Diploma thesis

Multi-centric, cross-sectional study about the prevalence and care of patients with inborn errors of immunity in Austria according to The European Society for Immunodeficiencies (ESID) Registry

submitted by

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for the attainment of the Academic Degree

Doctor of Medicine

(Dr.med.univ.)

at the

Medical University of Graz

carried out at the

Department of Paediatrics/

Division of Paediatric Haematology/Oncology

under the Supervision of

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Graz, August 31st, 2019

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Graz, am 31.08.2019 *Sabrina Taucher eh*

Acknowledgements

I would like to express special thanks to several people without whom I would not have been able to realise this work.

First, I would like to thank my family for the continuous support they were giving me during my time at university and in the process of this work, as well as for encouraging me to pursue my aims and ambitions. Special thanks to Sebastian, for always motivating me, listening to me whenever I needed to talk to somebody, for the great advice during this work; in all, for always being there for me and providing me with support whenever there were any kind of struggles.

I also would like to thank Raphael Scheible, MSc, of the University of Freiburg, Germany, for spending time to review the data in this work and providing useful advices on it.

Moreover, I would also like to express my special thanks to the participants of the survey, for investing time to answer the questionnaire and therefore providing me with valuable information that I could use in this work.

Finally, I would also like to particularly express my gratitude towards Univ. Prof. PD Dr.med.-univ. Markus Seidel, who continuously assisted me with great advices from the beginning on, provided me with various helpful information regarding this project and without whom I would not have been able to accomplish this work.

Zusammenfassung

Einleitung: PatientInnen mit primären Immundefekten zeigen ein variables klinisches Bild und können eine Reihe von unterschiedlichen Behandlungsmodalitäten erhalten. Das internationale Register der Europäischen Gesellschaft für primäre Immundefekte (ESID) stellt eine online Datenbank zur Dokumentation dieser PatientInnen dar. Das Hauptziel dieser Studie ist es, die aktuelle Situation zehn Jahre nach Aufnahme des Registers in Österreich darzustellen, hinsichtlich der Prävalenz einzelner Immundefekte, klinischer Manifestation und Altersverteilungen, sowie Diagnosemöglichkeiten, Behandlungsmodalitäten und diagnostischer Verzögerungen.

PatientInnen und Methoden: Die ESID Online Plattform sowie das ESID Reporting Tool wird verwendet, um eine umfassende Querschnittsstudie von österreichischen PatientInnen mit primären Immundefekten durchzuführen. Zudem wird ein Fragebogen dafür verwendet, um Vorteile und Hürden des Registers zu erforschen.

Ergebnisse: Im ESID Register sind derzeit 181 PatientInnen (104 männlich, 77 weiblich) in Österreich registriert, die sich auf sechs medizinische Abteilungen verteilen. Geographisch zeigt sich eine ungleiche Verteilung dieser Zentren durch mangelnde Teilnahme am Register. Derzeit sind 16.98% der erwarteten PatientInnen in Österreich dokumentiert, wie im ESID Reporting Tool ersichtlich. *Vorwiegend Antikörperdefekte* stellen mit 42% den häufigsten primären Immundefekt dar. In 63% der PatientInnen war Infektion das Erstsymptom, jedoch zeigten immerhin 13% der PatientInnen eine Immundysregulation als Erstmanifestation. 78 PatientInnen (43%) haben eine genetische Diagnose, die im Median mit 2,42 Jahren gestellt wird. Gensequenzierung wurde in beinahe der Hälfte (46%) aller genetischen Analysen verwendet. Siebenundsechzig PatientInnen werden mit Immunoglobulin-Substitution therapiert, welche die häufigste Behandlungsmodalität der dokumentierten PatientInnen darstellt; 11 PatientInnen erhielten Stammzelltransplantation.

Schlussfolgerung: Das ESID Register stellt in Österreich als einziges multi-zentrisches Register für primäre Immundefekte eine wichtige Dokumentationsmöglichkeit dar, das zudem zur besseren Vernetzung zwischen Zentren beiträgt und ein wichtiges Instrument für Forschung und gesundheitspolitische Überlegungen darstellt. Durch die mangelnde Teilnahme einzelner medizinischer Abteilungen sind die Daten derzeit für Österreich noch nicht

flächendeckend, weshalb die zukünftige Aufnahme des ESID-Registers in anderen Abteilungen sowie die vollständige Dateneintragung von höchster Priorität ist, um statistisch repräsentative Daten zu ermöglichen.

Abstract

Introduction: Patients with inborn errors of immunity (IEI) clinically present with a variety of symptoms and receive different types of treatment. The European Society for Immunodeficiencies (ESID) Registry displays an online platform to document those patients. The main purpose of this study is to demonstrate the current situation in Austria, after the first decade of participation in the ESID registry, regarding the prevalence of specific categories of IEI, clinical manifestation, and age distribution of patients, further focusing on diagnostic delay and the evaluation of applied diagnostic methods and treatment options using the patient data of the registry.

Patients/Methods: The online database of the ESID registry is used to perform a comprehensive, cross-sectional study of Austrian patients with IEI. Additionally, a survey among documenting centres and specific internal departments is conducted to investigate benefits and barriers of the registry.

