Diploma thesis

A comparative analysis of the utility and validity of the IMMUNE DEFICIENCY AND DYSREGULATION ACTIVITY (IDDA) and other clinical scores for inborn errors of immunity

submitted by

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Affirmation in lieu of an Oath

I hereby declare that I have written the submitted thesis independently and without any illegitimate assistance from third parties. Furthermore, I confirm to not have used any other than the declared sources for the preparation of this academic work. All used sources have been indicated as such and acknowledged by means of complete references in the text.

Graz, June 8, 2022 *Anna Lena Horn eh.*

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Abbreviations

ACR	American College of Rheumatology
AD	atopic dermatitis
ADASI	Atopic dermatitis area and severity index
AD-HIES	autosomal dominant form of Hyper-IgE-Syndrome
ADL	activities of daily living
AIDAI	Autoinflammatory disease activity index
AIHA	Autoimmune hemolytic anemia
AJCC	American Joint Committee on Cancer
AR-HIES	autosomal recessive form of Hyper-IgE-Syndrome
AT	Ataxia Telangiectasia
ATFS	Ataxia Telangiectasia Functional Scale
AWMF	Association of Scientific Medical Societies in Germany
BARS	Brief Ataxia Rating Scale
BMI	Body Mass Index
BSI	Bronchiectasis Severity Index
CAPS	cryopyrin-associated periodic syndromes
CD	cluster of differentiation
CGD	Chronic granulomatous disease
CGI	Clinical Global Impression
CHAI	CTLA-4 haploinsufficiency with autoimmune infiltration
CID	combined immunodeficiency of T and B cells
CNS	central nervous system
CPR	Clinical Prediction Rules
CRP	C-reactive protein
CTLA4	Cytotoxic T-lymphocyte antigen 4
CDSS	Common variable immunodeficiency disease severity score
CVID	Common variable immunodeficiency
DOCK8	dedicator of cytogenesis 8 protein
e.g.	for example, abbr. of Latin “exempli gratia“
EASI	Eczema Area and Severity Index
EBV	Epstein-Barr virus
ESID	European Society for Immunodeficiencies

EULAR	European League Against Rheumatism
FEV1	forced expiratory volume in one second
FMF	Familial Mediterranean fever
FOXP3	Forkhead-Box-Protein P3
F-SS	FMF-Severity Score
GCS	Glasgow Coma Scale
GLILD	granulomatous-lymphocytic interstitial lung diseases
GvHD	graft-versus-host disease
HIES	Hyper-IgE-Syndrome
HLH	Hemophagocytic lymphohistiocytosis
HPO	human phenotype ontology
HPV	human papillomavirus
HRF	hereditary recurrent fever syndrome
HSCT	hematopoietic stem cell transplantation
IBLS	Immune Thrombocytopenia Bleeding Scale
ICARS	International Cooperative Ataxia Rating Scale
ICD-9	International Classification of Disease Ninth Revision
ICU	Intensive Care Unit
IDDA	immune deficiency and dysregulation activity
IDR	Immunodeficiency disease-related
IEI	Inborn Error of Immunity
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin MINR international normalized ratio
IPEX	Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked
ISSF	international severity scoring system for familial Mediterranean fever
ITP	Immune Thrombocytopenia
IUIS	International Union of Immunological Societies
JMF	Jeffrey Modell Foundation
LRBA	Lipopolysaccharide-responsive beige-like anchor protein
mAIDAI	Modified Autoinflammatory Disease Activity Index
MAS	macrophage activation syndrome
MKD	mevalonate kinase deficiency

MODS	Multiple Organ Dysfunction Score
NANO	Neurologic Assessment in Neuro-Oncology
NESS	Nottingham Eczema Severity Score
NGT	nominal group technique
NIH	National Institutes of Health
OI	Organ involvement
P-CID	Profound combined immunodeficiency
PE	physical examination
PedsQL	Pediatric Quality of Life Inventory
PELOD	Pediatric Logistic Organ Dysfunction
PEMOD	Pediatric Multiple Organ Dysfunction
PICU	Pediatric Intensive Care Unit
PID(s)	Primary Immunodeficiency/Immunodeficiencies
PIRD	Primary Immune regulatory disorder
P-MODS	pediatric multiple organ dysfunction syndrome
PROMs	patient reported outcome measures
PUCAI	Pediatric Ulcerative Colitis Activity Index
QoL	Quality of Life
RA	Rheumatoid Arthritis
SAA	serum amyloid A protein
SAID	systemic auto-inflammatory disorders
SARA	Scale for the Assessment and Rating of Ataxia
SCID	severe combined immunodeficiency
SCORAD	SCORing Atopic Dermatitis
SD	standard deviation
SLIPI	Sveriges läkares intresseförening för primär immunbrist (Swedish primary immunodeficiency physicians' interest group)
SOFA	Sequential Organ Failure Assessment
SPIRIT	Software for Primary Immunodeficiency Recognition, Intervention, and Tracking
STAT3	Signal Transducer and Activator of Transcription-3
TNM	tumor, node, metastasis
TRAPS	tumour necrosis factor receptor-1- associated periodic syndrome
UICC	Union for International Cancer Control

WAS	Wiskott-Aldrich syndrome
WASp	Wiskott-Aldrich syndrome protein
XIAP	X-linked inhibitor of apoptosis
XLN	X-linked neutropenia
XLT	X-linked thrombocytopenia

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Zusammenfassung

Einleitung: Scores werden zur Diagnose, Klassifizierung und objektivierten Beurteilung der Krankheitsaktivität von primären Immundefekten (inborn error[s] of immunity, IEI) eingesetzt. Diese Arbeit umfasst eine detaillierte Beschreibung von klinischen Scores bei IEI. Insbesondere werden die Anwendbarkeit und Schwächen des Immune deficiency and dysregulation activity (IDDA) Scores, welcher mittlerweile als modifizierte Version 2.1 verfügbar ist, mit anderen etablierten Scores verglichen.

Methoden: Als Grundlage für eine Übersichtsarbeit wurde eine Literaturrecherche durchgeführt, um anhand publizierter Daten verschiedene Scores zu bewerten und vergleichen zu können.

Ergebnisse: In der Literatur findet sich eine Vielzahl krankheitsspezifischer Scores, welche sich wiederum in unterschiedliche Kategorien einteilen lassen:
Diagnostische Scores und jene Methoden zur Klassifizierung des Schweregrads und klinischer Subtypen, wie der *Hyper-Immunglobulin E (IgE)-Score*, der *H-Score* für Hämophagozytische Lymphohisozytose (HLH) und der *Wiskott Aldrich Syndrom (WAS) Score,* ermöglichen klare Resultate für die klinische Diagnose und eine einfache Subklassifizierung der zugrunde liegenden Krankheit. Einige weitere Scores dienen primär der Beurteilung der Organbeteiligung, der Bewertung der Morbidität und Krankheitsaktivität sowie des klinischen Verlaufs eines Patienten. Hier sind der *Autoinflammatory disease activity index (AIDAI)*, *Profound combined immunodeficiency (PCID) Morbidity Measure*, der *Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) Organ Impairment Score*, ein Score für Cytotoxic T-lymphocyte antigen 4 (CTLA4) Insuffizienz, sowie auch der *IDDA 2.1 Score* zu nennen. Scores zur Behandlungsstratifizierung, wie beispielsweise bei Hypogammaglobulinämie angewandt, werden als abschließende Kategorie beschrieben.

Schlussfolgerung/Diskussion: Die beschriebenen klinischen Scores sind heterogen und teils streng krankheitsspezifisch. Eine standardisierte Scoring-Methode, die einfach anwendbar ist und dennoch die Komplexität der Erkrankungen widerspiegelt, wäre zur Verbesserung der Aussagekraft und Vergleichbarkeit der Krankheitsaktivität notwendig. Der IDDA 2.1 Score, welcher auf viele Krankheiten mit Immundysregulation angewendet werden kann und bereits im ESID-Register (European Society for Immunodeficiencies) verfügbar ist, stellt hierfür eine mögliche Option

dar. Dies vereinfacht die Überwachung der Krankheitslast, zum Beispiel unter verschiedenen Therapieoptionen oder während der Induktionstherapie vor einer Stammzelltransplantation. Darüber hinaus kann, insbesondere in Kombination mit der ergänzenden "Kaleidoskop-Funktion", eine unterstützende Anleitung für phänotypgesteuerte Therapien gegeben werden.

Abstract

Background: Scoring methods in inborn errors of immunity (IEI) show a variety of possible applications. They can facilitate diagnosis, classification of a disorder, and objectification of disease activity or severity. An attempt will be made to provide an overview of clinical scores currently used in IEI. In particular, the applicability and weaknesses of the immunodeficiency and dysregulatory activity (IDDA) 2.1 score, will be reviewed in comparison with other established scores for IEI.

Methods: A comprehensive literature search was performed in order to provide a descriptive comparison of different scores and measures frequently used in IEI based on published data.

Results: Most scores or measures identified for an application in IEI be divided into at least three partly overlapping categories: The *Hyper-Immunoglobulin E (IgE) Score*, the *H Score* for hemophagocytic lymphohisiocytosis (HLH) and the *Wiskott Aldrich Syndrome (WAS) score* are diagnostic assistive tools and scores for classification of severity and clinical subtypes. Other scoring systems, as the *Common Variable Immune Deficiency (CVID) score, the Autoinflammatory disease activity index* (AIDAI), *Profound combined immunodeficiency (PCID) Morbidity Measure*, *the Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) Organ Impairment Score*, a score for Cytotoxic T-lymphocyte antigen 4 (CTLA4) insufficiency and the *IDDA 2.1 score* are primarily used to assess organ involvement, evaluation of morbidity and disease activity. The final category is addressing treatment stratification scores, such as those applied for hypogammaglobulinemia. Main characteristics of all these scores are presented and compared.

Conclusions and discussion: The described clinical scores are quite heterogeneous and several of them are strictly disease-specific. To improve informative value and comparability, a standardized, easy-to-use scoring method that reflects the complexity of diseases would be needed. A potential instrument for this purpose is the IDDA 2.1 score, which could be applied to many diseases with immune dysregulation. It is available in the ESID (European Society for Immunodeficiencies) registry as part of a prospective study to develop a machine learning based tool. This simplifies the monitoring of disease burden, for example, during induction therapy prior to HSCT. Furthermore, especially in combination with the "kaleidoscope feature", supportive guidance for phenotype-guided therapies can be provide

1 Previously published article

The paper "The Immune Deficiency and Dysregulation Activity (IDDA2.1 'Kaleidoscope') Score and Other Clinical Measures in Inborn Errors of Immunity" by Seidel et al. (1) was already published in 2021, demonstrating the clinical relevance of the subject of this thesis. The publication is based to some extent on this diploma thesis, particularly the data collection and described results, and will be referred to several times in the following thesis.

2 Introduction

More and more inborn errors of immunity (IEI) are defined on a genetic and mechanistic basis, and an increasing number of targeted therapies become available each year. However, in most instances of profound but not severe immunodeficiencies, especially in IEI with immune dysregulation, there is still a high proportion of situations, where both the longitudinal observation of one patient or a cohort, as well as the comparison of one with other patients with the same disease (cross-sectional studies) are hampered by the lack of standardized clinical parameters and measures. As a consequence, the decision whether and when to proceed to hematopoietic stem cell transplantation or gene therapy in this difficult-to-treat subgroup of IEI, needs to be failed on an individual, expert-derived opinion without much supportive measurable evidence. However, certain prospective or retrospective studies have directly or indirectly addressed this dilemma and used various modalities to assess the morbidity and disease activity. In this review a literature-based overview of these various types of clinical scores, that are currently used in IEI, and which are specifically invented for an application in primary immunodeficiencies, is provided.

Scores and scales are in general applied in a lot of different medical fields to differentiate and quantify diseases in the most objective way and facilitate monitoring and clinical decision making. Staging, grading and diagnostic criteria are applied under standardized guidelines in various medical specialties to define a diagnosis, to determine a subtype of a disease and to subsequently facilitate decisions surrounding patient management and treatment. In IEI scores are used for objective initial assessment, making and corroborating a diagnosis and to decide treatment requirement. In addition, they can be used to facilitate clinical decision finding, assess transplant indications, follow-up and document treatment response. Inborn errors of immunity with immune dysregulation often present with variable severity even within one family which makes it very difficult to establish one scoring method for this heterogenous family of diseases.

Preparing this thesis details of clinical scores, that have been used in IEI, were collected in order to categorize them, compare their depth, focus and aims, as well as to compare their potential use in clinical practice. Without claiming to be exhaustive, a particular emphasis of this thesis lies on the comparison of the applicability as well as the weaknesses of the immune deficiency and dysregulation activity (IDDA) score by Tesch et al. (2), with other established scores. The IDDA score by Tesch et al. (2) was especially developed to allow intraindividual, longitudinal monitoring and assess the interindividual disease burden carried by patients with Lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency, a severe primary immunodeficiency with a broad spectrum of clinical and immunologic manifestations (3–5). In the meantime, a newly adapted and more universal version of de IDDA score (IDDA score 2.1) by Seidel et al. (1,6) is available, which is already part of the European Society for Immunodeficiencies (ESID) registry (7) and the intended application as open monitoring tool in patient registries for similar disorders will be analyzed and discussed.

2.1 Inborn Errors of Immunity (IEI)

Human inborn errors of immunity (IEI), also known as primary immunodeficiencies (PIDs) are a heterogeneous group of diseases induced by monogenic germline mutations which cause a loss or gain in the function of the encoded protein. These genetic defects can be dominant or recessive, autosomal or X-linked, and with complete or incomplete penetrance and influence the development, function, or both, of immunity (8,9). IEI are thought to be individually and collectively rare and are thus still underdiagnosed and more common than generally thought (10). However, the frequency regarding specific forms of IEI is varying depending on the country as well as the population (11). The severity ranges from life-threatening disorders presenting in early infancy to IEI, that present with milder symptoms in adolescence or adulthood. At first most PIDs generally attract attention because of a clinical history of repeated infections (9). Gradually a phenotypic diversity of PIDs is present due to disease penetrance and expression variability and it is also caused by interactions between genetic and environmental factors (12). This results in an increased susceptibility to a range of infectious diseases, a growing diversity of autoimmune as

well as autoinflammatory phenotypes, allergy and an increased risk of developing malignancies (13).

The classification of the International Union of Immunological Societies (IUIS) of 2019 is currently covering a heterogeneous group of 406 different disorders with 430 various genetic defects as human innate defects of immunity. It is updated regularly, provides information on the broad variety of disorders and includes a genotypic as well as phenotypic classification, thus facilitates research on, diagnosis and clinical management of primary immunodeficiencies (13).

2.1.1 Warning Signs of Primary Immunodeficiencies

Since an early diagnosis of PID is highly challenging and not only requires recognition by physicians and health care professionals but also the general public, the so-called PID warning signs by the Jeffrey Modell Foundation (JMF) have been published. This screening tool gives an overview of typical clinical signs and symptoms of PID, in order to raise awareness and improve diagnosis (14,15). As there is still a significant delay between the onset of symptoms of PID and diagnosis, these warning signs should help to promptly recognize an underlying inborn error of immunity and thus prevent morbidity and mortality (15).

Ten warning signs of primary immunodeficiency	
1	≥4 ear infections in one year
2	≥2 serious sinus infections in one year
3	≥2 pneumonias in one year
4	Recurrent, deep skin or organ abscesses
5	Persistent thrush in mouth or fungal infection on skin
6	≥2 deep-seated infections including septicemia
7	≥2 months on antibiotics with little effect
8	Need for intravenous antibiotics to clear infections
9	Failure of an infant to gain weight or grow normally
10	Family history of primary immunodeficiency

Table 1: Modified version of PID warning signs provided by Jeffery Modell Foundation (JMF), taken from Arkwright et al. 2011 (14)

Table 1 shows the 10 major warning signs of PID, that can be summarized as increased frequency and severity of infections, the need for more intense or prolonged treatment of infections as well as reduced thriving and family history of PID. If two or more of these warning signs are present in an individual, the presence of an underlying PID should be taken into consideration (14,15). These general warning signs by JMF are also published on the official ESID web page (16).

Patients with PID can present with multiple symptoms, that are not necessarily included in the above mentioned 10 PID warning signs. These clinical features may include sporadic infections and granuloma, lymphoproliferation, eczema, inflammatory bowel disease as well as autoinflammation and autoimmunity or malignancy. Additionally, it is important to consider the type of pathogens, the circumstances in which infections occur as well as the organs and tissues affected. The occurrence of allergies and vaccine-related adverse effects must also be considered, as administration of inactivated (killed) vaccines is still recommended, although it has been observed that the response to vaccination is generally reduced in PID patients. (7,17–19).

As these complex symptoms are not part of the 10 warning signs, less classical presentation of PID can be missed or diagnosis can be delayed. Based on the PID warning signs by JMF, a modified guideline for the earliest possible diagnosis of PID was develop by the Association of Scientific Medical Societies in Germany (AWMF) in 2011. As shown in Table 2, in addition to an increased susceptibility to infections, failure to thrive in children, weight loss in adults and an indicative family history, which are already part of the JMF PID warning signs, this guideline also includes immune dysregulation, reproducible abnormal laboratory values and genetic indication of PID. The German acronym "ELVIS" can be used to differentiate between physiological and pathological susceptibility to infections. It includes the causative pathogen, localization, course, intensity and the sum of infections. In addition to an increased susceptibility to infections, a disturbance of immune regulation (acronym GARFIELD) is also one of the leading symptoms of PID. Patients with immune dysregulation can present with granuloma, autoimmunity, recurrent fever, eczema, lymphoproliferation and chronic intestinal inflammation (18).

	CHILDREN	ADULTS
1.	Pathological susceptibility to infections: **“ELVIS”** Pathogen, localization, course, intensity, sum of infections	
2.	Immune dysregulation: **"GARFIELD "** Granuloma, Autoimmunity, recurrent fever, unusual eczema, lymphoproliferation, chronic intestinal inflammation	
3.	Failure to thrive	Weight loss, usually with diarrhea
4.	Conspicuous family history e.g. (for example) consanguinity, immunodeficiency, pathologic susceptibility to infection	
5.	Laboratory: hypogammaglobulinemia, persistent or recurrent lymphopenia, neutropenia, thrombocytopenia	
6.	A genetic indication of a primary immunodeficiency or a positive neonatal screening for primary immunodeficiencies	

Table 2: Warning signs of the AWMF guideline for the purpose of identifying patients with PID, adapted from Farmand et al. 2017 (18)

It should be noted that some patients with PID do not present with clinical symptoms until adolescence or adulthood.

In order to not miss diagnosis in them, six warning signs for identification of PID in adulthood have been published by SLIPI (Sveriges läkares intresseförening för primär immunbrist = Swedish primary immunodeficiency physicians' interest group) and accepted as ESID criteria (18–20). In addition, the AWMF guideline provides a list of immunologic emergencies in the neonatal and infant period for which immediate contact with experienced clinicians is indicated. These include erythroderma, persistent fever and cytopenia, severe lymphopenia, severe neutropenia, and severe hypogammaglobulinemia (18,19). To summarize, all these clinical features can be referred to as PID warning signs. Combining these with well-trained physicians, genetic counseling of families affected by PID and genetic and clinical screening, helps to improve diagnosis, classification, prognosis, and therapy of PID (14,21,22).

2.1.2 PID Screening Tools

In addition to the above-mentioned warning signs, designed to increase awareness of PID, JMF created the SPIRIT (Software for Primary Immunodeficiency Recognition, Intervention, and Tracking) Analyzer tool to improve identification of patients

with PID who are undiagnosed. This software screening tool combines JMF's 10 PID warning signs with 352 International Classification of Disease Ninth Revision (ICD-9) codes for an earlier identification and diagnosis of PID patients. The Analyzer has no diagnostic value and is used as a screening tool to categorize patients into low, medium and high-risk for PID by scoring risk points and recommends further testing for medium and high-risk categories by educated physicians. As the Analyzer's name implies, its mission is early disease detection, intervention and electronic tracking, resulting in improved quality of life for affected patients and reduced healthcare costs (23). Another scoring method for identifying patients with undiagnosed IEI is the Immunodeficiency Disease Related (IDR) Score by Cunningham-Rundles et al. (24). It was developed to determine the incidence of primary immunodeficiencies in different populations and- because of existing health care disparities- for certain ethnic minorities, since most studies of PID are described in the context of individuals from European background. This algorithm and screening method is also based on ICD-9 codes. Table 3 shows the selected basic ICD-9 codes, which can be split into 174 subcodes, that are scored as 1, 2, or 3 according to severity. To avoid multiple counting, an already assigned diagnosis in the past 30 days and specific chronical symptoms, marked as chronic codes, were only counted once. The sum of all scores of a patient within the test period, which includes a primary diagnosis and up to 7 additional ones, results in the final IDR score. A final score of ≥6 indicates the presence of an underlying PID (24,25).

