online Repository*.

Figure 3. The subgroup of patients previously entered under CVID who were reclassified (*n*=176) is shown separately for adults (blue) and children (red), and represents the bottom 10.3% of the dark grey bar on the left panel of Figure 2. Reclassification from CVID on the left was undertaken by using clinical diagnostic criteria (green) or a genetic diagnosis (purple) on the right, distinguishing children (red) and adults (blue) out of the total of 1704 patients with the diagnosis of CVID (1477 adults and 227 children, of whom 1363 and 165, respectively, were verified as CVID and are shown in Figure 2). The thickness of lines/bars corresponds to the relative patient number. More detailed data are shown in Supplementary Table 2 in the *Online Repository*.

410 **Table 1. Examples of the *ESID Registry – Working Definitions for Clinical Diagnosis of PID* for *Common variable immunodeficiency (CVID), Unclassified (predominantly) antibody deficiencies,* and *Combined immunodeficiency (CID)*.**
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Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)
Common variable immunodeficiency disorders (CVID)	Vojtech Thon, Natalia Martinez, Maria Kanariou, Klaus Warnatz, Isabella Quinti, Helen Chapel	**At least one of the following:** • increased susceptibility to infection • autoimmune manifestations • granulomatous disease • unexplained polyclonal lymphoproliferation • affected family member with antibody deficiency **AND** marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2SD of the normal levels for their age); **AND** at least one of the following: • poor antibody response to vaccines (and/or absent isohemagglutinins); i.e., absence of protective levels despite vaccination where defined • low switched memory B cells (<70% of age-related normal value) **AND** secondary causes of hypogammaglobulinemia have been excluded (e.g., infection, protein loss, medication, malignancy) **AND** diagnosis is established after the 4th year of life (but symptoms may be present before) **AND** no evidence of profound T-cell deficiency, defined as 2 out of the following (y=years of life): • CD4 numbers/microliter: 2-6y <300, 6-12y <250, >12y <200 • % naïve of CD4: 2-6y <25%, 6-16y <20%, >16y <10% • T cell proliferation absent
Unclassified antibody deficiency	Esther de Vries, Nizar Mahlaoui, David Edgar, Isabella Quinti, Helen Chapel	**At least one of the following:** • Recurrent or severe bacterial infections • Autoimmune phenomena (especially cytopenias) • Polyclonal lymphoproliferation • Affected family member **AND at least one of the following**: • marked decrease of at least one of total IgG, IgG1, IgG2, IgG3, IgA or IgM levels • failure of IgG antibody response(s) to vaccines **AND** secondary causes of hypogammaglobulinemia have been excluded (e.g., infection, protein loss, medication, malignancy) **AND** no clinical signs of T-cell related disease **AND** does not fit **any** of the other working definitions (**ex**cluding 'unclassified immunodeficiencies')

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)
Combined immunodeficiency (CID)	Stephan Ehl, Maria Kanariou, Alain Fischer	**At least one of:** • at least one severe infection (requiring hospitalization) • one manifestation of immune dysregulation (autoimmunity, IBD, severe eczema, lymphoproliferation, granuloma) • malignancy • affected family member **AND** 2 of 4 T cell criteria fulfilled: • reduced CD3 or CD4 or CD8 T cells (using age-related reference values) • reduced naïve CD4 and/or CD8 T cells • elevated g/d T cells • reduced proliferation to mitogen or TCR stimulation **AND** HIV excluded **AND** exclusion of a clinical diagnosis associated with CID (e.g., defined syndromic diseases, DKC, AT, CHH)

413