Diagnosis or condition	Score	Diagnosis or condition	Score
Pneumonia, organism unknown	3	Malabsorption	2
Bacterial pneumonia	3	Giardiasis	2
Septicemia	3	Autoimmune hemolytic anemia	2
Empyema	3	Chronic bronchitis*	1
Bronchiectasis	3	Chronic sinusitis*	1
Osteomyelitis	3	Chronic otitis media	1
Other abscess	3	Chronic diarrhea*	1
Aseptic meningitis	3	Acute bronchitis	1
Splenic abscess	3	Acute sinusitis	1
Chronic mastoiditis*	3	Fever of unknown origin	1
Bacterial meningitis	3	Cutaneous candidiasis*	1
Liver abscess	3	Suppurative otitis media	1
Lung abscess	2	Failure to thrive	1
Lymphopenia	2	Thrush	1
Cellulitis	2	Lymphadenitis	1
Neutropenia	2	Gastroenteritis	1
Splenomegaly	2	Mycosis	1
Lymphadenopathy	2	Acute otitis media	1
Immune thrombocytopenia	2	Abnormal weight loss	1

***chronic conditions counted only once in a 12-month period.**

Table 3: Immunodeficiency disease related score, taken from Yarmohammadi et al. 2006 (26)

In their retrospective analysis of 204 potentially immunodeficient patients, Reda et al. (25) show that a family history of PID is the most important predictor of PID, followed by the requirement for intravenous antibiotics, recurrent deep-seated infections and failure to thrive. Furthermore, parental consanguinity and death of siblings due to infections, which are not part of the warning signs, were often found in pa-

tients with PID. This study demonstrates that if an inborn error of immunity is clinically suspected the absence of the major warning signs as well as a low IDR score, should by no means exclude a possible PID diagnosis (25).

2.2 Definition and classification of scoring systems

Scores and other implemented terms used as synonyms or in a similar context, such as scales, indices, and measures are methods allowing an objective clinical assessment and are used for a variety of diseases in several medical fields and show a wide range of applicability. Depending on the purpose of a clinical scoring system, it is also referred to as a clinical decision rule, clinical prediction tool, probability assessment, prediction algorithm, or risk score (27–29). According to research published by Challener et al. (30) in 2019, over 250.000 clinical scoring systems exist in the medical field. This high number of scoring systems varies between widely accepted tools that are broadly used and those that are very specialized and thus have a small scope of application. These tools are algorithms and in most cases provide numeric indices to facilitate clinical practice with a combination of highly valid variables including patient characteristics and specific examination results (28–30). Clinical prediction rules (CPR) can calculate a probability of the presence of a particular pathology or predict an outcome by combining relevant clinical findings, thus serving as a support tool for assessment and decision making and improving efficiency (27–29,31). In intensive care and emergency medicine, predictive scores are used to determine the severity of a condition as objectively as possible and to serve as a triage system and prognostic tool in medical emergencies (32). But scoring systems also find application in the diagnosis of diseases, monitoring of patients and are used in the classification and determination of phenotypes of complex diseases. Additional exemplary fields of application are assessment of disease activity, morbidity and burden of chronic disease. Ideally, surrogate parameters, biomarkers or tumor markers are used in addition to the clinical symptoms to establish and confirm a diagnosis and decide on the need for treatment. The scores as objective quantification also provide a stratification of patients into different disease categories and thus, in the case of PID, can also be used to assess a transplant indication (33).

Diagnostic scores exist in nearly every medical field due to a relevance as a quantification tool that facilitates diagnosis. Scores in the sense of a diagnostic criterion are probably the best-known type of scores, as they are defined by a number of points or by a certain cut-off value resulting from them.

A classification of diseases by their severity is an improvement that helps better monitoring and keeping an overview of individual patients. Medical treatment decisions and the adjustment of therapies can be made based on an index of disease severity or different phenotypic appearance of IEI. A disease severity classification is additionally an important tool to determine prognosis, analyze clinical correlates, and compare between surveys and different patient groups (34).

Furthermore, affected organ systems and/or additional parameters are included in the assessment of some medical conditions. These scores were developed to provide an overview of the patient's state of health at a specific time of measurement and as a consequence they are used as a prerequisite of therapeutic actions, are applied to evaluate therapeutic outcomes and to predict morbidity and survival of IEI. By systematically recording a disease using clinical and/or laboratory parameters, an initial assessment and follow-up can be quantified. Implementing eligible scores for IEI is intended to facilitate treatment decisions as well as the documentation of treatment responses, as to date validated disease activity scores as predictive and stratification-relevant tools are not available for these conditions (33).

2.3 Scores in other medical fields

The application of scoring systems in other medical fields has an enormous range. Most of related specialties work with the help of scoring systems, ranging from simple methods for the subjective assessment of pain, such as visual analog scales (35) and numeric rating scales, to Lansky (designed for recipients less than 16 years old) (36) and Karnofsky (designed for recipients aged 16 years and older) (37) Performance scales, that give us information about the overall functional status of patients, also applied in patients with PID.

Staging and grading in oncology for initial categorization of tumors on the basis of primary tumor characteristics and in addition response assessment and follow-up can also be considered a scoring system. Staging defines the extent of tumor

spread, provides a prognostic tool and strongly affects treatment decisions and individual treatment results. The most commonly used staging system is the tumor, node, metastasis (TNM) system developed as a collaborative effort of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) (38).

In emergency medicine a standardized method for evaluating the level of consciousness with the help of several neurologic conditions is well known and is widely used, known as the Glasgow Coma Scale (GCS). The GCS assigns points based on three parameters of neurologic function: eye opening, best verbal response, best motor response (39).

Different scoring methods are for example also used in conditions like autoimmune cytopenia, more precisely to facilitate treatment decisions and requirements in immune thrombocytopenia (IBLS – Immune thrombocytopenia Bleeding Scale (40)), for severity scoring in atopic dermatitis (NESS – Nottingham Eczema Severity Score (41)) or to help classify patients with Rheumatoid arthritis (2010 ACR/EULAR classification criteria (42)).

There are a lot of medical fields where scores and scales are applied to facilitate the clinical routine. In the following, a few relevant scores, that are also applied in association with PID are described in more detail.

2.3.1 Patient reported outcome measures (PROMs)

PROMs offer a further instrument for an assessment of outcomes regarding the health of patients and are directly reported by them. These are primarily used in scientific research for comparison of therapy outcomes and in drug development. But in various medical fields the interest for the routine use of PROMs in daily practice is growing, for example (e.g.) for clinical trials (screening, treatment outcomes), clinical practice (diagnosis, monitoring progress) and for information for patients or clinicians. A systematic use of patient-centered information from PROMs is an improvement of communication between doctors and patients and their decision making and represents a useful tool to increase patient satisfaction with care (43). PROMs help patients address problems with clinicians, and both, standardized and individualized PROMs, make patients think about their health and enable them to develop a deeper understanding of their own condition (44).

2.3.2 Pediatric Ulcerative Colitis Activity Index (PUCAI)

A noninvasive scoring method to quantify disease activity of ulcerative colitis in pediatric patients was developed by an expert committee in pediatric inflammatory bowel disease. The PUCAI was initially reduced to 11 items that best reflect the disease activity, but laboratory items were subsequently excluded since they did not improve the PUCAI performance. An index consisting of 6 items remained, ranging from 0 to a maximum of 85 points, classified into no symptoms (<10), mild (10-34), moderate (35-64) and severe activity (≥65). The validated PUCAI allows to monitor and reflect disease activity of pediatric ulcerative colitis without using invasive procedures such as endoscopy (45).

This scoring method is widely applied and inter alia also used for patients suffering from colitis associated with Chronic granulomatous disease (CGD), since there is no validated index for disease activity or criteria for induction of treatment available for this IEI. The clinical features included in the PUCAI, e.g. abdominal pain, rectal bleeding, stool consistency, number of stools, nocturnal stools, and thus disease activity level are applicable for pediatric ulcerative colitis as well as CGD colitis. Although more studies are required for further validation of the PUCAI, it is a noninvasive scoring method that has the potential to also reflect disease activity of CGD colitis and help determine the appropriate treatment (46).

2.3.3 Immune Thrombocytopenia Bleeding Scale (IBLS)

The Immune Thrombocytopenia Bleeding Scale (IBLS), shown in Table 4, is a method for objective quantification of bleeding symptoms in Immune Thrombocytopenia (ITP) and can be used as prerequisite for the examination of laboratory parameters correlating with bleeding propensity in thrombocytopenia. This bleeding assessment system comprising 11 anatomical site-specific grades between 0 (none) and 2 (marked bleeding) is a useful clinical tool for monitoring bleeding. The 11 evaluated subjects contain skin, oral, epistaxis, gastrointestinal, urinary, gynecological and pulmonary symptoms, intracranial haemorrhage and subconjunctival haemorrhage by history over the previous week and two of these, skin and oral, are additionally assessed by physical examination (PE). The accurate and objective recording of bleeding symptoms is indicative to enable more information about the heterogeneity in bleeding propensity (40).

Parameter	*Localization*	*Grade 0 (none)*	*Grade 1*	*Grade 2*
Patient-reported	Skin	None	1-5 hematomata and/or scattered petechiae	>5 hematomata >2cm diameter and/or diffuse petechiae
	Oral	None	1 blood blister or >5 petechiae or gum bleeding that clears easily with rinsing	Multiple blood blisters and/or gum bleeding
Clinical examination	Skin	None	See above	See above
	Oral	None	See above	See above
History	Epistaxis	None	See above	See above
	Stool	None	Occult	Gross
	Urin	None	Microhematuria	Macrohematuria
	Menstrual	Normal period	Spotting between period	Metrorrhagia or very heavy period
	Pulmonary	None	n.a.	yes
	Subconjunctival	None	Yes	n.a.
	Intracranial	None	n.a.	Yes
Sum	=			

Table 4: Immune Thrombocytopenia Bleeding Scale (IBLS), modified version by Seidel et al. 2017 (47), original published by Page et al. 2007 (40)

According to a French study of 2016, patients with PID are reported to have an extremely increased risk of developing autoimmune cytopenia compared to the unaffected population (48). Supporting this strong association of the two conditions, in another French study, 13% of cases with isolated autoimmune hemolytic anemia (AIHA) were diagnosed with PID (49). In particular, in the differential diagnosis of childhood cytopenias, it is important to consider inborn errors leading to single- or multicellular cytopenias due to bone marrow failure and additional factors such as persistent/chronic infections (47). Thus, objective and frequently applied diagnostic assessment of clinically relevant immune cytopenias is indispensable to identify any underlying PIDs and to allow disease-specific treatment decisions (50).

2.3.4 Severity Scoring of atopic dermatitis

Atopic dermatitis may be present in some primary immunodeficiencies, such as selective Immunoglobulin A (IgA) deficiency, common variable immunodeficiency, Wiskott-Aldrich syndrome, X-linked agammaglobulinemia, Hyper-Immunoglobulin E (IgE) syndrome (HIES), and Omenn syndrome, an autosomal recessive form of severe combined immunodeficiency (SCID) (51).

The Nottingham Eczema Severity Score (NESS) is an assessment tool for disease severity of atopic dermatitis (AD) in children. This scoring method was developed from an existing system for monitoring disease activity of atopic dermatitis, first described by Rajka and Langeland in 1989, categorizing disease activity of AD into mild, moderate and severe (52). The three modified parameters of disease intensity, clinical course and examined extent of disease are weighted equally and give information about the disease severity. The final score summarizes all three parameters, ranges from 3 to 15 and classifies the children in 3 degrees of severity (mild, moderate and severe). A higher numerical value is associated with a more significant severity of the disease. Construct validity of the NESS has been demonstrated in comparison to a clinical assessment according to a dermatologist and parental severity assessment. Further validation is needed regarding the use at older children, the use by researchers/health professionals, and the development as a fully questionnaire-based tool (41).

Especially for atopic dermatitis other severity scoring tools are available, e.g. Six Area, Six Sign atopic dermatitis severity assessment (53), the Eczema Area and Severity Index (EASI) (54,55), the Atopic Dermatitis Area and Severity Index (ADASI) (56) or the SCORing Atopic Dermatitis (SCORAD) Index (57). The SCORAD index is the most widely used of published tools for severity assessment of AD. It consists of three parts: the extent graded 0-100, the intensity consists of six items each graded on a scale 0-3 (erythema, oedema/papulation, excoriations, lichenification, oozing/crusts and dryness) and two subjective items (daily pruritus and sleeplessness) that are graded on a 10-cm visual analogue scale. Those three subscores are part of a defined formula with the maximum score being 103. The SCORAD defines mild eczema as a score less than 25, moderate eczema represents a score of more than 25 and less than 50, and severe eczema is defined by a score greater than 50. It is a representative and well evaluated method, but naturally also shows intra- and interobserver variations (57,58). Since early diagnosis and treatment of PID are of major importance, attention should be paid to severe forms of AD that may also not respond to standard therapies, as these may be the first indications of underlying immunodeficiency (51).

2.3.5 Classification criteria for Rheumatoid Arthritis

For Rheumatoid arthritis (RA), a chronic inflammatory autoimmune disease characterized by joint swelling, joint tenderness and the destruction of synovial joints with the consequence of severe disability and premature mortality, classification criteria sets with the help of joint examination and imaging, as well as the presence of RA-related autoantibodies, systemic inflammation, and the duration of joint symptoms and findings, are available (59).

The 1987 American College of Rheumatology (ACR; formerly the American Rheumatism Association) criteria (60) involves the following subjects: 1) morning stiffness in and around joints lasting at least 1 hour; 2) soft tissue swelling (arthritis) of 3 or more joint areas; 3) arthritis of hand joints; 4) symmetric swelling (arthritis); 5) rheumatoid nodules; 6) the presence of serum rheumatoid factor; and 7) radiographic changes. For a specific diagnosis of rheumatoid arthritis, the presence of four or more criteria is required and criteria one through four must have been present for at least six weeks. But this classification scoring shows a significant limitation in identifying patients with no long-lasting symptoms and therefore leads to insufficient intervention in early stages and prevention of a chronic, erosive disease state. As a consequence a new classification tool for RA by a joint working group of the ACR and the European League Against Rheumatism (EULAR) to facilitate the study of patients at earlier stages of the disease and a relatively short duration of symptoms was implemented. The working group designed the 2010 ACR/EULAR classification criteria for Rheumatoid arthritis with a new criterion set. After two phases a user-friendly tool was developed and “definite RA” is now characterized by the presence of synovitis in at least one joint, absence of an alternative diagnosis with a better explanation of the synovitis and a total score of at least six (with ten being the highest possible)..The score criteria are divided into four simplified categories: number and site of involved joints (range 0-5), serological abnormality (range 0-3), elevated acute-phase response (range 0-1) and symptom duration (two levels; range 0-1) (42).

2.3.6 FACED score and Bronchiectasis Severity Index

Bronchiectasis is a chronic respiratory disease, defined by permanently dilated bronchi on high resolution chest computerized tomography (61). IEI account for 1-17% of etiologies of patients with bronchiectasis (61). The FACED score is an assessment tool published in 2014, that classifies the severity of non-cystic fibrosis bronchiectasis according to its prognosis (62). It is a seven-point score analyzing five dichotomized variables with a significant capacity to predict the probability of five-year all-cause mortality. The chosen variables to construct the scoring method are also an acronym for the score's name:

- **F**EV1 (forced expiratory volume in one second) % predicted
- **A**ge
- **C**hronic colonization by Pseudomonas aeruginosa
- **E**xtension (radiological): number of lobes affected
- **D**yspnea

A maximum of seven points is reachable and the severity is categorized into three groups: 0-2 points signifies mild bronchiectasis, 3-4 points moderate bronchiectasis and 5-7 points describes severe bronchiectasis. The constructed FACED score's validity is confirmed by a validation cohort consisting of 422 patients of the initial sample comprised (62).

The Bronchiectasis Severity Index (BSI) was also published in 2014 and is another severity score using four end-points: mortality, frequency of exacerbations, hospital admissions, and health-related quality of life (63). The BSI corresponds to a scale that evaluates the severity and prognosis of non-cystic fibrosis bronchiectasis by including nine parameters with different values for each: age, body mass index (BMI), FEV1% predicted, hospitalization and exacerbations before study, degree of dyspnea, chronic colonization by Pseudomonas aeruginosa and other microorganisms and radiological extension of the disease. The BSI was also validated in independent cohorts of patients from four European centers. In comparison to the FACED score the BSI scoring system is relatively complex and includes multiple predictors, but an online calculator is accessible (63).

Both scoring tools stratify patients into severity risk categories in order to predict the probability of mortality (64). As bronchiectasis is the most frequent non-infectious respiratory complication of IEI the FACED score as well as the BSI find application in this medical field (61,65–67).

2.3.7 Scores for Pediatric Organ Dysfunction

In Pediatric Intensive Care the assessment of severity of organ failure in children is very important as the multiple organ dysfunction syndrome is the main cause of death not only in adult Intensive Care Units (ICUs) but also in Pediatric Intensive Care Units (PICUs) (68). As patients with IEI have a high rate of PICU admission and the following tools are highly relevant for this patient group in order to estimate the severity of multiple organ dysfunction syndrome and show the mortality-related risk factors and outcome of these critically ill patients (69). For pediatric multiple organ dysfunction syndrome (P-MODS) a few well established scores exist and were also updated over time.

The Sequential Organ Failure Assessment (SOFA) score was developed to assess the acute morbidity and predict mortality of critically ill patients. It is based on the degree of dysfunction of six different organ systems (respiratory, cardiovascular, hepatic, coagulation, renal and neurological system) evaluated by individual scores for each. Every organ system is scored from zero to four with an increasing score reflecting worsening organ dysfunction.

Leteurtre et al. (68,70,71) introduced two other scoring systems to evaluate organ function in critically ill children. The first method is based on the Multiple Organ Dysfunction Score (MODS) described by Marshall et al. (72) and is called Pediatric Multiple Organ Dysfunction (PEMOD) system. It is a method consisting of 5 selected organ systems each represented by a single “ideal” clinical or laboratory measure: cardiovascular (lactic acid), respiratory (PaO2/FIO2 ratio), hepatic (bilirubin), hematologic (fibrinogen), and renal (blood urea nitrogen). Same as in SOFA score each organ system is scored from zero to four points and the final score is the sum of these subscores (70,73).

The Pediatric Logistic Organ Dysfunction (PELOD) system, based on a publication of Le Gall et al. (74) is by far the most frequently used scoring system for assessing pediatric organ dysfunction (71). It is a summation of selected organ parameters

(70). The 13 parameters included in the score are GCS, pupillary response, heart rate, systolic blood pressure, serum creatinine, Pao2/Fio2, Paco2, mechanical ventilation, white blood cell count, platelets, aspartate transaminase, prothrombin time and international normalized ratio (INR). Since the PELOD scoring system was already developed in 1999, an updated and improved version of the score was published in 2013 by Leteurtre et al. (71). This updated version includes ten variables evaluating the function of five organ systems and is called PELOD-2. In comparison to the previous version, the PELOD-2 does not contain hepatic function which was only accounted for 0.1% of its variance, and it did not predict death in the original P-MODS score (68,73). The updated score additionally includes mean arterial pressure and lactatemia to predict cardiovascular dysfunction, measures that are part of both the SOFA and the P-MODS scores.

The main aim of organ dysfunction scores, such as the PELOD (68), SOFA (75), P-MODS (73), MODS (72), and Logistic Organ Dysfunction System (74), is however to evaluate the severity of illness, complications and organ dysfunction of critically ill patients and not only to predict mortality rates (71,75).

3 Material and Methods

A systematic literature search was performed on PubMed and OVID Medline. Sample terms in the search strategy included “primary immunodeficiency”, “inborn errors of immunity” and “immune dysregulation” crossed with “scor*”, “scale”, “measure”, and “perform*” in various combinations in order to screen titles, keywords and abstracts. This search strategy was adapted and conducted until November 2021 (1). From originally 880 results on OVID Medline and 559 results on PubMed (n=1439) after screening the literature by title and abstract 75 publications were left. Duplications were excluded and furthermore the scanning process by title and abstract screening excluded literature with diagnostic methods for immunologic testing and standard scores (Z score). The reason why screening literature started by analyzing both title and abstract is that a large number of publications do not involve information about scoring methods in the title itself, therefore screening titles only would have been insufficient in this case.

After excluding scoring methods that only cover quality of life and psychological aspects of patients 57 publications were left. After outsourcing scores and indices that are not only used in primary immunodeficiencies but also in other medical fields the 44 remaining articles which include 21 scoring methods were classified into different categories.

Scores that included too few criteria or that were too specific were not included in the comparison.

An Excel sheet was created to provide an overview of the final selection of the ten most important and comparable clinical assessment tools for IEIs, that were further classified into diagnostic scores, morbidity and disease activity measures and treatment stratification scoring systems.

In order to allow a more objective comparison, the included parameters and items were classified in a uniform way and divided into specific subgroups:

Anatomical, autoimmunity, inflammatory, infection related, laboratory, “quality of life (QoL), supportive measures, performance scales”, other additional information, not categorized, malignancy and age correction.

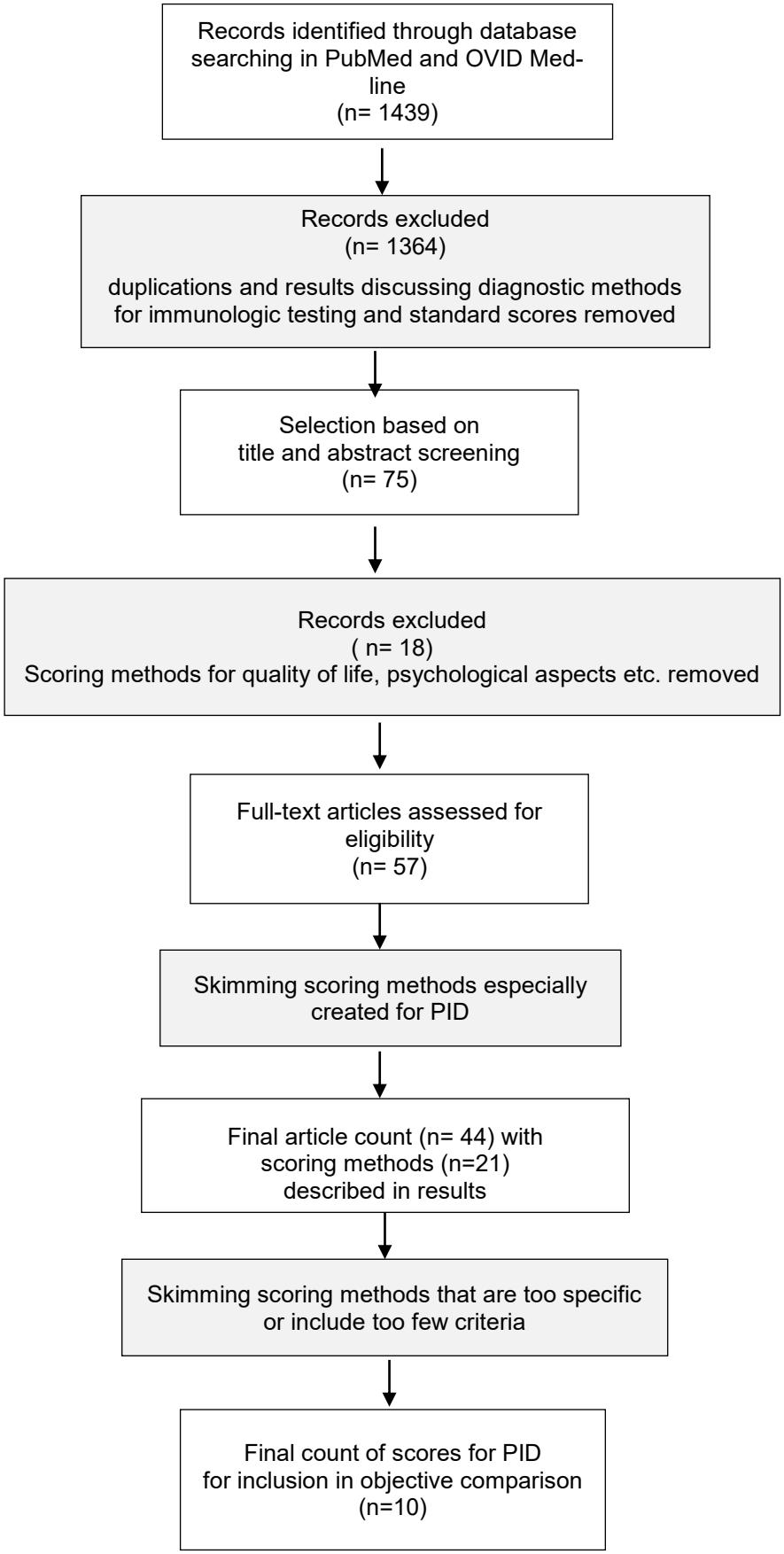


Figure 1: Flow Chart of the Systematic Literature Review – resulting in 10 representative and comparable scoring methods and measures frequently used in IEI

4 Results – Outcomes

4.1 Description of Clinical Scores and Morbidity Measures established in IEI Research

The main objective of this thesis is, without claiming to be exhaustive, the thorough description and comparison of applicability of the scores available for primary immunodeficiencie.

Based on the performed literature review the detected scores used in PID were divided into three different categories, reflecting the main objectives and fields of application respectively:

1) specific diagnosis, classification of severity and subclassifying a diagnosis, 2) evaluation of morbidity, organ impairment and disease activity and 3) treatment stratification. A schematic proportional comparison of used parameters and items is depicted as a heatmap in Figure 2. At the end of this chapter, a very comprehensive overview of comparable and representative scores with their parameters is given in Table 14. As a lot of factors, including disease-inherent and user dependent, make a broader application of scores, mostly designed for a single disease, difficult, the IDDA 2.1. score was created by Seidel et al. and will also be presented in this thesis. The original IDDA score was developed for LRBA deficiency and applied in a retrospective study. However, this new version aims to provide a standardized, comparable evaluation and monitoring of diseases with immune dysregulation and may be used in all of them (1).

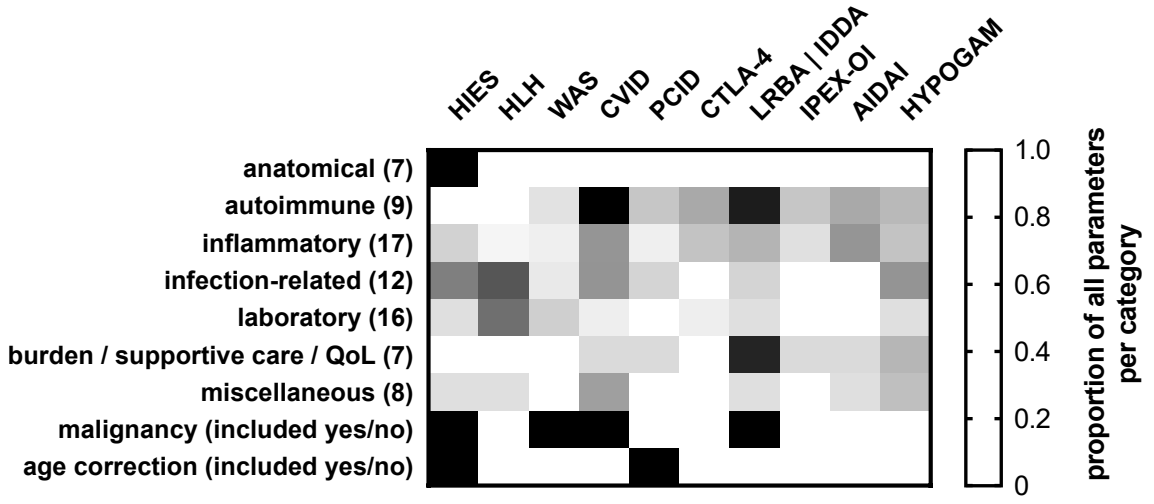


Figure 2: Schematic comparison of an exemplary choice of clinical scores and morbidity measures used for IEI, taken from Seidel et al. 2021 (1)

4.1.1 Diagnostic assistive tools and scores for classification of severity and clinical subtypes

Scores of this type include a set of disease-specific criteria that increase the likelihood of a particular diagnosis or specific criteria for subclassifications of a diagnosis. Some of these scoring systems aim to classify patients suffering from the same disorder into different categories or subtypes, mostly according to disease severity, in order to improve patient management and possibly predict outcome (55). Unlike scores defining disease activity, they can include consistent items and variables, such as age of disease onset, that do not change over time (56). Especially since many IEI are clinically very heterogenous and present with different phenotypes, even within the same disorder, categorization of patients to distinguish mild from severe conditions can help clinicians to adapt management and treatment accordingly (1).

4.1.1.1 Hyper-IgE-Score

HIES, first described as Job's Syndrome (76), is a rare primary immunodeficiency characterized by a triad of recurrent skin and lung infections, atopic dermatitis and elevated serum levels of IgE (77–80).

The majority of HIES cases are sporadic and result from mutations in the human signal transducer and activator of transcription 3 (STAT3) gene. However, autosomal recessive, autosomal dominant as well as X-linked patterns of inheritance do exist. Autosomal recessive HIES (AR-HIES) is most commonly caused by dedicator of cytogenesis 8 protein (DOCK8) mutations, while the autosomal dominant variant (AD-HIES) predominantly results from underlying mutations in the STAT3 gene. Recently discovered monogenic disorders caused by mutations in e.g. Phosphoglucomutase 3 (PGM3), Caspase recruitment domain family member 11 (CARD11) or zinc finger protein 341 (ZNF431) (78,81–86) displaying an HIES phenotype are leading to an expanded genetic heterogeneity of this syndrome. AD-HIES patients typically present with the above-mentioned characteristic triad, but furthermore display nonimmunological features such as skeletal, dental and connective tissue abnormalities, that are not found in AR-HIES patients. The autosomal recessive variant

of HIES on the other hand is characterized by severe, recurrent viral infections, susceptibility to allergies and autoimmune manifestations and neurologic manifestations, making it easy to distinguish from the autosomal dominant variant (78,87,88). Patients with HIES furthermore show a predisposition to developing malignancies, especially lymphomas. Leukemia as well as malignancies of the vulva, liver and lung can, amongst others, additionally be associated with STAT3 deficiency. Patients with DOCK8 deficiency are at risk to develop malignancies that are typically virally-driven, including human papillomavirus (HPV)-induced squamous cell carcinoma, Epstein-Barr virus (EBV)-driven smooth muscle tumors and lymphomas (80,89–95). The fact that the HIES triad is frequently present in other distinct immunodeficiency disorders and primary skin disorders, that often present in a similar way clinically, but require different treatment, adds to the diagnostic challenge of this rare disease (78).

In 1999, a now widely used and well-established diagnostic tool for HIES, using both clinical criteria as well as laboratory measures, called the National Institutes of Health (NIH) clinical HIES scoring system, was developed by Grimbacher et al. (77). The quantitative-phenotype score contains 20 disease-specific clinical and laboratory test criteria with a point value for each finding, based on its incidence in HIES and specificity for HIES. The point values for each finding were assigned using the literature and an analysis of 30 patients with HIES and 70 of their relatives. Highly specific findings to HIES, such as failure of dental exfoliation, serum IgE levels >10.000 IU/ml or pneumatocele formation, were higher weighted than those that are typical for HIES, but also commonly found in the general population. Additionally, the scoring system contains an age-correction as additional feature to reflect diagnostic uncertainty and to avoid false-negative scores in children. Inversely age-dependent points are given to individuals below the age of five years as some of the clinical findings, such as scoliosis, the characteristic facies and retained primary teeth may first be noticed during adolescence. Furthermore, the number of infections, the fracture risk and the chance of developing pneumatoceles increase with age. A total-point score of 15 and above in this study implied that an individual is likely to carry an HIES genotype, between ten and 14 points the presence of an HIES genotype was indeterminate and a score below ten points made it unlikely for a subject to carry a HIES genotype. The scoring system was applied on all enrolled

patients in this genetic linkage study, which also included two validation cohorts (77). Over the years, the HIE Score was applied and validated in various other studies (78,87,93,95–99). Included features and the weighting of the point values in this scoring system were initially tailor-made for AD-HIES with underlying STAT3 gene mutations, which make it particularly useful for diagnosis of this same condition, but less so for AR-HIES. In 2010 Schimke et al. (96) confirmed that by showing that 96% of 48 AD-HIES patients with STAT3 mutations, that were evaluated using the HIES score, scored >40. Scores >40 thus indicate a high probability for carrying a STAT3 mutation, whereas scores <20 make the diagnosis rather unlikely. However high scores can also be found in patients with AR-HIES, albeit far more seldom and a distinction between different underlying genotypes cannot be made by using the scoring system alone. To address this problem and assist physicians to predict if STAT3 or DOCK8 deficiency is more likely to be present in a patient, modified weighted scores have been developed. Woellner et al. (97) proposed an adjusted scoring system to discern HIES patients with STAT3 mutations from those without by introducing a set of highly specific clinical features to best predict the underlying genotype. In 2015 a “DOCK8” score based on DOCK8 relevant clinical features, was proposed by Engelhardt et al. (95). Most of the cases could be correctly distinguished by a linear classifier using five out of the 20 variables (parenchymal lung abnormalities, eosinophilia, sinusitis/otitis, retained primary teeth, and fracture with minor trauma.) included in the NIH score, which facilitates early diagnosis of AR-HIES patients, who often show severe courses of disease and thus frequently need to be considered for hematopoietic stem cell transplantation (HSCT), preferably as early as possible.

Furthermore, Schimke et al. showed that the identification of 7 key findings out of the complex NIH score, allowed to distinguish HIES patients from patients suffering from conditions with similar symptoms such as severe forms of atopic dermatitis, confirming the specificity of the NIH score for HIES (96). A lot of studies over the years have thus validated, that the HIES score, including modified versions and weighted scores based on key findings, is a diagnostic tool, that can be used to sensitively identify patients with HIES (95–97).

Clinical Features	POINTS A									
	0	1	2	3	4	5	6	7	8	10
Highest IgE (IU/ml) b	<200	200-500			501-1,000				1,001-2,000	>2,000
Skin abscesses	None		1-2		3-4				>4	
Pneumonia (episodes over lifetime)	None		1		2		3		>3	
Parenchymal lung anomalies	Absent						Bronchiectasis		Pneumatocele	
Retained primary teeth	None	1	2		3				>3	
Scoliosis, maximum curvature	<10˚		10°-14°		15°-20°				>20°	
Fractures with minor trauma	None				1-2				>2	
Highest eosinophil count (cells/µl) c	<700			700-800			>800			
Characteristic face	Absent		Mildly present			Present				
Midline anomaly d	Absent					Present				
Newborn rash	Absent				Present					
Eczema (worst stage)	Absent	Mild	Moderate		Severe					
Upper respiratory infections per year	1-2	3	4-6		>6					
Candidiasis	None	Oral	Fingernails		Systemic					
Other serious infections	None				Severe					
Fatal infection	Absent				Present					
Hyperextensibility	Absent				Present					
Lymphoma	Absent				Present					
Increased nasal width	<1 SD	1-2 SD		>2 SD						
High palate	Absent		Present							
Young-age correction	>5 years			2-5 years		1-2 years		<1 year		

a The entry in the furthest-right column is assigned the maximum points allowed for each finding.
b Normal <130 IU/ml.
c 700/µl = 1SD, 800/µl = 2 SD above the mean value for normal individuals.
d For example cleft palate, cleft tongue, hemivertebrae, other vertebral anomaly, etc. (see Grimbacher et al. 1999a).
e Compared with age- and sex-matched controls (see Farkas et al. 1994)

˚SD standard deviation

Table 5: HIES score – clinical features and laboratory tests for individuals in kindreds with HIES, taken from Grimbacher, Schäffer, Holland et al. 1999 (77)

4.1.1.2 H Score

The H Score is an easy-to-use diagnostic tool designed for the diagnosis of Reactive Hemophagocytic Syndrome, representing the acquired form of Hemophagocytic lymphohistiocytosis (HLH) (100).

HLH, a clinical syndrome of immune dysregulation, is characterized by hyperinflammation and thus typically by prolonged fever, hepatosplenomegaly, and cytopenias. It comprises a hereditary form with genetic causes and an acquired, the so-called Reactive Hemophagocytic Syndrome, which are difficult to distinguish from each other (13,101,102). The underlying causes of acquired HLH usually are infections, malignant diseases, autoinflammatory and autoimmune diseases, and acquired immune suppression (103–107).

The extreme variety of potential signs of symptoms represents major diagnostic and therapeutic difficulties for Reactive Hemophagocytic Syndrome. As a result, the H Score was constructed and combines nine clinical, biologic, and cytologic criteria associated with the diagnosis of haemophagocytic syndrome (see Table 6). These variables are taken from the results of a Delphi consensus study involving experts on the reactive form of hemophagocytic syndrome combined with logistic regression analysis to calculate the weight of each criterion included in the score (108). The maximum possible score for each variable is different and ranges from 18 points for underlying immunosuppression to 64 points for the triglyceride level. The best cut-off value of the H score, and thus the value starting to indicate a probable presence of the syndrome, was defined at 169, with a sensitivity of 93%, a specificity of 86% and a precise classification of 90% of the patients. Nevertheless, both, clinical features (e.g. fever, hepatosplenomegaly) and biologic features (e.g. cytopenia, hyperferritinemia) observed in patients with hemophagocytic syndrome may also be present in other disorders, making it difficult to distinguish the syndrome from other diseases such as severe sepsis or hematologic malignancies. Thus, the availability of a simple score is a major advance, making it possible to predict the likelihood of an individual patient suffering from the syndrome and allowing clinicians to make appropriate treatment decisions. Prospective validation of the diagnostic score in other patient samples is required before the H Score can be recommended for broad application, as only a few patients were used for cross-validation of the instrument

in combination with the retrospective study design. Further investigations may therefore also be able to assess the performance of the H Score in diagnosing the primary form of haemophagocytic syndrome (100).

Clinical/laboratory parameters	**No. of points (criteria for scoring)**
Known underlying immunosuppression [1]	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4-39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
Number of cytopenias [2]	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (ng/ml)	0 (<2,000), 35 (2,000-6,000), or 50 (>6,000)
Triglyceride (mmoles/liter)	0 (<1.5), 44 (1.5-4), or 64 (>4)
Fibrinogen (gm/liter)	0 (>2.5) or 30 (≤2.5)
Serum glutamic oxaloacetic transaminase (IU/liter)	0 (<30) or 19 (≥30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)
[1] HIV positive or receiving long-term immunosuppressive therapy (glucocorticoids, cyclosporine, azathioprine etc.) **[2] Defined as either haemoglobin concentration of 9.2 g/dL or less, a white blood cell (WBC) count of 5000/mm³ or less, or platelet count of 110.000/mm³ or less**	

Table 6: Clinical and laboratory parameters of the HScore – a scoring system to diagnose hemophagocytic syndrome, taken from Fardet et al. 2014 (100)

4.1.1.3 Wiskott-Aldrich-Syndrome (WAS) Score

The WAS disease severity scoring system was introduced to define clinical phenotypes associated with WAS gene mutations. This scoring method facilitates the clinical categorization of patients, paving the way to individualized treatment strategies. Additionally, it may predict disease severity, risk of morbidity and mortality as well as outcome after HSCT (109,110).

The Wiskott-Aldrich syndrome (WAS) is a complex and potentially life-threatening, X-linked disease. It is based on WAS gene mutations, encoding for Wiskott-Aldrich syndrome protein (WASp) and manifests with microthrombocytopenia and variable degrees of eczema, combined immunodeficiency and an increased risk for autoimmunity and lymphoid malignancies in affected young males. Although many patients with WAS present with all of the described clinical features, some may only show a

partial or variant phenotypic expression (111–114). This implies that patients with mutated WAS genes may present with a broad spectrum of disease severity. Three major clinical phenotypes can be differentiated: classic WAS, X-linked thrombocytopenia (XLT) and X-linked neutropenia (XLN) (113). While 'loss of function' mutations in the WAS gene either cause XLT or WAS, a unique 'gain of function' mutation in the GTPase-binding domain of WASp leads to XLN, a disease with profound neutropenia, sometimes associated with lymphopenia and increased risk for myelodysplastic changes in the bone marrow. The severity score consists of 8 characteristic clinical features associated with WAS mutations and ranges from 0 to 5, depending on how many of the features are present in a patient. The WAS score only indicates the severity of the clinical phenotype, without considering the type of mutation or whether WASp is expressed. A severity score of 1 or 2 identifies patients with XLT, which represents a milder form of the disease, whereas a score of 3 and 4 defines patients with classic WAS. A score of 5 classifies patients with WAS gene mutations that develop autoimmunity and/or malignancies. Patients with classic WAS are very likely to develop autoimmune disorders and malignancies, especially lymphoma. Thus, hematologic and immune reconstitution by HCST is required to prevent early death. Patients with XLT who generally have excellent overall survival, also are at risk for severe disease-related events such as life-threatening infection (especially post splenectomy), severe bleeding or autoimmunity and malignancy, which leads to an increase in the score from the original 1-2 to 5. This existing risk for patients with XLT should always be taken into consideration in therapeutic decision making, since this disease is frequently misdiagnosed as idiopathic thrombocytopenic purpura, which does not increase the risk of malignancy. Therefore, a WASp expression and WAS gene mutation should be assessed in any male patient presenting with small platelets and thrombocytopenia. The clinical phenotype and the development of autoimmunity or cancer of the multifaceted disease evolves over time and is often not fully developed in patients younger than two years of age. For this reason, disease prediction and assessing its severity using the WAS score for infantile patients should be omitted (109). In general this score, that has been used in several clinical cohort studies, can be applied to classify patients with WAS from mild to severe forms. However, when it comes to development of malignancy or autoimmunity, predictive relevance of the WAS score has shown to be rather limited (1,115).

Disease	*XLN*	*iXLT*	*XLT*		*Classic WAS*		
Score	**0**	**<1**	**1**	**2**	**3**	**4**	**5**
Thrombocytopenia	-	-/+	+	+	+	+	+
Small platelets	-	+	+	+	+	+	+
Eczema	-	-	-	(+)	+	++	-/(+)/+/++
Immunodeficiency	-/(+)	-	-/(+)	(+)	+	+	-/(+)/+/++
Infections	-/(+)	-	-	(+)	+	+/++	-/(+)/+/++
Autoimmunity and/or malignancy	-	-	-	-	-	-	+
Congenital neutropenia	+	-	-	-	-	-	-
Myelodysplasia	-/+	-	-	-	-	-	-

Scoring system:

- *Absent*
-/+ *Intermittent (thrombocytopenia) or may/may not be present (myelodysplasia)*
(+) *Mild (eczema, immunodeficiency, infections)*
\+ *Moderate (eczema, immunodeficiency, infections) or finding present (thrombocytopenia, small platelets, autoimmunity, malignancy, congenital neutropenia)*
++ *Severe*

XLN X-linked neutropenia

iXLT intermittent X-linked thrombocytopenia

XLT X-linked thrombocytopenia

Table 7: Disease severity scoring system for disorders associated with WAS mutations, modified from Albert et al. 2011 (109)

4.1.1.4 Severity scoring in Familial Mediterranean fever

There are several scores for severity classification of the most common periodic fever syndrome - Familial Mediterranean fever (FMF), an autosomal recessive inherited disorder with recurrent inflammation causing episodes of fever and serositis (13,116).

In 1998, Pras et al. (117) published a disease severity score for FMF that includes disease-specific parameters: age of disease onset, frequency of febrile attacks per month, joint involvement, erysipelas-like erythema, amyloidosis, and dose of colchicine treatment,. Each parameter is graded differently and more severe symptoms are represented by a higher score (see Table 8) (117).

Degrees of severity	Age of onset (yr)	Number of attacks per month	Presence of arthrtis	Presence of erysipelas-like erythema	Presence of amyloidosis	Colchicine dose (mg/day)
0	>31					
1	21-31	<1				1
2	11-20	1-2	Acute	+		1.5
3	6-10	>2	Protracted		+	2
4	<6					>2*

*Not responsive to 2 mg/day

Table 8: Disease Severity Score for FMF by Pras et al. 1998 (117)

Mor et al. (34) assumed that the scoring method proposed by Pras et al. (117) had several disadvantages, such as the absence of a cause and effect correlation between severity markers and disease severity and the use of arbitrary differential values for each parameter, using a statistical approach rather than expert opinion to develop the required measures. Hence, they created the new FMF severity score (F-SS), which includes more objective parameters using a questionnaire. The six most distinctive features for the new established F-SS were collected and contain age of onset, dose of colchicine, number of involved sites in a single attack and during the disease, the presence of pleuritic and erysipelas-like attacks during the course of the disease. The resulting score can categorize patients into severe disease when ≥3 criteria are met, moderate disease (2 criteria), and mild disease (≤1 criterion)(34). In 2009, Ozen et al. (118) published modified versions of these two common scoring methods for assessing disease severity in pediatric patients by including age-adjusted dose of colchicine, parameters for subclinical inflammation and excluding the age factor (118). According to Kalkan et al. (119) the reliability of severity assessment using these two modified methods is uncertain due to a lack of statistical consistency and correlation between the scoring systems (119). However, the work of Kalkan et al. (119) also shows some limitations and as a consequence, the International group of FMF experts wanted to reach a consensus on international and easily applicable severity criteria, both for adults and children with FMF (120,121). The international severity scoring system for familial Mediterranean fever (ISSF) was developed in three steps using a Delphi technique to gather information from pediatric and adult rheumatologists, a consensus conference using nominal group technique (NGT) and, as a third phase, the validation of the selected criteria.

The score's final set of variables contains nine items (chronic sequela, organ dysfunction, organ failure, frequency of attacks, increased acute-phase reactants, involvement of more than two sites during an attack, involvement of more than two different types of attack during the course of the disease, duration of attacks, leg pain), which are then scored.

Table 9 shows the included criteria used for scoring and ultimately classifiying patients from mild to severe disease. In comparison with the scoring systems developed by Pras et al. (117) and Mor et al. (34), both established for adults only, this method is the only one validated and developed for both adults and children (121).

	Criteria	Points
1	Chronic sequela (including amyloidosis, growth retardation, anaemia, splenomegaly)	1
2	Organ dysfunction (nephrotic range proteinuria, FMF related)	1
3	Organ failure (heart, renal, etc, FMF related)	1
4a*	Frequency of attacks (average number of attacks between 1 and 2 per month)	1
4b*	Frequency of attacks (average number of attacks >2 per month)	2
5	Increased acute-phase reactants (any of C-reactive protein, serum amyloid A, erythrocyte sedimentation rate, fibrinogen) during the attack-free period, ≥2 weeks after the last attack (at least two times 1 months apart)	1
6	Involvement of more than two sites during an individual acute attack (pericarditis, pleuritis, peritonitis, synovitis, ELE, testis involvement, myalgia, and so on)	1
7	More than two different types of attack during the course of the disease (isolated fever, pericarditis, pleuritis, peritonitis, synovitis, ELE, testis involvement, myalgia, and so on)	1
8	Duration of attacks (more than 72 h in at least three attacks in a year)	1
9	Exertional leg pain (pain following prolonged standings and/or exercising, excluding other causes)	1
Total score		10

Severe disease ≥6, intermediate disease 3-5, mild disease ≤2.

*Criterion 4a/4b can give 0 or 1 or 2 points altogether according to the definition.

ELE, erysipelas-like erythema; FMF, familial Mediterranean fever.

Table 9: The international severity scoring system for familial Mediterranean fever (ISSF), taken from Demirkaya et al. 2016 (121)

4.1.1.5 Severity Scoring in Ataxia Telangiectasia

Ataxia Telangiectasia (AT) is a neurodegenerative disorder with cerebellar and extrapyramidal features caused by the ataxia-telangiectasia mutated gene that comes with additional morbidity caused by combined immune deficiency, malignancies, pulmonary impairment, failure to thrive and dysphagia (122–125). A recently published review identified a total of nine rating scales and five functional tests available for patients with ataxia in general (126). In 1997 the Committee of the World Federation of Neurology developed the most frequently used clinician-rated measure to quantify the level of impairment in patients with Ataxia Telangiectasia, the so called International Cooperative Ataxia Rating Scale (ICARS) (127). It is a 100-point semi-quantitative scale including 19 items, divided into four subscales of postural and stance disturbances (maximum score = 34), limb movements disturbances (maximum score = 52), speech disorders (maximum score = 8) and oculomotor disorders (maximum score = 6) (127,128). This scale has been validated for focal cerebellar lesions and spinocerebellar ataxia and despite robust evidence supporting its use in various cerebellar disorders, it has some limitations including insufficient sensitivity to noncerebellar aspects, some redundancy in items, a plateau in patients with a long duration of disease as well as length limits in clinical setting (128–132). Another frequently applied scoring system to measure severity of ataxia in patients with AT and other cerebellar disorders is the Scale for the Assessment and Rating of Ataxia (SARA), including 8-items that yield a total score of 0-40. It is, in comparison to ICARS, easier to apply for clinicians, less time-consuming and includes less repetitive items. However, the lack of functional tests and assessment of non- ataxia symptoms represent limitations of this scoring system, that is not recommended to use in pediatric patients under the age of 12 (126,127,129,132,133). The Brief Ataxia Rating Scale (BARS), a sufficiently fast, valid and reliable score designed for clinical purposes including 5 subsets and a maximum of 30 points, that strived to overcome limitations of the scoring systems mentioned beforehand, was developed by Schmahmann et al. (129) in 2009 (126,129,134). As these three scores have neither been developed for nor validated in patients with AT, Nissenkorn et al. (123) developed a scale of Clinical Global Impression (CGI) type specific for AT in two versions, structured and unstructured, containing five domains: ataxia, dysmetria, dysarthria, oculomotor apraxia, and extrapyramidal involvement. Both versions of

the CGI scale classify the severity of AT in asymptomatic, mild, moderate, severe and very severe according to the clinician's view (123,135,136). The Ataxia Telangiectasia Functional Scale (ATFS), considering and emphasizing the effect of decreased abilities due to multisystem involvement, is another disease specific scale developed for patients with AT. It was created by using retrospectively collected longitudinal data regarding functional mobility of children and young adults with ataxia telangiectasia and total point scores range from 0 to 51. Nine items, combining mobility and activities of daily living, were selected for this functional scale: three mobility (mobility-home, mobility-school, mobility-outdoors), five activities of daily living (ADL) items (drinking, swallowing, dressing, grooming, toilet hygiene), and one schooling. By combining all the mentioned items, the ATFS closely approximates the course of the disease with its three-step progression. However, further validation through larger, prospective studies is needed (124).

4.1.2 Assessment of morbidity, organ impairment and disease activity

Morbidity measures and scoring systems involving organ impairment are used to evaluate and grade disease activity during a patients clinical course. Usually, these scores are reevaluated at defined time points in order to reflect disease burden and severity during distinct phases of the underlying IEI and furthermore provide guidance in therapy decisions by assessing efficacy of different treatment options.

4.1.2.1 Common Variable Immune Deficiency (CVID) Score

Common variable immunodeficiency (CVID) is the most frequent symptomatic IEI with a prevalence of 1:25.000 and is characterized by a distinct reduction of serum Immunoglobulin G (IgG), IgA and/or Immunoglobulin M (IgM) levels (137,138). Individuals suffering from CVID typically present with recurrent and chronic infections, most commonly of the respiratory and gastrointestinal tract. However, they can also display symptoms of immune dysregulation such as autoimmune disorders, enteropathy, lymphoproliferative and granulomatous disease as well as an increased risk of malignancy (137,139). As the underlying basic mechanisms of this heterogenous group of diseases, especially the non-infectious aspects, are not yet fully understood, many attempts to categorize patients with CVID, based on both clinical and

immunological features, have been made (137,140,141). Studies have shown that patients with signs of immune dysregulation generally show a more severe phenotype and thus higher mortality. Furthermore, amongst others, diagnostic delay, early onset of the disease and inadequate treatment (142,143) are associated with worse survival. Grimbacher et al. (144) hence proposed a severity scoring system for CVID patients, that could be helpful to improve management and follow-up of high risk patients and ultimately help to predict the severe conditions and prognosis as early as possible (137). The CVID severity score includes 15 features, referred to as the "15 unlucky complications of CVID", such as chronic sinusitis, the bouts of past pneumonia, meningitis or encephalitis, the presence of bronchiectasis or other parenchymatous lung pathologies, granulomas, splenomegaly or lymphoproliferation, coexistence of autoimmune diseases or malignancies, as depicted in Table 10 (144). Most of the features included in the point score are rated from 0 (absent) to 3 points and a higher numerical value is associated with a more severe disease condition. However, the original literature gives no information about recommended cut off values to define disease severity or categorization of patients. Mokhtari et al. (137) have assessed this scoring system in 2016 on a cohort of 113 CVID patients by dividing them into groups based on their total point score. Patients with a CVID severity score lower than mean ± standard deviation (SD) were defined as group A and demonstrate a mild/infections only phenotype, whereas patients with a score higher than mean ± SD were categorized as group B, meaning they manifest severe clinical complications. The two groups were then thoroughly compared in order to identify factors significantly influencing disease severity, which included laboratory factors such as higher levels of IgG, higher percentage of cluster of differentiation (CD) 8 lymphocytes, diminished percentage of switched memory B cells and low frequency of regulatory T cells (137). In 2018 Ameratunga R. (145) proposed a modified severity score for CVID and CVID-like patients with a focus on target organ damage, which has been proven to determine outcome and prognosis. The 20 included parameters, reflecting cumulative organ damage resulting from immunodeficiency and immune dysregulation, have mainly been taken from descriptions of large cohorts of CVID and CVID-like patients and divided into three categories according to severity (66,67,140,145–148). Mild, easily treatable, conditions, that do not account for long term-morbidity are assigned one-point, moderate manifestations, that might not be reversible and can cause short as well as long-term morbidity

are rated with 5 points and 10 points are assigned for severe, potentially life threatening, conditions. The CVID disease severity score (CDSS) has been assessed in two kindreds in this study and compared with the CVID severity score. The two scores correlated closely in both families and also both reflected the clinical phenotype. However, the CDSS covers more of the affected organ systems, which could make it more sensitive. Ameratunga R. (145) lists many advantages, such as the possibility to compare CVID cohorts, assistance with treatment decisions as well as to predict prognosis and mortality risk, but also disadvantages, including the fact that the absolute score might not reflect disease severity, intra/interobserver variability and the missing reflection of treatment response, of this scoring system. However, further studies to prospectively validate and assess reliability of severity scoring systems for CVID are needed (137,145).

Points	*0*	*1*	*2*	*3*
1. Chronic sinusitis	Absent	Present		
2. Past meningitis or encephalitis	Absent	One bout	Two bouts	>Two bouts
3. Past pneumonia	Absent	One bout	Two bouts	>Two bouts
4. Bronchiectasis	Absent	One lobe	Two lobes	>Two lobes
5. Other parenchymal lung pathology such as fibrosis, LIP, BOOP, etc.	Absent	Suspected		Confirmed
6. Lung surgery (lobectomy or pneumonectomy)	Absent			Performed
7. Splenomegaly	Absent	11-14.9 cm	15-20 cm	>20 cm
8. Splenectomy	Absent			Performed
9. Lymphadenopathy (largest node)	Absent	<2 cm	2-3 cm	>3 cm
10. CVID enteropathy	Absent	Intermittent	Chronic but mild	Severe
11. Autoimmune condition	Absent	Suspected		Confirmed
12. Other rheumatological complaints such as arthralgia	Absent	Suspected	Confirmed	
13. Granulomata	Absent	Skin only	Lung, liver or spleen	CNS (incl. eye)
14. Lymphoma	Absent			Present
15. Cancer (solid tumors) such as bowel, skin or stomach	Absent			Present

Table 10: Suggested "Grimbacher CVID – disease severity score", taken from Yong, Thaventhiran and Grimbacher, 2011 (144)

4.1.2.2 Profound combined immunodeficiency (P-CID) morbidity measure

Combined immunodeficiencies (CID) are a very heterogenous group of IEI, characterized by impaired T-cell development or function, that clinically present with an increased susceptibility to infections and/or dysregulation of the immune system (149).

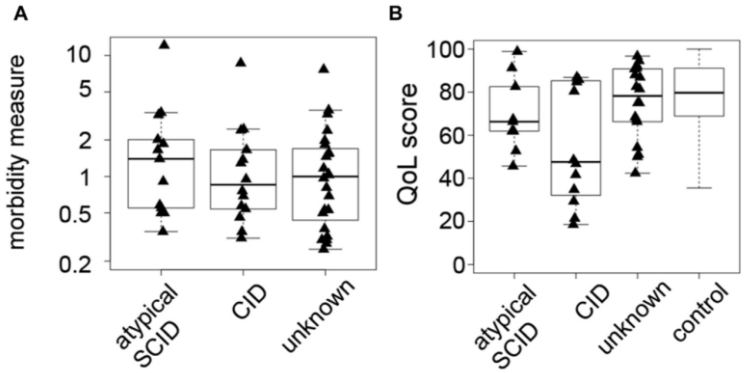
The P-CID study is an ongoing prospective international multicenter observational cohort study on the natural history of patients with profound combined immunodeficiency, a severe and potentially life-threatening form of CID that can neither be classified as SCID nor as CVID (149).

Both, CID and "atypical" SCID present with a reduction but not complete lack of T-cell immunity, and thus several degrees of residual function (150). If associated with either infections or autoimmunity the condition is referred to as P-CID. Outcome data for this group of patients, in which impaired T-cell immunity leads to significant, but not severe enough complications to justify an unambiguous early transplant decision, is lacking.

The P-CID study was hence conducted in order to provide an answer to the omnipresent therapeutic dilemma of whether and when to proceed to HSCT in less profound than severe immunodeficiencies. Analyzation of prospectively collected data on morbidity, mortality, QOL, treatment decisions, T-cell immunity as well as genetic results in initially nontransplanted pediatric patients should help to define clinical events and immunological parameters predictive for outcome (149,151). To quantify clinical problems due to immunodeficiency a morbidity measure was established on the basis of 5 items: invasive bacterial infection (including pneumonia), viral or opportunistic infection, autoimmune cytopenia, other immune dysregulation, and chronic lung disease. The number of clinical events per morbidity item counted from birth to study inclusion divided by the age of the patient to obtain a correction for exposure time results in a measure of morbidity. Additionally, a patient and parent-reported quality of life assessment, using the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales, was obtained and compared to a reference population of healthy children (149,152). Morbidity measure showed no relevant differences between patient groups (see Figure 3). The fact that acute versus chronic symptoms and their severity are not distinguished and weighted represents a major

limitation of the measure. Thus, all persistent immune dysregulations (e.g., thyroiditis, chronic inflammatory bowel disease or splenomegaly) and infections (e.g., EBV, HPV or molluscum) are classified as single events. Furthermore, the time correction might undervalue recurring, severe symptoms. To counteract these limitations, patients were classified as either "severe" or "mild" at the beginning of the study according to the treating physician's assessment in order to evaluate their clinical status at the beginning of the study (82).

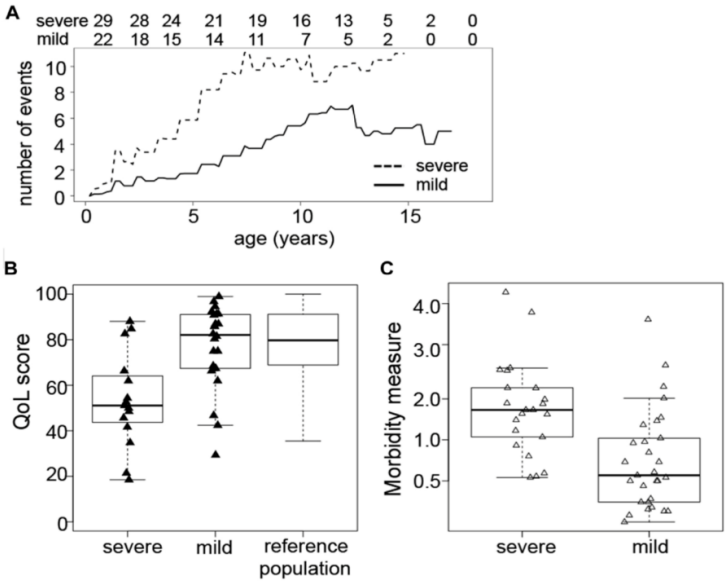
The term "morbidity measure" instead of "score" was purposefully used to reflect the fact of it being a preliminary tool in need of further adaption and validation (149).



A. Morbidity measure in patients with atypical SCID, CID, and patients with unknown molecular diagnosis.

B. **B.** QOL at study entry as assessed by PedsQL Generic Core Scales of patients with atypical SCID, CID, and unknown molecular diagnosis vs a reference population of healthy children

Figure 3: Morbidity assessment and baseline QOL of the P-CID study cohort, taken from Speckmann et al. 2017 (149)



A. Mean cumulative number of events at a given age for patients judged to have a severe (dashed line) or a mild disease course (solid line) at study entry. The absolute number of patients at risk at a given time is indicated in the line above the figure.

B. QOL scores at study entry for patients with a severe or a mild disease score.

C. Morbidity measure in patients with severe and mild disease course as judged by the treating physician.

Figure 4: Correlation of different parameters assessing disease severity of profound combined immunodeficiency (P-CID), taken from Speckmann et al. 2017 (149)

4.1.2.3 Organ involvement scoring system for Immunodysregulation polyendocrinopathy enteropathy x-linked (IPEX) syndrome

A large, international multicenter long-term follow-up of 96 patients with IPEX syndrome was performed and published in 2018 to provide a comprehensive view of this rare monogenic autoimmune disease, caused by Forkhead-Box-Protein P3 (FOXP3) gene mutations, its evolution and outcome under different treatment modalities, including immunosuppression and HSCT (153). An organ involvement (OI) scoring system, based on the number of affected organs or systems by autoimmune damage or by secondary complications before undergoing either HSCT or immunosuppressive treatment, was developed for this study. The total point score ranges from 0-5, with one point being assigned for the presence of each of the five involved organs and symptoms (intractable diarrhea, malnutrition, liver dysfunction, respiratory impairment, and kidney dysfunction) that were included due to their relevance

to IPEX syndrome. The presence of clinical symptoms in the patient's history was assessed by caring physicians at a single, arbitrary time point without grading severity and without considering the quality of life or performance indices. Furthermore, only a small number of variables is included in this score, although patients with IPEX can present with a variety of autoimmune manifestations, especially as disease progresses. As the only potentially curative treatment option for patients with IPEX is HSCT, this study also aimed at analyzing transplantation outcome and influencing factors, since long-term follow up data for this patient population was lacking. Interestingly, the pretreatment OI score was the only factor significantly predicting HSCT outcome, as a low OI score (0-2) before transplantation was associated with a higher chance of survival (153–157).

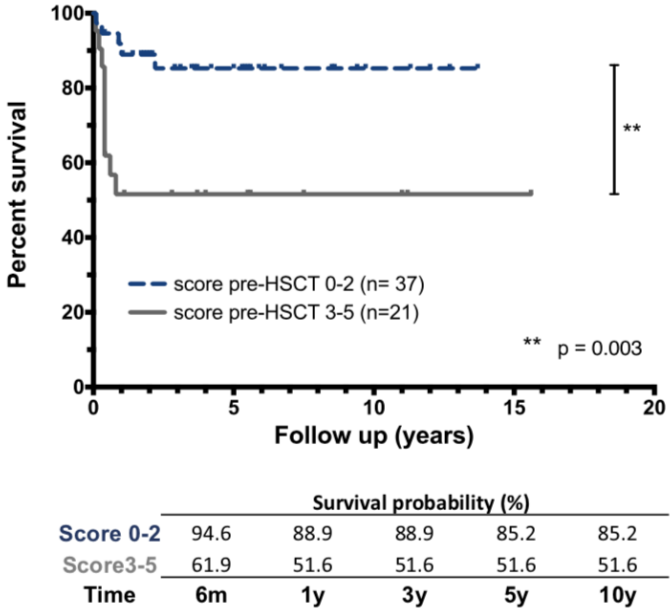


Figure 5: Organ involvement score of patients with IPEX syndrome before HSCT and correlating survival analysis, taken from Barzaghi et al. 2018 (153)

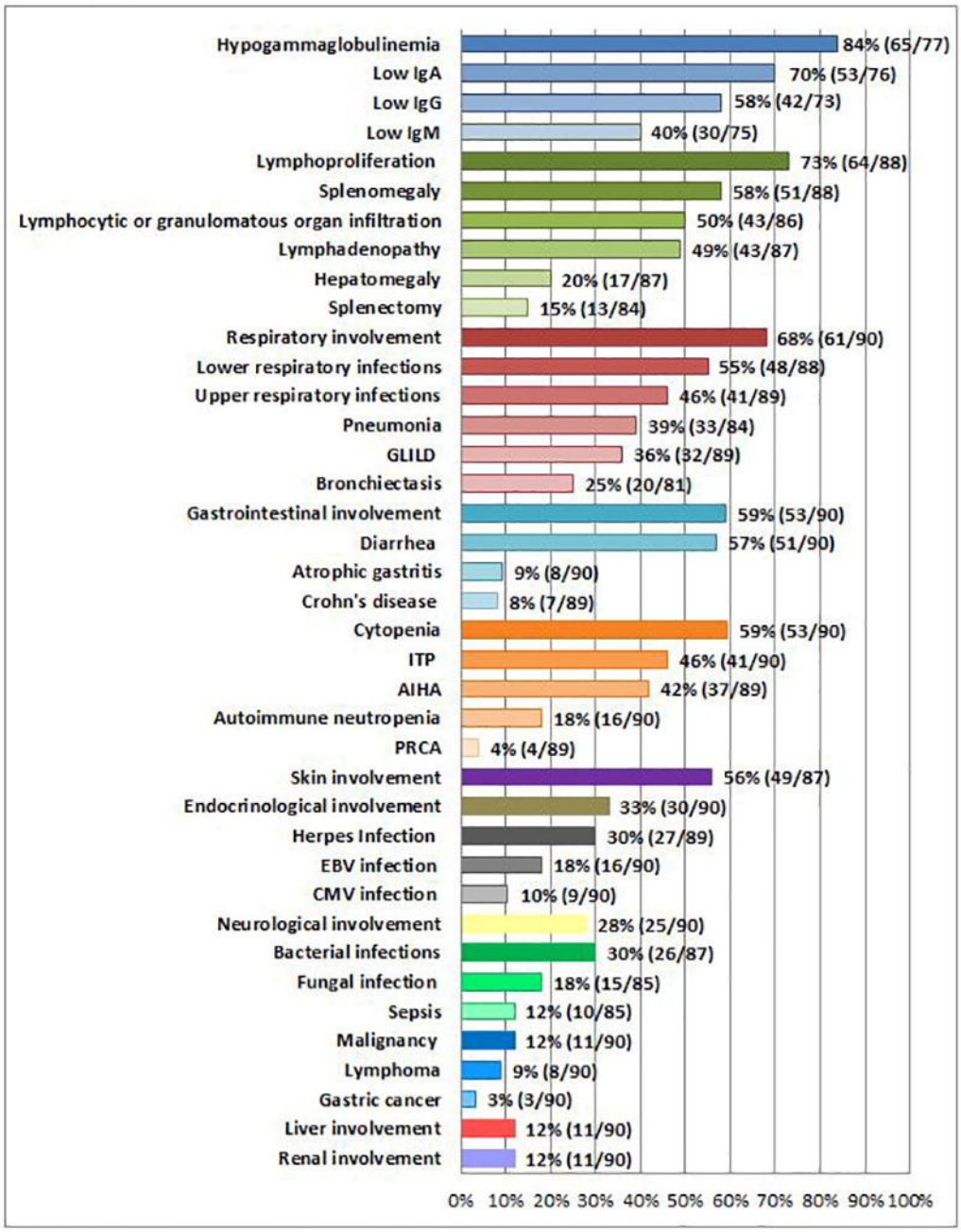
4.1.2.4 Unpublished CTLA-4 haploinsufficiency with autoimmune infiltration (CHAI) Morbidity Measure

The Cytotoxic T lymphocyte antigen (CTLA-4) haploinsufficiency with autoimmune infiltration (CHAI) Morbidity Measure, used in the ongoing abatacept-CHAI study

(Grimbacher and Warnatz, 000972-40 EU Clinical Trial Registry, personal communication), is an item especially developed for the broad clinical spectrum of CHAI disease but not yet published or validated.

CTLA4 is an inhibitory receptor expressed on regulatory T-cells. CTLA4 haploinsufficiency induces dysregulation of FOXP3+ regulatory T-cells and hyperactivation of effector T cells, which results in a severe loss of T lymphocyte self-tolerance and infiltrative autoimmune disease (158). This disease specific scoring system was established based on the description of a cohort of CTLA 4 mutation carriers published by Schwab et al in 2018 (159), and additionally on unpublished data from 72 patients included in the world-wide cohort of CTLA4 insufficiency patients. The CHAI morbidity measure is based on the quantification of organ involvement by scoring specific lab values, imaging studies and clinical examination results according to their severity (1). Lung involvement, more specifically granulomatous-lymphocytic interstitial lung diseases (GLILD), is quantified by using diagnostic criteria of computerized tomography scan and diffusion capacity. Enteropathy is assessed by evaluating stool frequency and quality, as well as changes in weight and serum potassium. Central nervous system (CNS) involvement is measured by CNS imaging and clinical assessment based on neurological examination using the Neurologic Assessment in Neuro-Oncology (NANO) Scale (160). Additional components of the score are laboratory parameters including FACS analyses, lymphoproliferation (splenomegaly, lymphadenopathy and lymphoproliferation measured via sIL2-receptor amount) and skin involvement assessed by distribution and severity of skin lesions. A score of 0 to 3 points is assigned to each of these 20 defined items. A separate evaluation of each organ system, including various non-routine investigations, is carried out during each study visit. The items chosen for the scoring method are selected based on their significance in CHAI disease and represent a small selection of possible clinical manifestations, since CTLA-4 insufficiency can present with a great variablitiy of clinical manifestations, depicted in Figure 6 (1,159).

Additional information such as duration of characteristic symptoms, quality of life and performance evaluation are not considered in the CHAI-Morbidity Score *(Grimbacher and Warnatz,* 000972-40 EU Clinical Trial Registry, personal communication).



AIHA: Autoimmune hemolytic anemia
ITP: Idiopathic thrombocytopenic purpura
PRCA: Pure red cell aplasia

Figure 6: Percentage distribution of clinical manifestations in patients with CTLA-4 insufficiency, taken from Schwab et al. 2018 (159)

4.1.2.5 The Autoinflammatory disease activity index (AIDAI)

The AIDAI is a preliminary score for the assessment of disease activity in hereditary recurrent fevers (HRF). Standardized and validated disease activity assessment tools are required to evaluate the level of disease activity and efficacy of the constantly developing new therapies for systemic autoinflammatory diseases (SAID), that consist of a wide, clinically variable spectrum of disorders including HRF (161–167).

This tool, aiming to ultimately improve clinical management by using a rational approach, was specifically designed for the four main HRF: familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), tumour necrosis factor receptor-1-associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndromes (CAPS) (13,161).

The preliminary AIDAI was developed using a two-step Delphi technique, in which expert-suggested potential variables were reduced to a manageable number, followed by patient and parent interviews with regard to the proposed parameters, that were further defined by NGT. As the different SAID have some clinical manifestations in common, the activity scores share the same format, but are adapted to each disease.

The AIDAI is using an easy-to-use single-format disease-adapted patient diary, including different selected variables for each HRF (see Table 11). Disease-specific clinical variables were scored from 0 to 3 points according to their severity, while fever was simply rated as either absent (0) or present (1). The final score was generated by dividing the sum of the scores for all variables by the number of days over the diary was completed and could vary from 0 to 16 points (0-13 for CAPS) for the period of evaluation. Usage of rescue treatment was noted in the prospective diary, but not calculated in the final score. Duration and frequency of attacks are important indicators for disease activity. Even though standardized consensus formation techniques were used selecting the variables and creating the score, there are some limitations to the process, such as response rate and number of included patients. Furthermore, disease activity, that is aimed to be measured by this scoring system, does not reflect the entireness of the overall effect of the disease on a patient. Other important parameters for assessing the impact of the disease and management of SAID, that could be included in a composite score, could include monitoring the

need for rescue treatment (e.g. corticosteroids), the results of biological measurements such as C-reactive protein (CRP) and serum amyloid A protein (SAA), quality of life, organ-specific inflammation and disease-related damage (including joint destruction, growth retardation, hearing and vision loss, AA amyloidosis). However, since the consensus effort emphasized the clinical activity score, the above mentioned additional data were not included (161).

As a second step an international prospective data-collection process followed by a consensus conference and statistical analysis to formally validate the AIDAI was conducted and results were published in 2013 by Piram et al. (162). A simplified version of the AIDAI score including 12 yes (1)/no (0) items as part of the prospective diary was used in this study as statistical performance did not differ from the previously published scoring system with graded values. Furthermore, disease activitiy was assessed by the physician using a questionnaire. Though the small number of included patients (n=106) represents a limitation of the study, the AIDAI proved to be a valid and simple tool to assess disease activity in HRF, discriminating active from inactive disease. It could, however, also be applied to other SAID and future longitudinal studies should

further investigate this disease activity assessment tool, that can facilitate comparison and meta-analysis of clinical trials, assess treatment efficacy and might even predict long-term complications before they develop (162).

Recently the score has been modified to monitor disease activity and treatment response to Tadekinig alfa, a recombinant Interleukin-18 (IL 18) Binding Protein, in patients with monogenic, interleukin-18 (IL 18) driven autoinflammation due to Nucleotide-binding oligomerization domain, leucine-rich repeat and caspase recruiting domain (CARD domain) containing 4 (NLRC4) - Macrophage activation syndrome (MAS) mutation (NLRC4-MAS mutation) or X-linked inhibitor of apoptosis (XIAP) deficiency. A phase 3 study on this matter is currently ongoing (168). Furthermore, a case report published in 2020 by Stephenson et al. (169) describes the first use of AIDAI in a pediatric patient with interleukin-36-receptor antagonist deficiency (DITRA), which represents an emerging group of autoinflammatory diseases with hyperkeratotic skin involvement, referred to as autoinflammatory keratinization diseases (AIKD). Addressing the limitations of existing assessment tools as well as the lack of a disease-specific scoring system, hindering diagnosis and management of this relatively new autoinflammatory disease, a preliminary 15-item modified AIDAI,

the so called DITRA/Autoinflammatory Keratinization Diseases Activity Index (DITRA/AIKD-AI) was introduced. Even if the use of AIDAI proved to be beneficial, application of the diary was adapted, skin manifestations were specified and the presence of a geographic tongue was added. Both the use of AIDAI in this patient population as well as the application of the DITRA/AIKD-AI will, however, need to be further studied and validated (169–173).

FMF	MKD	TRAPS	CAPS
Fever ≥38˚C (100.4˚F)	Fever ≥38˚C (100.4˚F)	Fever ≥38˚C (100.4˚F)	Fever ≥38˚C (100.4˚F)
Abdominal pain	Abdominal pain	Abdominal pain	Limb pain
Arthralgia or myalgia	Nausea/vomiting	Limb pain	Conjunctivitis
Swelling of the joints	Diarrhoea	Eye manifestations	Headaches
Chest pain	Limb pain	Skin rash	Skin rash
Skin rash	Painful lymph nodes	Overall TRAPS symptoms	

CAPS: cryopyrin-associated periodic syndromes
FMF: familial Mediterranean fever
MKD: mevalonate kinase deficiency
TRAPS: TNF receptor-1-associated periodic syndrome

Table 11: Individual variables selected for each HRF for disease activity assessment, adapted from Piram et al. 2011 (161)

4.1.2.6 Immune Deficiency and Dysregulation activity (IDDA 2.1) "kaleidoscope" Score

The IDDA 2.1 score by Seidel et al. (1), represents an assessment tool reflecting the sum and severity of organ involvement and additional clinical information of immune deficiency and dysregulation.

The original version of the score was developed by Tesch et al. (2) and reflects the full potential clinical spectrum of patients with LRBA deficiency. The absence of LRBA protein causes a decreased CTLA4 expression and leads to symptoms that partly resemble those of CTLA4 insufficiency. This regulatory T-cell defect results in immune dysregulation and autoimmunity (2,174). The scoring method consists of an assessment of ten organ systems as well as failure to thrive and severe infections, quantified using a 5-step scale from 0 to 4 depending on the severity of symptoms and treatment requirements. For these 12 features, a score of 1 implies a mild,

transient involvement not requiring any treatment, 2 stands for moderate involvement and intermittent therapy is needed, 3 indicates severe involvement and continuous therapy is required and a scoring of 4 implies life-threatening and irreversible organ involvement or symptoms. The sum of these parameters is weighted by age specific performance indices of Karnofsky (37,175) or Lansky (36). The resulting score is added to the percentage of days of hospitalization and the need for intensive or supportive care (mechanical ventilation or other ICU measures, except elective procedures). Additionally, the need for Immunoglobulin replacement therapy is weighed in detail, scored (0 = absent, 2 = sporadic or 3 = regularly) and added. Likewise any relevant chronic or recurring infestation/infection, any other organ dysfunction or malady (e.g. cardiomyopathy, hepatopathy, kidney failure) and nutritional habits are scored from 0 to 4. Separately, possible malignancy and lymphoma can be noted, but are not scored (2).

In the newly adapted version 2.1. by Seidel et al. (1) the item hemophagocytosis was added to expand the list of included parameters and thus extend the utility to other primary immune regulatory disorders (PIRDs) or IEI with immune dysregulation. Thus, in the IDDA 2.1 score the involvement of 12 organ systems in immune dysregulation, failure to thrive and severe infections are assessed and graded (from 0-4, reflecting the degree of severity and need for treatment), shown in more detail in Table 12. Further, the calculation method depicted in Table 12 shows a modified version in order to correct for very low performance scales. All parameters can be filled and evaluated in a score sheet, which is already available on the ESID registry for caring physicians (176). This sheet, like the original version by Tesch et al. (2), also provides the possibility to monitor medication and eventual malignancy and lymphoma to demonstrate a better description of the clinical situation, as both are not included in the final score. The score may be used for a wide range of applications in clinical documentation. It operates as a possible decision-making tool for therapeutic pathways, for example whether and when to proceed to HSCT. The combination of parameters involved in the original IDDA score by Tesch et al. were developed using a retrospectively collected dataset of patients with LRBA deficiency to assess the clinical course and treatment responses to conventional immunosuppressive therapies or HSCT over time (Figure 7, A, C). For this purpose, the score should be applied at the beginning and at further specific time points during a therapy regimen to objectify the treatment response. Tesch et al. illustrated the severity

of organ involvement in LRBA patients under different immunosuppressive therapy options as well as before and after HSCT (Figure 7, D) with heatmaps. In addition, the clinical course and outcome within a disease group or genetic defect can be compared and monitored. Exemplarily, an objective comparison of the average disease burden of patients with residual protein expression and those with absence of LRBA protein was presented by Tesch et al., shown in Figure 7, B (2).

	Modified IDDA score 2.1 for IEI with immune dysregulation Parameters (for grading 0-4 see below[1]; line titles serve as examples)
1	Autoimmune-cytopenia
2	Hemophagocytosis | Hemophagocytic lymphohistiocytosis (according to clinical AND lab criteria of the HS)
3	Enteropathy | inflammatory bowel disease
4	Lymphoproliferation | splenomegaly | hepatomegaly
5	Parenchymal lung disease | lymphocytic interstitial pneumonia | GLILD
6	Skin or eye manifestations | eczema, uveitis, alopecia, vitiligo, other
7	Granulomatous disease in any organ (except GLILD)
8	Endocrinopathy | insulin dependent diabetes mellitus, thyreoiditis, other
9	Arthritis | other musculoskeletal
10	AI-hepatitis | cholangitis | pancreatitis
11	Glomerulonephritis | nephropathy, tubulopathy
12	Neurologic manifestations
13	Failure to thrive | malresorption, wasting
14	Severe infections | opportunistic (excl. chronic infestation, see below)
	Other factors and symptoms (will multiply or add to the Score)[2]
15	Karnovsky / Lansky Performance Scale (%)
16	Hospitalization (days out of 100 days; including day clinic stays, excl. ICU)
17	Mechanical ventilation or other ICU measures (days out of 100 days; except elective procedures)
18	Immunoglobulin substitution therapy§ | hypogammaglobulinemia
19	Any relevant chronic or recurring infestation/infection (e.g. Norovirus, EBV...)
20	Any other organ dysfunction / malady (e.g. hepatopathy, cardiomyopathy, kidney failure, allergies...)
21	Nutrition / dietary status and habits &
22	Malignancy, lymphoma (separately noted, not added to numeric score)
Formula for IDDA 2.1 score total (Excel® format) =(SUM(line1:line14)+IF(line16<40;line16*0.1;4)+IF(line17<10;line17*0.8;8)+SUM(line18:line21))*IF(line15>29;150/line15;6)	

[1] **Grading for lines 1-14:** 0 = absent, inactive; 1 =mild, transient, not requiring treatment; 2 = moderate, intermittent therapy needed; 3 = severe, continuous therapy needed; 4 = life-threatening, refractory, irreversible.

[2] **Lines 15-17 are percentages, lines 18-21 are scored as follows:**

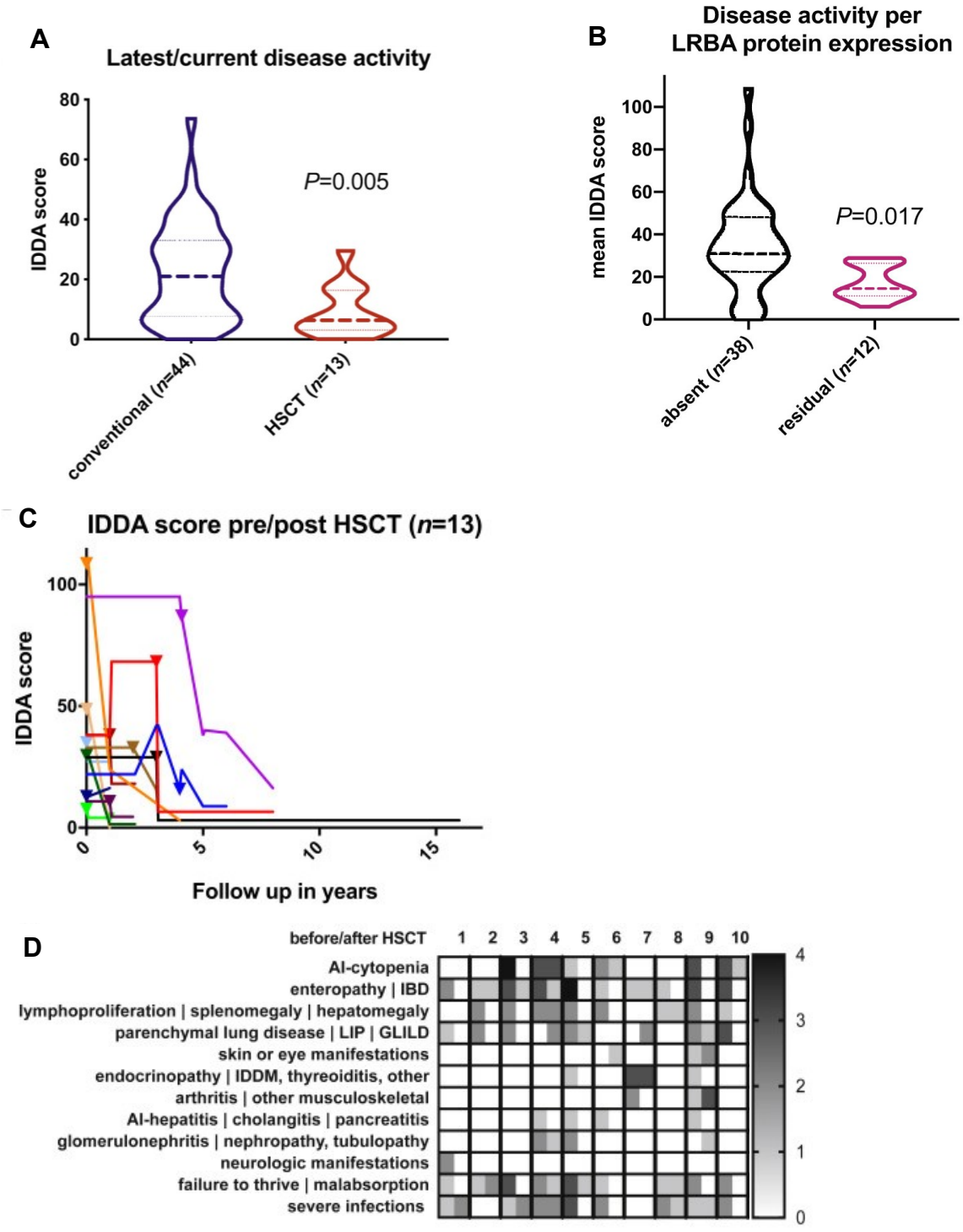
Line 18: 0 = no; 2 = sporadic; 3 (intravenous) = regularly intravenous immunoglobulin; 3 (subcutaneous) = regularly subcutaneous immunoglobulin.

Line 19: 0 = no; 1 = asymptomatic infestation; 2 = oligosymptomatic recurring infection; 3 = recurring symptomatic infection requiring on/off treatment; 4 = chronic infection requiring permanent treatment or refractory infection; only score one (worst) infection if more microbial agents are relevant.

Line 20: 0 = no organopathy; 1 = mild transient dysfunction; 2 = chronic mild dysfunction; 3 = moderate-to-severe dysfunction; 4 = clinically compromising dysfunction requiring treatment or replacement therapy; only score 1 (worst) if more organs are involved.

Line 21: 0 = normal; 1 = modified, disease-adjusted; 2 = part-formula, medically advised; 3 = tube feeding, full-formula, partial parenteral nutrition (irregularly); 4 = total parenteral nutrition

Table 12: The immune deficiency and dysregulation activity (IDDA 2.1) score, originally published by Tesch et al. 2020 (2) and in the modified version 2.1 by Seidel et al. 2021 (1)



A. Patients receiving conventional treatment (blue) versus HSCT (red) are compared by their latest reported disease activity.

B. Patients with residual protein expression (pink) as compared to those with absent LRBA protein (black).

C. The longitudinal changes in disease activity pre and post HSCT is shown as the graphical illustration.

D. Graded organ manifestation in patients with LRBA deficiency before and after HSCT is shown as a heatmap.

Figure 7: Graphical data visualization of possible applications of the original version of the IDDA score, as it was applied in a retrospective study of patients with LRBA deficiency by Tesch et al. 2020 (2)

The simply designed scoring method (0-4) is beneficial in many ways, but holds limitations when it comes to the severity of infections. In this regard, Seidel et al. mention that, e.g., the quantification of molluscum or mucocutaneous HSV infection in a patient with DOCK8 deficiency and a patient with CVID, are to be assessed differently but always receive 3 or 4 points in the scoring based on the grading criteria. Moreover, it can be difficult to distinguish whether organ lesions are caused by infection or triggered immune dysregulation due to infections and should hence be considered as organ involvement. However the general focus of the score and longitudinal assessment are not affected by these judgemental difficulties (1).

Since the score is supposed to be applied to all IEI with immune dysregulation an additional new feature, the so-called "kaleidoscope function", was added and serves as a phenotype visualization and documentation tool. This "kaleidoscope function" relies on the same underlying data as the IDDA 2.1 score and covers 17 of the 22 parameters (represented as rows 1-14, 18, 20 and 22, shown in Table 12) (1).

The information on organ manifestations as well as additional characteristics within a patient cohort are illustrated in a radar chart on 17 circularly arranged y-axes. Thus the “kaleidoscope function” provides the possibility of a visual comparison of different diseases showing the frequency of phenotypic characteristics. Seidel et al. exemplarily applied this feature to 18 different IEIs, categorizing them for educational purposes into primary immune regulatory disorders (Tregopathies), CVID/CVID-like disorders, and PIRDs with EBV susceptibility. Figure 8 depicts the group of primary immunoregulatory disorders as an excerpt of the created kaleidoscope patterns by Seidel et al. The kaleidoscope patterns of checkpoint defects (CTLA-4 insufficiency, LRBA deficiency, and DEF6 deficiency) show a high degree of similarity, and, in contrast, these patterns differ from those of IPEX syndrome or CVID. In combination with the rest of the described observations, it could be demonstrated that no definite conclusion of similarity of kaleidoscope patterns based on the biomechanical basis and no treatment recommendations could be derived just from this first, retrospectively generated plot (1,6).

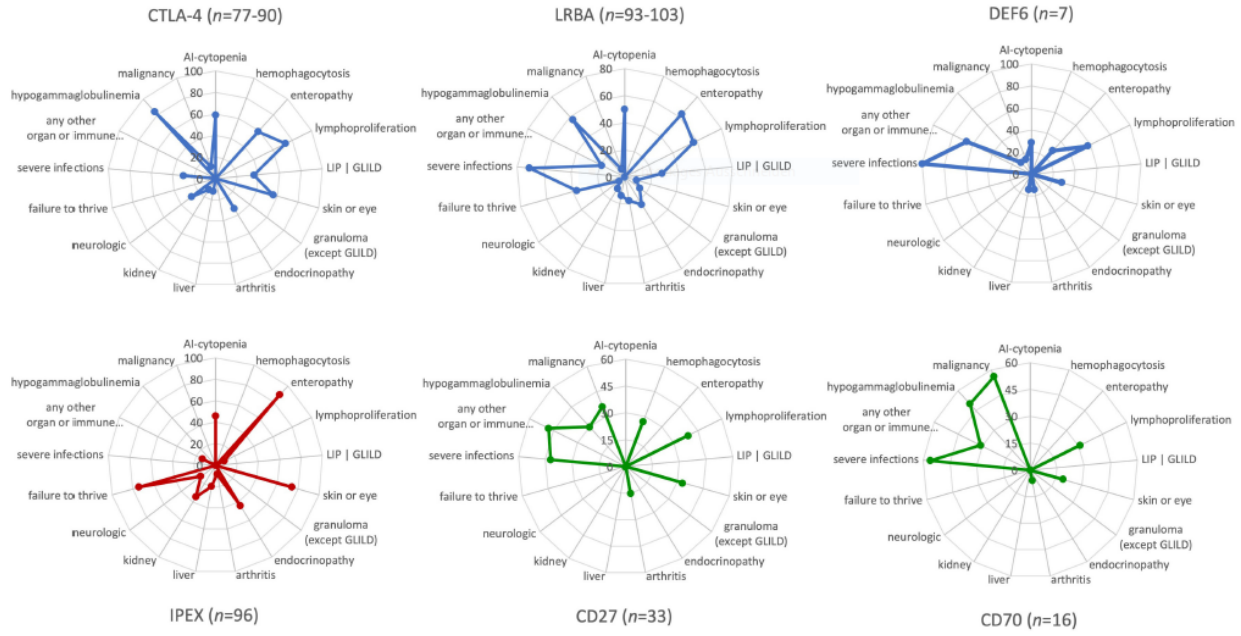


Figure 8: Visualization of Immune deficiency and dysregulation phenotype variance and possible application illustrated by the Clinical Immune Deficiency and Dysregulation Activity (IDDA Version 2.1) "Kaleidoscope" Score, taken from Seidel et al. 2021 (1)

Most of the other established scoring methods for IEI described above tend to be highly specialized, such as disease-specific anatomical (e.g. HIES), infectious (e.g. CVID), or inflammatory (HScore, CVID, AIDAI). Compared with these and especially with the other measures of morbidity and disease activity, the IDDA 2.1 score operates as a semiquantified, organ-specific tool, captures the most important features of immune dysregulation in IEI and information about the actual burden of disease. Due to practical aspects, results of specific functional, laboratory, and imaging analyses (e.g. in CHAI study) or questionnaire-based assessment of patient-reported symptoms and quality of life as used in the AIDAI or P-CID studies were not incorporated. This comprehensive but simple composition of the score allows retrospective chart review after patient visits by a medical professional without additional effort. The IDDA 2.1 score's assessment should take place regularly and in a standardized manner for a detailed representation of the clinical status and course of a patient with PIRD or IEI with immune dysregulation (1).

4.1.3 Treatment stratification scoring systems

Scoring systems can be an assistive tool to specifically guide therapy decisions and procedures based on laboratory parameters and patients' clinical status.

4.1.3.1 Scoring systems to guide the initiation of immunoglobulin therapy in patients with hypogammaglobulinemia

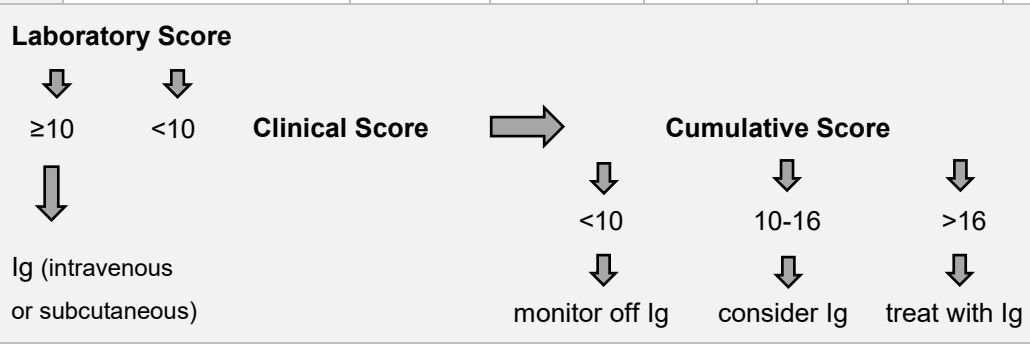
A widely used tool to decide whether to initiate immunoglobulin replacement in adult patients with varying degrees of hypogammaglobulinemia (including CVID) is the scoring system by Agarwal et al., published in 2013 (177).

This scoring method includes clinical and laboratory data combined with a decision tree. Laboratory parameters include immunoglobulin levels (IgG, IgA, and IgM) as well as vaccination titers scored from 0 to 5. The clinical parameters include a wide range of manifestations associated with immune deficiency, more detailed shown in Table 13 and are also assigned with point values from 0 to 5.

Agarwal et al. additionally propose a decision tree, shown in Table 13. For patients with laboratory scores of 10 or more points, immunoglobulin therapy is recommended. For laboratory scores <10, additional clinical parameters should be considered and for cumulative scores >16, immunoglobulin therapy is advised. In patients with cumulative scores of 10 to 16, the treatment decision is based on further critical medical judgement, but immunoglobulin therapy may be considered. In contrast, in patients with cumulative scores of less than 10 points, immunoglobulin substitution is less useful and therefore further monitoring of these patients is required(177).

Another tool with a similar purpose is provided by the AWMF as an interdisciplinary consensus and evidence-based guideline and has recently been updated by Hanitsch et al. (178). This instrument, however, is not designed as a "score" but as an algorithm for patients with primary antibody deficiencies and provides support for indication, application and monitoring of immunoglobulin replacement therapy (178,179).

	POINT VALUE	0	1	2	3	4	5
Laboratory	IgG (mg/dl)	600+	350-599		150-349		0-149
	IgA (mg/dl)	normal			reduced		≤10
	IgM (mg/dl)	normal			reduced		≤15
	Diphteria or tetanus	protective					non protective
	% of pneumococcal serotypes	≥50%			20-49%		0-19%
Clinical History	Pneumonia/lifetime	none	1	2	3	4	five or more
	Upper Respiratory Infection/year	none	1	2	3		>3
	Antibiotic Courses/year	none	1	2	3	4	five or more or prophylactic
	Autoimmune Disease - ITP, AIHA, or other	none			present		
	Sepsis / Meningitis / Osteomyelitis / Empyema / Septic Arthritis	none					present
	Splenomegaly or Splenectomy	none			present		
	Lymphadenopathy	none			present		
	Infectious Diarrhea (excluding Clostridium difficile)	none			present		
	Malabsorption, Chronic Gastroenteritis, Inflammatory Bowel-like Disease	none			present		
	Weight loss/Failure to thrive	none			present		
	Hospitalizations/5 years	none	1	2	3	4	five or more
Other	Pulmonary Function Tests	normal	FEV1/FVC or TLC<80% predicted		FEV1/FVC or TLC<70% predicted		FEV1/FVC or TLC<60% predicted
	Bronchiectasis	none					present



AIHA: Autoimmune hemolytic anemia
FVC: forced vital capacity
ITP: idiopathic thrombocytopenic purpura
TLC: total lung capacity
Ig: Immunoglobulin

Table 13: Scoring system and scoring decision tree for indications for initiation of immunoglobulin therapy in patients with hypogammaglobulinemia, adapted from Agarwal et al. 2013 (177).

4.1.4 Comparison of established scoring methods for IEI by category

	DIAGNOSTIC, SEVERITY AND CLINICAL SUBTYPES			MORBIDITY, ORGAN IMPAIRMENT AND DISEASE ACTIVITY						TREATMENT STRATIFICATION
Parameters	**HIES[1]**	**HLH[2]**	**WAS[3]**	**CVID[4]**	**P-CID[5]**	**CTLA-4[6]**	**IPEX-OI[8]**	**LRBA-IDDA[7]**	**AIDAI[9]**	**Hypo-gam[10]**
Anatomical[11]										
Skoliosis	✓									
Facial dysmorphia	✓									
Inadequate fractures	✓									
Mid line defect, high palate	✓									
Nose width	✓									
Hyperextensible joints	✓									
Retained primary teeth	✓									
Autoimmunity										
Not further specified (n.f.s.)[12]			✓	✓	✓					✓
Endocrinopathies				✓				✓		
CNS incl. Neurological n.f.s.[13]				✓		✓		✓		
Eye[13]				✓				✓	✓	
Skin[13]				✓		✓		✓	✓	
Lung (see below)	-	-	-	-	-	-	-	-	-	-
Gut (see below)	-	-	-	-	-	-	-	-	-	-
Liver				✓			✓	✓		
Kidney				✓			✓	✓		
Immune cytopenias				✓	✓	✓		✓		✓
Musculoskeletal[13]				✓				✓	✓	
Inflammatory[1]										
Fever		✓							✓	
Splenomegaly[13]		✓		✓		✓		✓		✓
Lymphadenopathy, non-malignant lymphoproliferative disease				✓		✓		✓		✓

Parameters	HIES[1]	HLH[2]	WAS[3]	CVID[4]	P-CID[5]	CTLA-4[6]	IPEX-OI[8]	LRBA-IDDA[7]	AIDAI[9]	Hypo-gam[10]
Parenchymal lung disease, GLILD, LIP	✓			✓	✓	✓		✓		
Granuloma (except GLILD)				✓				✓		
Carditis				✓						
Vasculitis				✓						
Enteropathy, celiac disease, gastritis, inflammatory bowel disease, protein-losing enteropathy				✓		✓	✓	✓		✓
Neonatal exanthema	✓									
Eczema n.f.s.	✓		✓							
Respiratory impairment n.f.s.							✓			
Abdominal pain									✓	
Nausea, Vomiting									✓	
Diarrhoea									✓	✓
Headaches									✓	
Chest pain									✓	
Painful nodes									✓	
Infection-related										
Abscesses	✓ (skin, organ)									
Pneumonia	✓									✓
Bronchiectasis				✓						✓
ENT and respiratory infections	✓			✓						✓
Candidiasis	✓									
Other invasive infections	✓			✓						✓
Infections n.f.s.			✓		✓			✓		
Infections viral or opportunistic n.f.s.					✓					
Gut incl. Helicobacter pylori				✓						✓
CNS				✓						
Fatal infection	✓									
Asymptomatic / chronic infestation								✓		

Parameters	HIES[1]	HLH[2]	WAS[3]	CVID[4]	P-CID[5]	CTLA-4[6]	IPEX-OI[8]	LRBA-IDDA[7]	AIDAI[9]	Hypo-gam[10]
Laboratory										
Genetic diagnosis		✓								
IgE	✓									
Eosinophil count	✓									
Cytopenias (usually not autoimmune)		✓	✓							
Small platelets			✓							
Hypertrigliceridemia		✓								
Hypofibrinogenemia		✓								
Hyperferritinemia		✓								
Increased sIL2R		✓				✓				
Hemophagocytosis		✓		✓				✓		
Myelodysplasia			✓							
Reduced NK cell activity		✓								
Serum aspartate aminotrans-ferase (AST)		✓								
Cellular markers of immune acti-vation, naivety, memory formation						✓				
Hypogammaglobulinemia (see below IVIG or SCIG therapy)								✓		✓
Specific antibody concentrations										✓
QoL, supportive measures, performance scales										
Patient-reported quality of life, symptom burden					✓				✓	
Failure to thrive, malnutrition, weight loss				✓		✓	✓	✓		✓
Karnofsky/Lansky scale								✓		
Hospitalization (except ICU)								✓		✓
ICU, mechanical ventilation								✓		
IVIG or SCIG therapy								✓		
Nutrition / dietary status								✓		

Parameters	HIES[1]	HLH[2]	WAS[3]	CVID[4]	P-CID[5]	CTLA-4[6]	IPEX-OI[8]	LRBA-IDDA[7]	AIDAI[9]	Hypo-gam[10]
Other										
Allergies				✓						
Vascular disease n.f.s.	✓									
Known underlying immunosupp-ression		in H score								
Iatrogenic complications				✓						
Amyloidosis				✓						
Other organ dysfunction n.f.s.								✓		✓
Antibiotic (courses/year)										✓
Pain relief drugs taken									✓	
Malignancy										
Malignancy n.f.s.		in FHL: absence	✓	✓				✓		
Lymphoma	✓									
Age correction	✓				✓					

1, extracted from the HIES score for STAT3LOF (77,97)
2, a sum of parameters for familial hemophagocytic lymphohistiocytosis (FHL) and secondary hemophagocytic syndrome (H score) (100,101)
3, summarized from (109)
4, extracted from the modified version by Ameratunga, 2018 (145)
5, taken from (149)
6, extracted from the ABACHAI trial that evaluates the safety and efficacy of abatacept in patients with CTLA- 4 insufficiency and LRBA deficiency (000972-40 EU Clinical Trial Registry)
7, modified from (2)
8, IPEX organ involvement score, taken from (153)
9, summarized from (161,162)
10, Hypogam, slightly simplified from hypogammaglobulinemia treatment (immunoglobulin therapy) indication scoring system (177)
11, in the wide sense, including also results of functional defects that cause secondary changes
12, n.f.s., not further specified
13, overlap between infectious, autoimmune and inflammatory pathogenesis of features n.f.s.
ENT, ear nose throat
CNS central nervous system
QoL, quality of life
ICU, intensive care unit
IVIG, SCIG, intravenous or subcutaneous immunoglobulin therapy.

Table 14: The immune deficiency and dysregulation activity (IDDA) and other current clinical scores for inborn errors of immunity compared by their main characteristics and divided into categories derived from their application, adapted from Seidel et al. 2021 (1)

5 Discussion

The use of scores in patients with IEI can be clinically helpful in finding a diagnosis, severity classification, disease activity assessment and treatment decisions. Due to the existence of this variety of very specific tools, the implementation of more general disease scores should be accelerated, as this ensures the comparability of scoring results of different diseases and treatments, both cross-sectionally and over a period of time. Ideally, it provides a standardized quantitative definition of the clinical phenotype of IEI in its entirety and its impact on the patient's quality of life and burden of disease. Additionally, it could demonstrate the need for supportive care and is relevant in both disease- or drug-specific studies and prospective patient registry studies (1).

The ability to make a genetic diagnosis is steadily improving due to the increasing availability of next generation sequencing, and thus the list of monogenic PID with immune dysregulation is also expanding. As a consequence, we are faced with the challenge of linking the diagnosed genotype to the phenotype and finding standardized treatment or making predictions – things that can be simplified by standardized treatment protocols involving a scoring method (33).

The heterogeneity of IEI, frequently lacking genotype-phenotype correlation, makes the cross-disease application of specific scores, mostly designed for one disease or phenotype, very difficult. The first group of measures, comprising HIES scoring system, H-score, and WAS score, allow clear results for clinical diagnosis and simple subclassification of the underlying disease. They are based mainly on yes/no criteria to assign specific symptoms to a diagnosis or on a semiquantitative scale to distinguish severity and clinical subtypes (1). However, because they are scoring methods for diagnostic purposes and, for example, the HIES score includes highly specific clinical and laboratory criteria for the diagnosis of an HIES genotype, a more detailed comparison with morbidity measures can be considered as irrelevant. The other morbidity measures and treatment stratification scoring systems find application in evaluating the clinical course of a patient or for interindividual comparison. Therefore, all scoring systems belonging to these two groups rely on repeated applications, as only follow-up assessments can detect additional or altered manifestations and complications. Thus, the burden of disease or specifically the severity at different stages of the underlying disease or group of IEI, as in the CVID score, is

reflected (1). By evaluating the efficacy of different treatment options, these scoring methods can provide guidance for treatment decisions. However, these methods also hold limitations, such as a lack of differentiation between acute and chronic symptoms in the PCID morbidity measure. In comparison, the IDDA-2.1 score distinguishes between acute and chronic events, thus chronic and recurrent infections are counted separately and scored differently than acute ones. While the AIDAI represents a valid tool to distinguish active from inactive disease, activity cannot provide information about the entirety of the disease's impact on a patient. As the name implies, the organ involvement scoring system for IPEX syndrome only measures organ involvement and assigns points based on their relevance to IPEX syndrome. However, this score has very limited applicability and does not sufficiently reflect a patient's actual disease burden. In contrast, the IDDA 2.1 score captures organ involvement and disease activity using the comprehensive parameters and shows disease burden using additional parameters that include performance scales and needed supportive care (1,2,149,161,180).

However, applying one particular score, as aimed with the IDDA score, to more than one IEI results in a number of challenges. First off in terms of user-friendliness maintaining simplicity and feasibility while still acknowledging the complexity and specificity of the various disorders represents a balancing act. Furthermore score-comparibility may be compromised since the assessment and thus grading of items such as organ manifestations and especially their severity depends on the user. On top of that some definitions, for instance autoimmunity or granulomatous disease, may not necessarily be understood in a uniform way. Moreover, it is unclear whether specific organ manifestations that do not occur in the more precisely described parameters should be assigned to "other factors and symptoms" or "any other organ dysfunction". This possible confusion due to lack of further description regarding pathomechanism or target organ might hinder accurate scoring. In addition, some IEI have a tendency to present with specific manifestations in particular organ systems or are characterized by very distinct features (e.g. HIES) and are thus not proportionally represented by a general score. Hence, the weighting of organ manifestation can vary significantly and could lead to a potential bias. In these individual cases, a disease-specific score can still be applied in addition to a more general score to provide a more adequate assessment (1).

Another very important factor is that disease activity is therapy-dependent and therefore it is not always possible to draw conclusions about a patient's actual condition. Since medication, e.g. immunosuppressive therapy, can obviously reduce disease activity and organ manifestations and thus also lower the score, it may mask information regarding the underlying disease. Therefore, as already described above, it is important that scores assessing organ involvement, morbidity, and disease activity, such as the IDDA 2.1 score, are reevaluated regularly. The add-on feature of documentation of changes in therapeutic interventions should also be performed, which may be helpful for timely correlation with ongoing therapy and thus evaluating the therapeutic effect (1).

No field of medicine would ever rely exclusively on a score and consider it a stand-alone criterion, although this appears to be convenient. Particularly in IEI, due to the complexity of the diseases, the many possible phenotypic manifestations, and the fact that we are still in the process of learning how to diagnose and treat IEI, it is not possible to simply rely on a specific score. Instead it should only be applied as an assistive tool and the assessment of a patient in its entirety needs to be done by a physician to ensure excellent care (1).

The human phenotype ontology (HPO) project, that has already been applied to a number of IEIs by now (181–184), aims to define phenotypic characteristics, disease manifestations, clinical symptoms, and laboratory values using standardized terminology. In order to improve the applicability of HPO terms in IEIs, constant efforts are being made and an international initiative is ongoing (1,181). Initially, Seidel et al. tried to integrate these HPO codes into the IDDA 2.1 score. This attempt was postponed as the inclusion of the 22 parameters into the ESID registry database had to be as simple as possible and without any obstacles. Thus, an inclusion of the HPO codes operating in the background of data entry fields, is intended in the future. By adding this feature to the IDDA 2.1 score, each entry in the score sheet could automatically be assigned to the codes. This could significantly simplify the documentation of clinical data and increase the accuracy of documentation by further adding more specific subitems (1).

Clinical evaluation of other IEIs with immune dysregulation could be facilitated by using the IDDA 2.1 score as the range of included parameters and combination with other objective factors and additional features are not only applicable for LRBA deficiency. Seidel et al. have already initiated an international prospective study in the

ESID registry, which aims to obtain sufficient data on IEIs and, most importantly, a large number of patient time points in different treatment regimens. With these data and the IDDA 2.1. score as a basis, a machine-learning-powered tool is intended to be constructed. Seidel et al. aim to use data of the prospective study to optimize the composition and applicability of the ESID registry. With special statistical tools, a ranking of the relevance of the information is intended to achieve a potential improvement in diagnostics and treatment decisions. Furthermore, an intraindividual longitudinal monitoring to allow an objective assessment of a patient's clinical course and potential complications can consequently be ensured. It also provides the possibility of an interindividual comparison (e.g. in drug trials or multicenter studies) and the comparison of different genetic defects or immunodeficiencies among each other. In particular, the newly added "kaleidoscope" function can be used for this purpose, which shows the phenotypic features of IEIs and how they partly overlap in a visual and thus easy-to-understand way. These illustrations can be used to highlight similarities of presenting symptoms in specific IEIs and patients, respectively. Especially if these patients are still undiagnosed, the "kaleidoscope feature" in combination with unsupervised machine learning algorithms for detection of pattern similarities can serve as a supporting guidance for phenotype-driven therapies (1).

Since in certain IEIs the best outcomes of long-term follow-up after HSCT have been noted with low organ manifestations and disease activity prior to HSCT, reduction of these should be performed with the help of an induction therapy (2,180). Targeted therapy, if available for the specific disease, would be favoured as "remission induction therapy". A comprehensive and detailed observation of a patient's condition is necessary before, during and after HSCT. Especially in the preparative phase before HSCT, known as "bridging", a minimization of potential infections, inflammation and organ damage is required and must be monitored precisely. Consequently, the goal of this score-monitored induction therapy may be to identify a specific cutoff at which HSCT can be performed. For this purpose, the IDDA-2.1 score can be used to provide an objective monitoring tool to ensure best possible pre-transplant conditions (2,33,153). Nevertheless, it is important that HSCT should not be postponed under any circumstances, even if remission has not been achieved previously. In addition, the IDDA 2.1 score can be used to document engraftment after HSCT. Close monitoring of engraftment and, particularly, detection of possible graft-versus-

host disease (GvHD) with an appropriate instrument is required over an extended period of time. Protective recovery of the immune system can take months or even years, and GvHD can thus occur at any time. In most cases affecting the gastrointestinal tract, liver, skin and lungs, all potential manifestations captured by the IDDA score. Of course, stable transplant conditions cannot be guaranteed, but potential side effects, e.g. graft failure, GVHD or infections, can be detected at an early stage using the IDDA 2.1 score. Thus, life-threatening complications or possible long-lasting impairment of quality of life can be prevented by appropriate supportive treatment. Considering that supportive care is necessary during and after HSCT to prevent and treat infections and other complications, the IDDA 2.1 score could also be used as a decision support whether and to what extent additional supportive care is needed (185). The further implementation and clinical application of the IDDA 2.1 score as standard for monitoring patients with PIRDS and other IEI with immune dysregulation aims to provide a clinical assessment of disease burden and activity under different long-term treatments. With the implemented background information and its user-friendly handling, it can serve as a perfect support in treatment decisions for caring physicians, as well as for documentation of the treatment response and its effects. The IDDA 2.1 score is regarded as complementary measure to clinical experience to enhance the awareness regarding the complexity of these diseases and to provide an improvement in the quality of care and patient outcomes.

6 References

1. Seidel MG, Tesch VK, Yang L, Hauck F, Horn AL, Smolle M, et al. The Immune Deficiency and Dysregulation Activity (IDDA2.1 'Kaleidoscope') Score and Other Clinical Measures in Inborn Errors of Immunity. J Clin Immunol. 2021;42(3):484–98.
2. Tesch VK, Abolhassani H, Shadur B, Zobel J, Mareika Y, Sharapova S, et al. Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score. J Allergy Clin Immunol. 2020;145(5):1452–63.
3. Gámez-Díaz L, August D, Stepensky P, Revel-Vilk S, Seidel MG, Noriko M, et al. The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency. J Allergy Clin Immunol. 2016;137(1):223–30.
4. Alkhairy OK, Abolhassani H, Rezaei N, Fang M, Andersen KK, Chavoshzadeh Z, et al. Spectrum of Phenotypes Associated with Mutations in LRBA. J Clin Immunol. 2016;36(1):33–45.
5. Habibi S, Zaki-Dizaji M, Rafiemanesh H, Lo B, Jamee M, Gámez-Díaz L, et al. Clinical, Immunologic, and Molecular Spectrum of Patients with LPS-Responsive Beige-Like Anchor Protein Deficiency: A Systematic Review. J Allergy Clin Immunol Pract. 2019 Sep 1;7(7):2379–86.
6. Gámez-Díaz L, Seidel MG. Different Apples, Same Tree: Visualizing Current Biological and Clinical Insights into CTLA-4 Insufficiency and LRBA and DEF6 Deficiencies. Front Pediatr. 2021;9(April):1–9.
7. (ESID) ESfI. ESID Registry - Working definitions for clinical diagnosis of PID 2019 [Available from: https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria].
8. Parvaneh N, Casanova J-L, Notarangelo LD, Conley ME. Primary immunodeficiencies: A rapidly evolving story. J Allergy Clin Immunol. 2013 Feb;131(2):314–23.
9. Abbas AK, Lichtmann AH, Pillai S. Cellular and Molecular Immunology. Revised. Philadelphia, United States: Elsevier - Health Sciences Division; 2017.
10. Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova JL, et al. Primary immunodeficiency diseases worldwide: More common than

generally thought. J Clin Immunol. 2013;33(1):1–7.

11. Notarangelo LD, Fischer A, Geha RS, Casanova JL, Chapel H, Conley ME, et al. Primary immunodeficiencies: 2009 update. J Allergy Clin Immunol. 2009;124(6):1161–78.
12. Notarangelo LD. Primary immunodeficiencies. J Allergy Clin Immunol. 2010;125:182–94.
13. Bousfiha A, Jeddane L, Picard C, Al-Herz W, Ailal F, Chatila T, et al. Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification. J Clin Immunol. 2020;40(1):66–81.
14. Arkwright PD, Gennery AR. Ten warning signs of primary immunodeficiency: A new paradigm is needed for the 21st century. Ann N Y Acad Sci. 2011;1238(1):7–14.
15. Waltenburg R, Kobrynski L, Reyes M, Bowen S, Khoury MJ. Primary immunodeficiency diseases: Practice among primary care providers and awareness among the general public, United States, 2008. Genet Med. 2010;12(12):792–800.
16. ESID Clinical Working Party 10 Warning Signs of PID - General [Available from: https://esid.org/Working-Parties/Clinical-Working-Party/Resources/10-Warning-Signs-of-PID-General].
17. Eibl MM, Wolf HM. Vaccination in patients with primary immune deficiency, secondary immune deficiency and autoimmunity with immune regulatory abnormalities. Immunotherapy. 2015;7:1273–92.
18. Farmand S, Baumann U, von Bernuth H, Borte M, Borte S, Boztug K, et al. Leitlinie “Diagnostik auf Vorliegen eines primären Immundefekts.” AWMF-Reg-Nr 112/001 Klasse S2k [Internet]. 2017;(112):1–52. Available from: https://www.awmf.org/leitlinien/detail/ll/112-001.html
19. Farmand S, Baumann U, Borte M, Franke K, Habermehl P, Kapaun P, et al. Interdisziplinäre AWMF-Leitlinie zur Diagnostik von primären Immundefekten (S2k) Interdisciplinary AWMF Guideline for the Diagnostics of Primary Immunode ficiency. Klin Padiatr. 2011;223(6):378–85.
20. SLIPI (Sveriges Läkares Intresseförening för Primär Immunbrist) [Internet]. 2015. Available from: http://slipi.nu/medicinsk-info/
21. Bahrami A, Sayyahfar S, Soltani Z, Khodadost M, Moazzami B, Rezaei N. Evaluation of the frequency and diagnostic delay of primary immunodeficiency

disorders among suspected patients based on the 10 warning sign criteria: A cross-sectional study in Iran. Allergol Immunopathol (Madr). 2020;48(6):711–9.

22. Costa-Carvalho BT, Grumach AS, Franco JL, Espinosa-Rosales FJ, Leiva LE, King A, et al. Attending to warning signs of primary immunodeficiency diseases across the range of clinical practice. J Clin Immunol. 2014;34(1):10–22.
23. Jeffrey Modell Foundation. Spirit Analyzer Tool [Internet]. Available from: http://www.info4pi.org/town-hall/spirit
24. Cunningham-Rundles C, Sidi P, Estrella L, Doucette J. Identifying undiagnosed primary immunodeficiency diseases in minority subjects by using computer sorting of diagnosis codes. J Allergy Clin Immunol. 2004;113(4):747–55.
25. Reda SM, El-Ghoneimy DH, Afifi HM. Clinical predictors of primary immunodeficiency diseases in children. Allergy, Asthma Immunol Res. 2013;5(2):88–95.
26. Yarmohammadi H, Estrella L, Doucette J, Cunningham-Rundles C. Recognizing primary immune deficiency in clinical practice. Clin Vaccine Immunol. 2006;13(3):329–32.
27. Cowley LE, Farewell DM, Maguire S, Kemp AM. Methodological standards for the development and evaluation of clinical prediction rules: a review of the literature. Diagnostic Progn Res. 2019;3(1):1–23.
28. Dambha-Miller H, Everitt H, Little P. Editorials: Clinical scores in primary care. Br J Gen Pract. 2020;70(693):162–3.
29. Adams ST, Leveson SH. Clinical prediction rules. BMJ. 2012;344(7842):1–7.
30. Challener D, Prokop L, Abu-Saleh O. The Proliferation of Reports on Clinical Scoring Systems - Issues About Uptake and Clinical Utility. JAMA - J Am Med Assoc. 2019;321:2405–6.
31. Beattie P, Nelson R. Clinical prediction rules: What are they and what do they tell us? Aust J Physiother. 2006;52(3):157–63.
32. Winterhalter M. Scoring (Schweregradklassifikation). In: Checkliste Intensivmedizin. 2017. p. 134–9.
33. Bakhtiar S, Fekadu J, Seidel MG, Gambinieri E. Allogeneic Hematopoietic Stem Cell Transplantation for Congenital Immune Dysregulatory Disorders.

Front Pediatr. 2019;7(November):1–10.

34. Mor A, Shinar Y, Zaks N, Langevitz P, Chetrit A, Shtrasburg S, et al. Evaluation of disease severity in familial Mediterranean fever. Semin Arthritis Rheum. 2005;35(1):57–64.
35. Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. Anaesthesia. 1976;31(9):1191–8.
36. Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. Cancer. 1987;60(7):1651–6.
37. Karnofsky D a, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma. Cancer. 1948;1(4):634–56.
38. Amin M, Edge S, Greene F. American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th ed. New York: Springer International Publishing;
39. Teasdale G, Jennett B. Assessment of Coma and impaired Consciousness: A Practical Scale. Lancet. 1974;81–3.
40. Page LK, Psaila B, Provan D, Michael Hamilton J, Jenkins JM, Elish AS, et al. The immune thrombocytopenic purpura (ITP) bleeding score: Assessment of bleeding in patients with ITP. Br J Haematol. 2007;138(2):245–8.
41. Emerson RM, Charman CR, Williams HC. The Nottingham Eczema Severity Score: Preliminary refinement of the Rajka and Langeland grading. Br J Dermatol. 2000;142(2):288–97.
42. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69(9):1580–8.
43. Nelson EC, Eftimovska E, Lind C, Hager A, Wasson JH, Lindblad S. Patient reported outcome measures in practice. BMJ. 2015;350(February):1–3.
44. Greenhalgh J, Gooding K, Gibbons E, Dalkin S, Wright J, Valderas J, et al. How do patient reported outcome measures (PROMs) support clinician-patient communication and patient care? A realist synthesis. J Patient-Reported Outcomes. 2018;2(42).
45. Turner D, Otley AR, Mack D, Hyams J, de Bruijne J, Uusoue K, et al. Development, Validation, and Evaluation of a Pediatric Ulcerative Colitis Activity Index: A Prospective Multicenter Study. Gastroenterology.

2007;133(2):423–32.

46. Kawai T, Arai K, Harayama S, Nakazawa Y, Goto F, Maekawa T, et al. Severe and Rapid Progression in Very Early-Onset Chronic Granulomatous Disease-Associated Colitis. J Clin Immunol. 2015;35(6):583–8.
47. Seidel MG, Benesch M, Schwinger W. Sic-reg.org. 2017.
48. Fischer A, Provot J, Jais JP, Alcais A, Mahlaoui N, Adoue D, et al. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immunol. 2017;140(5).
49. Aladjidi N, Leverger G, Leblanc T, Picat MQ, Michel G, Bertrand Y, et al. New insights into childhood autoimmune hemolytic anemia: A French national observational study of 265 children. Haematologica. 2011;96(5):655–63.
50. Mahlaoui N, Warnatz K, Jones A, Workman S, Cant A. Advances in the Care of Primary Immunodeficiencies (PIDs): from Birth to Adulthood. J Clin Immunol. 2017;37(5):452–60.
51. Aghamohammadi A, Moghaddam ZG, Abolhassani H, Hallaji Z, Mortazavi H, Pourhamdi S, et al. Investigation of underlying primary immunodeficiencies in patients with severe atopic dermatitis. Allergol Immunopathol (Madr). 2014;42(4):336–41.
52. Rajka G, Langeland T. Grading of the severity of atopic dermatitis. Acta Derm Venereol Suppl. 1989;144:13–4.
53. Berth-Jones J. Six Area, Six Sign Atopic Dermatitis (SASSAD) seventy score: A simple system for monitoring disease activity in atopic dermatitis. Br J Dermatology, Suppl. 1996;135(48):25–30.
54. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): Assessment of reliability in atopic dermatitis. Exp Dermatol. 2001;10(1):11–8.
55. Barbier N, Paul C, Luger T, Allen R, De Prost Y, Papp K, et al. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. Br J Dermatol. 2004;150(1):96–102.
56. Bahmer FA, Schubert HJ. Quantification of the Extent and the Severity of Atopic Dermatitis: The ADASI Score. Arch Dermatol. 1991;127(8):1239–40.
57. European Task Force on Atopic Dermatitis. Severity Scoring of Atopic Dermatitis: The SCORAD Index (consensus report of the European Task

Force on Atopic Dermatitis). Dermatology. 1993;23–31.
58. Oranje AP, Glazenburg EJ, Wolkerstorfer A, De Waard-Van Der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: The SCORAD index, objective SCORAD and the three-item severity score. Br J Dermatol. 2007;157(4):645–8.
59. Deane KD, Holers VM. The Natural History of Rheumatoid Arthritis. Clin Ther. 2019;41(7):1256–69.
60. Matsumoto Y, Uemura M, Hibino N, Yamamoto M. Clinical usefulness of the 1987 revised criteria for rheumatoid arthritis by American Rheumatism Association. Nihon Naika Gakkai Zasshi. 1988;77(5):742–3.
61. Goussault H, Salvator H, Catherinot E, Chabi ML, Tcherakian C, Chabrol A, et al. Primary immunodeficiency-related bronchiectasis in adults: Comparison with bronchiectasis of other etiologies in a French reference center. Respir Res. 2019;20(1):1–10.
62. Martínez-García MA, De Gracia J, Relat MV, Girón RM, Carro LM, De La Rosa Carrillo D, et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: The FACED score. Eur Respir J. 2014;43(5):1357–67.
63. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index an international derivation and validation study. Am J Respir Crit Care Med. 2014;189(5):576–85.
64. Costa JC, Machado JN, Ferreira C, Gama J, Rodrigues C. The Bronchiectasis Severity Index and FACED score for assessment of the severity of bronchiectasis. Rev Port Pneumol (English Ed. 2018;24(3):149–54.
65. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol. 1999;92(1):34–48.
66. Oksenhendler E, Gérard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, et al. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis. 2008;46(10):1547–54.
67. Gathmann B, Mahlaoui N, Gérard L, Oksenhendler E, Warnatz K, Schulze I, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol. 2014;134(1):7–9.
68. Leteurtre S, Martinot A, Duhamel A, Proulx F, Grandbastien B, Cotting J, et al. Validation of the paediatric logistic organ dysfunction (PELOD) score:

Prospective, observational, multicentre study. Lancet. 2003;362(9379):192–7.

69. Ödek Ç, Kendirli T, Doğu F, Yaman A, Vatansever G, Çipe F, et al. Patients with primary Immunodeficiencies in pediatric intensive care unit: Outcomes and mortality-related risk factors. J Clin Immunol. 2014;34(3):309–15.
70. Leteurtre S, Martinot A, Duhamel A, Gauvin F, Grandbastien B, Nam TV, et al. Development of a pediatric multiple organ dysfunction score: Use of two strategies. Med Decis Mak. 1999;19(4):399–410.
71. Leteurtre S, Duhamel A, Salleron J, Grandbastien B, Lacroix J, Leclerc F. PELOD-2: An update of the PEdiatric logistic organ dysfunction score. Crit Care Med. 2013;41(7):1761–73.
72. Marshall JC, Cook DJ, Christou N V, Bernard GR, Sprung CL, Sibbald WJ. Multiple Organ Dysfunction Score. Crit Care Med. 1995;23.
73. Graciano AL, Balko JA, Rahn DS, Ahmad N, Giroir BP. The Pediatric Multiple Organ Dysfunction Score (P-MODS): Development and validation of an objective scale to measure the severity of multiple organ dysfunction in critically ill children. Crit Care Med. 2005;33(7):1484–91.
74. Le Gall J-R, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, et al. The Logistic Organ Dysfunction System, A New Way to Assess Organ Dysfunction in the Intensive Care Unit. JAMA - J Am Med Assoc. 1996;1–9.
75. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA score to describe organ dysfunction/failure. Intensive Care Med. 1996;22(7):707–10.
76. Davis SD, Schaller J, Wedgwood RJ. Job's Syndrome. Recurrent, "cold", staphylococcal abscesses. Lancet. 1966;1(7445):1013–5.
77. Grimbacher B, Schäffer AA, Holland SM, Davis J, Gallin JI, Malech HL, et al. Genetic linkage of hyper-IgE syndrome to chromosome 4. Am J Hum Genet. 1999;65(3):735–44.
78. Al-Shaikhly T, Ochs HD. Hyper IgE syndromes: clinical and molecular characteristics. Immunol Cell Biol. 2019;97(4):368–79.
79. Freeman AF, Holland SM. The Hyper-IgE Syndromes. Immunol Allergy Clin North Am. 2008;28(2):277–91.
80. Freeman AF, Holland SM. Clinical manifestations, etiology, and pathogenesis of the Hyper-IgE syndromes. Pediatr Res. 2009;65:32–7.

81. Sassi A, Lazaroski S, Wu G, Haslam SM, Fliegauf M, Mellouli F, et al. Hypomorphic homozygous mutations in phosphoglucomutase 3 (PGM3) impair immunity and increase serum IgE levels. J Allergy Clin Immunol. 2014;133(5).
82. Zhang Y, Yu X, Ichikawa M, Al. E. Autosomal Recessive Phosphoglucomutase 3 (PGM3) Mutations Link Glycosylation Defects to Atopy, Immune Deficiency, Autoimmunity, and Neurocognitive Impairment. J Allergy Clin Immunol. 2014;133(5):181–2.
83. Ma CA, Stinson JR, Zhang Y, Abbott JK, Weinreich MA, Hauk PJ, et al. Germline hypomorphic CARD11 mutations in severe atopic disease. Nat Genet. 2017;49(8):1192–201.
84. Dadi H, Jones TA, Merico D, Sharfe N, Ovadia A, Schejter Y, et al. Combined immunodeficiency and atopy caused by a dominant negative mutation in caspase activation and recruitment domain family member 11 (CARD11). J Allergy Clin Immunol. 2018;141(5):1818–30.
85. Béziat V, Li J, Lin JX, Ma CS, Li P, Bousfiha A, et al. A recessive form of hyper-IgE syndrome by disruption of ZNF341-dependent STAT3 transcription and activity. Sci Immunol. 2018;3(24):1–19.
86. Frey-Jakobs S, Hartberger JM, Fliegauf M, Bossen C, Wehmeyer ML, Neubauer JC, et al. ZNF341 controls STAT3 expression and thereby immunocompetence. Sci Immunol. 2018;3(24):1–12.
87. Yong PFK, Freeman AF, Engelhardt KR, Holland S, Puck JM, Grimbacher B. An update on the hyper-IgE syndromes. Arthritis Res Ther. 2012;14(6):1–10.
88. Holland SM, Puck JM. Hyper-IgE syndromes. 2005;203:244–50.
89. Gorin LJ, Jeha SC, Sullivan MP, Rosenblatt HM, Shearer WT. Burkitt's lymphoma developing in a 7-year-old boy with hyper-IgE syndrome. J Allergy Clin Immunol. 1989;83(1):5–10.
90. Kumánovics A, Perkins SL, Gilbert H, Cessna MH, Augustine NH, Hill HR. Diffuse large B cell lymphoma in hyper-IgE syndrome due to STAT3 mutation. J Clin Immunol. 2010;30(6):886–93.
91. Oztop I, Demirkan B, Tarhan O, Kayahan H, Yilmaz U, Kargi A, et al. The development of pulmonary adenocarcinoma in a patient with Job's syndrome, a rare immunodeficiency condition. Tumori. 2004;90(1):132–5.
92. Biggs CM, Keles S, Chatila TA. DOCK8 deficiency: Insights into

pathophysiology, clinical features and management. Clin Immunol. 2017;181:75–82.

93. Holland S, DeLeo F, Elloumi H, Al E. STAT3Mutations in the Hyper-IgE Syndrome. N Engl J Med. 2007;68–9.
94. Aydin SE, Kilic SS, Aytekin C, Kumar A, Porras O, Kainulainen L, et al. DOCK8 Deficiency: Clinical and Immunological Phenotype and Treatment Options - a Review of 136 Patients. J Clin Immunol. 2015;35(2):189–98.
95. Engelhardt KR, McGhee S, Winkler S, Sassi A, Woellner C, Lopez-Herrera G, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. J Allergy Clin Immunol. 2009;124(6):1289–302.
96. Schimke LF, Sawalle-Belohradsky J, Roesler J, Wollenberg A, Rack A, Borte M, et al. Diagnostic approach to the hyper-IgE syndromes: Immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. J Allergy Clin Immunol. 2010;126(3):611–7.
97. Woellner C, Gertz EM, Schäffer AA, Lagos M, Perro M, Glocker EO, et al. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. J Allergy Clin Immunol. 2010;125(2):424–32.
98. Alyasin S, Esmaeilzadeh H, Ebrahimi N, Nabavizadeh SH, Kashef S, Esmaeilzadeh E, et al. Phenotyping and long-term follow up of patients with hyper IgE syndrome. Allergol Immunopathol (Madr). 2019;47(2):152–8.
99. Renner ED, Rylaarsdam S, Aňover-Sombke S, Rack AL, Reichenbach J, Carey JC, et al. Novel signal transducer and activator of transcription 3 (STAT3) mutations, reduced TH17 cell numbers, and variably defective STAT3 phosphorylation in hyper-IgE syndrome. J Allergy Clin Immunol. 2008;122(1):181–7.
100. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the hscore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66(9):2613–20.
101. Henter J-I, Horne A, Aricó M. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124–31.
102. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med. 2012;63:233–46.

103. Fukaya S, Yasuda S, Hashimoto T, Oku K, Kataoka H, Horita T, et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: Analysis of 30 cases. Rheumatology. 2008;47(11):1686–91.
104. Bae CB, Jung JY, Kim HA, Suh CH. Reactive hemophagocytic syndrome in adult-onset still disease: Clinical features, predictive factors, and prognosis in 21 patients. Med (United States). 2015;94(4):1–9.
105. Fardet L, Lambotte O, Meynard JL, Kamouh W, Galicier L, Marzac C, et al. Reactive haemophagocytic syndrome in 58 HIV-1-infected patients: Clinical features, underlying diseases and prognosis. Aids. 2010;24(9):1299–306.
106. Dhote R, Simon J, Papo T, Detournay B, Sailler L, Andre MH, et al. Reactive Hemophagocytic Syndrome in Adult Systemic Disease: Report of Twenty-Six Cases and Literature Review. Arthritis Care Res. 2003;49(5):633–9.
107. Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. Lancet Infect Dis. 2007;7(12):814–22.
108. Hejblum G, Lambotte O, Galicier L, Coppo P, Marzac C, Aumont C, et al. A web-based Delphi study for eliciting helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients. PLoS One. 2014;9(4).
109. Albert MH, Notarangelo LD, Ochs HD. Clinical spectrum, pathophysiology and treatment of the Wiskott-Aldrich syndrome. Curr Opin Hematol. 2011;18(1):42–8.
110. Shekhovtsova Z, Bonfim C, Ruggeri A, Nichele S, Page K, Alseraihy A, et al. A risk factor analysis of outcomes after unrelated cord blood transplantation for children with Wiskott-Aldrich syndrome. Haematologica. 2017;102(6):1112–9.
111. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr. 1994;125(6 PART 1):876–85.
112. Ochs HD, Thrasher AJ. The Wiskott-Aldrich syndrome. J Allergy Clin Immunol. 2006;117(4):725–38.
113. Ochs HD, Rosen FS. The Wiskott-Aldrich syndrome. In: Ochs HD, Smith CIE, Puck JM, editors. Primary Immunodeficiency Diseases: A Molecular and Genetic Approach. New York: Oxford University Press; 2007. p. 454–69.
114. Ochs HD, Filipovich AH, Veys P, Cowan MJ, Kapoor N. Wiskott-Aldrich

Syndrome: Diagnosis, Clinical and Laboratory Manifestations, and Treatment. Biol Blood Marrow Transplant. 2009;15:84–90.

115. Albert MH, Freeman AF. Wiskott-Aldrich Syndrome (WAS) and Dedicator of Cytokinesis 8- (DOCK8) Deficiency. Front Pediatr. 2019;7(November):1–8.
116. Cassidy JT, Petty RE. Textbook of Pediatric Rheumatology. 3rd ed. Philadelphia, United States: Saunders; 1995.
117. Pras E, Livneh A, Balow JEJ, Pras E, Kastner DL, Pras M, et al. Clinical differences between North African and Iraqui Jews with familial Mediterranean fever. Am J Med Genet. 1998;82(5):442.
118. Ozen S, Aktay N, Lainka E, Duzova A, Bakkaloglu A, Kallinich T. Disease severity in children and adolescents with familial Mediterranean fever: A comparative study to explore environmental effects on a monogenic disease. Ann Rheum Dis. 2009;68(2):246–8.
119. Kalkan G, Demirkaya E, Acikel CH, Polat A, Peru H, Karaoglu A, et al. Evaluation of the current disease severity scores in paediatric FMF: Is it necessary to develop a new one? Rheumatology. 2012;51(4):743–8.
120. Livneh A. Diagnosis: Severity scoring system for paediatric FMF. Nat Rev Rheumatol. 2012;8(6):309–10.
121. Demirkaya E, Acikel C, Hashkes P, Gattorno M, Gul A, Ozdogan H, et al. Development and initial validation of international severity scoring system for familial Mediterranean fever (ISSF). Ann Rheum Dis. 2016;75(6):1051–6.
122. Nissenkorn A, Ben-Zeev B. Ataxia telangiectasia. 1st ed. Vol. 132, Handbook of Clinical Neurology. Elsevier B.V.; 2015. 199–214 p.
123. Nissenkorn A, Borgohain R, Micheli R, Leuzzi V, Hegde AU, Mridula KR, et al. Development of global rating instruments for pediatric patients with ataxia telangiectasia. Eur J Paediatr Neurol. 2016;20(1):140–6.
124. Shenhod E, Benzeev B, Sarouk I, Heimer G, Nissenkorn A. Functional parameter measurements in children with ataxia telangiectasia. Dev Med Child Neurol. 2020;62(2):207–13.
125. Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L, et al. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. Science (80-). 1995;268(5218):1749–53.
126. Perez-Lloret S, van de Warrenburg B, Rossi M, Rodríguez-Blázquez C, Zesiewicz T, Saute JAM, et al. Assessment of Ataxia Rating Scales and

Cerebellar Functional Tests: Critique and Recommendations. Mov Disord. 2021;36(2):283–97.

127. Trouillas P, Takayanagi T, Hallett M, Currier RD. International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. J Neurol Sci. 1997;145(2):205–11.
128. Storey E, Tuck K, Hester R, Hughes A, Churchyard A. Inter-rater reliability of the International Cooperative Ataxia Rating Scale (ICARS). Mov Disord. 2004;19(2):190–2.
129. Schmahmann JD, Gardner R, MacMore J, Vangel MG. Development of a brief ataxia rating scale (BARS) based on a modified form of the ICARS. Mov Disord. 2009;24(12):1820–8.
130. Weyer A, Abele M, Schmitz-Hübsch T, Schoch B, Frings M, Timmann D, et al. Reliability and validity of the scale for the assessment and rating of ataxia: A study in 64 ataxia patients. Mov Disord. 2007;22(11):1633–7.
131. Schmitz-Hübsch T, du Montcel ST, Baliko L, Boesch S, Bonato S, Fancellu R, et al. Reliability and validity of the International Cooperative Ataxia Rating Scale: A study in 156 spinocerebellar ataxia patients. Mov Disord. 2006;21(5):699–704.
132. Subramony SH. SARA - A new clinical scale for the assessment and rating of ataxia: Commentary. Nat Clin Pract Neurol. 2007;3(3):136–7.
133. Brandsma R, Spits A, Kuiper M, Lunsing R, Kremer H, Burger H, et al. Ataxia rating scales are age-dependent in healthy children. Eur J Paediatr Neurol. 2013;17:109.
134. Camargos S, Cardoso F, Maciel R, Huebra L, Silva TR, Campos VG, et al. Brief Ataxia Rating Scale: A Reliable Tool to Rate Ataxia in a Short Timeframe. Mov Disord Clin Pract. 2016;3(6):621–3.
135. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7):28–37.
136. Busner J, Targum SD, Miller DS. The Clinical Global Impressions scale: errors in understanding and use. Compr Psychiatry. 2009;50(3):257–62.
137. Mokhtari M, Shakeri A, Mirminachi B, Abolhassani H, Yazdani R, Grimbacher B. Important Factors Influencing Severity of Common Variable Immunodeficiency. Arch Iran Med. 2016;19(8):544–50.
138. Cunningham-Rundles C. How I treat common variable immune deficiency.

Blood. 2010;116(1):7–15.

139. Aghamohammadi A, Abolhassani H, Moazzami K, Parvaneh N, Rezaei N. Correlation between common variable immunodeficiency clinical phenotypes and parental consanguinity in children and adults. J Investig Allergol Clin Immunol. 2010;20(5):372–9.
140. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common Variable immunodeficiency disorders: Division into distinct clinical phenotypes. Blood. 2008;112(2):277–86.
141. Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. Br J Haematol. 2009;145(6):709–27.
142. Mouillot G, Carmagnat M, Gérard L, Garnier JL, Fieschi C, Vince N, et al. B-cell and T-cell phenotypes in CVID patients correlate with the clinical phenotype of the disease. J Clin Immunol. 2010;30(5):746–55.
143. Seymour B, Miles J, Haeney M. Primary antibody deficiency and diagnostic delay. J Clin Pathol. 2005;58(5):546–7.
144. Yong PFK, Thaventhiran JED, Grimbacher B. “A Rose is a Rose is a Rose,” but CVID is Not CVID. Common Variable Immune Deficiency (CVID), What do we Know in 2011? 1st ed. Vol. 111, Advances in Immunology. Elsevier Inc.; 2011. 47–107 p.
145. Ameratunga R. Assessing Disease Severity in Common Variable Immunodeficiency Disorders (CVID) and CVID-Like Disorders. Front Immunol. 2018;9:1–8.
146. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119(7):1650–7.
147. Cunningham-Rundles C. The many faces of common variable immunodeficiency. Hematology Am Soc Hematol Educ Program. 2012;2012:301–5.
148. Farmer JR, Ong MS, Barmettler S, Yonker LM, Fuleihan R, Sullivan KE, et al. Common variable immunodeficiency non-infectious disease endotypes redefined using unbiased network clustering in large electronic datasets. Front Immunol. 2018;8:1–15.
149. Speckmann C, Doerken S, Aiuti A, Albert MH, Al-Herz W, Allende LM, et al.

A prospective study on the natural history of patients with profound combined immunodeficiency: An interim analysis. J Allergy Clin Immunol. 2017;139(4):1302–10.

150. Roifman CM, Somech R, Kavadas F, Pires L, Nahum A, Dalal I, et al. Defining combined immunodeficiency. J Allergy Clin Immunol. 2012;130(1):177–83.
151. Neven B, Ferrua F. Hematopoietic Stem Cell Transplantation for Combined Immunodeficiencies, on Behalf of IEWP-EBMT. Front Pediatr. 2020;7(January):1–8.
152. Varni JW, Seid M, Kurtin PS. PedsQL™ 4.0: Reliability and Validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in Healthy and Patient Populations. Med Care. 2001;39(8):800–12.
153. Barzaghi F, Amaya Hernandez LC, Neven B, Ricci S, Kucuk ZY, Bleesing JJ, et al. Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: An international multicenter retrospective study. J Allergy Clin Immunol. 2018;141(3):1036–49.
154. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet. 2001;27(1):20–1.
155. Azizi G, Yazdani R, Rae W, Abolhassani H, Rojas M, Aghamohammadi A, et al. Monogenic polyautoimmunity in primary immunodeficiency diseases. Autoimmun Rev. 2018;17(10):1028–39.
156. Jamee M, Zaki-Dizaji M, Lo B, Abolhassani H, Aghamahdi F, Mosavian M, et al. Clinical, immunological, and genetic features in patients with Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) and IPEX-like Syndrome. J Allergy Clin Immunol Pract. 2020;8(8):2747–60.
157. Lu L, Barbi J, Pan F. The regulation of immune tolerance by FOXP3. Nat Rev Immunol. 2017;17(11):703–17.
158. Kuehn HS, Ouyang W, Lo B, Deenick EK, Niemela JE, Avery DT, et al. Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. Science (80-). 2014;345(6204):1623–7.
159. Schwab C, Gabrysch A, Olbrich P, Patiño V, Warnatz K, Wolff D, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4–insufficient subjects. J Allergy Clin Immunol. 2018;142(6):1932–46.

160. Nayak L, Deangelis LM, Brandes AA, Peereboom DM, Galanis E, Lin NU, et al. The Neurologic Assessment in Neuro-Oncology (NANO) scale: A tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria. Neuro Oncol. 2017;19(5):625–35.
161. Piram M, Frenkel J, Gattorno M, Ozen S, Lachmann HJ, Goldbach-Mansky R, et al. A preliminary score for the assessment of disease activity in hereditary recurrent fevers: Results from the AIDAI (Auto-Inflammatory Diseases Activity Index) consensus conference. Ann Rheum Dis. 2011;70(2):309–14.
162. Piram M, Koné-Paut I, Lachmann HJ, Frenkel J, Ozen S, Kuemmerle-Deschner J, et al. Validation of the Auto-Inflammatory Diseases Activity Index (AIDAI) for hereditary recurrent fever syndromes. Ann Rheum Dis. 2014;73(12):2168–73.
163. Touitou I, Koné-Paut I. Autoinflammatory diseases. Best Pract Res Clin Rheumatol. 2008;22(5):811–29.
164. Hoffman HM, Throne ML, Amar NJ, Sebai M, Kivitz AJ, Kavanaugh A, et al. Efficacy and safety of rilonacept (Interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: Results from two sequential placebo-controlled studies. Arthritis Rheum. 2008;58(8):2443–52.
165. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, et al. Use of Canakinumab in the Cryopyrin-Associated Periodic Syndrome. N Engl J Med. 2009;360(23):2416–25.
166. Gillespie J, Mathews R, McDermott MF. Rilonacept in the management of cryopyrin-associated periodic syndromes (CAPS). J Inflamm Res. 2010;3(1):1–8.
167. Singh JA, Solomon DH, Dougados M, Felson D, Hawker G, Katz P, et al. Development of classification and response criteria for rheumatic diseases. Arthritis Care Res. 2006;55(3):348–52.
168. EUCTR2018-003297-27-DE. Therapeutic Use of Tadekinig Alfa in NLRC4 Mutation and XIAP Deficiency. 2017.
169. Stephenson C, Prajapati VH, Hunter C, Miettunen P. Novel use of Autoinflammatory Diseases Activity Index (AIDAI) captures skin and extracutaneous features to help manage pediatric DITRA: A case report and a proposal for a modified disease activity index in autoinflammatory

keratinization disorders. Pediatr Dermatol. 2020;37(4):670–6.
170. Renert-Yuval Y, Horev L, Babay S, Tams S, Ramot Y, Zlotogorski A, et al. IL36RN mutation causing generalized pustular psoriasis in a Palestinian patient. Int J Dermatol. 2014;53(7):866–8.
171. Liang J, Huang P, Li H, Zhang J, Ni C, Wang Y, et al. Mutations in IL36RN are associated with geographic tongue. Hum Genet. 2017;136(2):241–52.
172. Akiyama M, Takeichi T, McGrath JA, Sugiura K. Autoinflammatory keratinization diseases. J Allergy Clin Immunol. 2017;140(6):1545–7.
173. Akiyama M. Early-onset generalized pustular psoriasis is representative of autoinflammatory keratinization diseases. J Allergy Clin Immunol. 2019;143(2):809–10.
174. Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulou C, et al. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science (80-). 2015;349(6246):436–40.
175. KARNOFSKY, A. D. The clinical evaluation of chemotherapeutic agents in cancer. Eval Chemother Agents. 1949;191–205.
176. ESID Registry Working Party. ESID Registry - Working definitions for clinical diagnosis of PID. 2019;(Cid):1–33.
177. Agarwal S, Cunningham-Rundles C. Treatment of hypogammaglobulinemia in adults: A scoring system to guide decisions on immunoglobulin replacement. J Allergy Clin Immunol. 2013;131(6):1699–701.
178. Hanitsch L, Baumann U, Boztug K, Burkhard-Meier U, Fasshauer M, Habermehl P, et al. Treatment and management of primary antibody deficiency: German interdisciplinary evidence-based consensus guideline. Eur J Immunol. 2020;50(10):1432–46.
179. Krudewig J, Baumann U, Borte M, Dueckers G, Franke K, Habermehl P, et al. Interdisziplinäre AWMF-Leitlinie zur Therapie primärer Antikörpermangelerkrankungen Interdisciplinary AWMF Guideline for the Treatment of Primary Antibody De fi ciencies. 2012;404–15.
180. Barzaghi F, Amaya Hernandez LC, Neven B, Ricci S, Kucuk ZY, Bleesing JJ. Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: An international multicenter retrospective study. Physiol Behav. 2017;176(12):139–48.
181. Haimel M, Pazmandi J, Heredia RJ, Dmytrus J, Bal SK, Zoghi S, et al.

Curation and expansion of Human Phenotype Ontology for defined groups of inborn errors of immunity. J Allergy Clin Immunol. 2021;1–10.

182. Köhler S, Carmody L, Vasilevsky N, Jacobsen JOB, Danis D, Gourdine JP, et al. Expansion of the Human Phenotype Ontology (HPO) knowledge base and resources. Nucleic Acids Res. 2019;47(D1):D1018–27.
183. Köhler S, Gargano M, Matentzoglu N, Carmody LC, Lewis-Smith D, Vasilevsky NA, et al. The human phenotype ontology in 2021. Nucleic Acids Res. 2021;49(D1):D1207–17.
184. Gasteiger LM, Robinson PN, Pazmandi J, Boztug K, Seppänen MRJ, Seidel MG. Supplementation of the ESID registry working definitions for the clinical diagnosis of inborn errors of immunity with encoded human phenotype ontology (HPO) terms. J Allergy Clin Immunol Pract. 2020;8(5):1778.
185. Carreras E, Dufour C, Mohty M, Kröger N, Editors. THE EBMT Handbook - Hematopoietic Stem Cell Transplantation and Cellular Therapies. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. Springer Nature Switzerland AG; 2019.