Results: 181 patients (104 males, 77 females) are currently registered by six different documenting centres, which geographically show an unequal distribution since the western part of Austria is not represented in the ESID registry. The coverage of patients with IEI is currently 16.98%, according to the ESID Reporting Tool. *Predominantly antibody deficiencies* display the most common IEI category (42%). In 63% of patients, the initial onset symptom was infection; however, 13% of patients still clinically manifested with immune dysregulation. Regarding quality of diagnosis, 78 patients were genetically tested, with a median age of 2,42 years at genetic diagnosis. For genetic analyses, gene sequencing was used in almost half of cases (46%). 69 patients have been receiving Ig-replacement therapy, being the most common treatment type of documented Austrian patients, while 11 patients were undergoing hematopoietic stem cell transplantation (HSCT).

Conclusions: The ESID registry as the only multi-centric registry for IEI patients in Austria represents a valuable database for documentation of patients and aims to improve networking between centres. It displays an important instrument in terms of research and a basis for health-related decisions. However, as certain medical centres are currently not participating in the ESID registry, the data still fails to represent the entirety of Austrian patients with IEI. Thus, further participation by Austrian centres caring for patients with IEI as well as completeness of data is needed in order to provide statistically representative data.

Table of Contents

Abbreviations

ADA-SCID	adenosine deaminase deficiency severe combined immunodeficiency disorder
AGPI	Arbeitsgruppe für Pädiatrische Immunologie der Österreichischen Gesellschaft für Kinder- und Jugendheilkunde
AIRE	autoimmune regulator
ALPS	autoimmune lymphoproliferative syndrome
AMC	Academic Medical Centre Amsterdam
APECED	autoimmune polyendocrine syndrome type I
APSID	Asian Pacific Society for Immunodeficiency
AR-HIGM	autosomal recessive hyper immunoglobulin M syndrome
ASID	African Society for Immunodeficiencies
ATM	ataxia telangiectasia mutated
BTK	Bruton tyrosine kinase
CCI	Centre for Chronic Immunodeficiency
CCI	Center for Chronic Immunodeficiency
CD31+	cluster of differentiation 31+
CeMM	Centre for Molecular Medicine
CGD	chronic granulomatous disease
CID	combined immunodeficiency disorders
CIS	Clinical Immunology Society
CVID	common variable immunodeficiency disorder
DGS	DiGeorge Syndrome
DNA	deoxyribonucleic acid
DOCK 8	dedicator of cytokinesis 8
EBMT	European Society for Blood and Marrow Transplantation
ESID	European Society for Immunodeficiencies
FDA	U.S. Food and Drug Administration
FHLH	familial hemophagocytic lymphohistiocytosis
FOXP3	forkhead box protein 3
G-CSF	granulocyte-colony stimulating factor
GDPR	General Data Protection Regulation
GSD I	glycogen storage disease type I
GvHD	Graft-versus-host disease
HIES	hyper immunoglobulin E syndrome
HIV	human immunodeficiency viruses
HLA	human leukocyte antigen

HLH	hemophagocytic lymphohistiocytosis
HSCT	hematopoietic stem cell transplantation
ID	identifier
IEI	inborn errors of immunity
Ig	immunoglobulin
IgA	immunoglobulin A
IgD	immunoglobulin D
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IKT	Institute for Clinical Transfusion Medication and Immunological Genetics
IPEX	immunodysregulation polyendocrinopathy enteropathy X-linked
ISPID	Indian Society for Primary Immunodeficiency
IUIS	The International Union of Immunological Societies
JSIAD	Japanese Society for Immunodeficiency and Autoinflammatory diseases
LAD	leukocyte adhesion deficiency
LASID	Latin American Society for Immunodeficiencies
LMU	Ludwig Maximilian University of Munich
LRBA	lipopolysaccharide (LPS)-responsive and beige-like anchor protein
MPV	mean platelet volume
MSD	matched sibling donor
MUG	Medical University of Graz
MUW	Medical University of Vienna
NGS	Next Generation Sequencing
NK cells	natural killer cells
ÖGKJ	Österreichische Gesellschaft für Kinder- und Jugendheilkunde
PID	primary immunodeficiency disorders
RALD	RAS-associated autoimmune leukoproliferative disease
RAS	Rat sarcoma
RTE	recent thymic emigrants
SCETIDE	Stem Cell Transplantation for Immunodeficiencies in Europe
SCID	severe combined immunodeficiency disorders
SOPs	standard operating procedures
TCR	T cell receptor
TRAPS	tumor necrosis factor receptor-associated periodic syndrome
TREC	T cell receptor excision circles
UKPID	United Kingdom Primary Immunodeficiency Registry

UKPIN	United Kingdom Primary Immunodeficiency Network
US	the United States
WAS	Wiskott-Aldrich syndrome
WASp	Wiskott-Aldrich syndrome protein
WHO	World Health Organization
WIP	Wiskott-Aldrich syndrome protein-interacting protein
XLA	X-linked agammaglobulinemia
XLP	X-linked lymphoproliferative syndrome
X-SCID	X-linked severe combined immunodeficiency disorder

List of Figures and Tables

1 Introduction

1.1 Inborn errors of immunity

1.1.1 Introduction

Primary immunodeficiencies (PID), also referred to as inborn errors of immunity (IEI), can develop when host defense mechanisms do not function in a normal way due to an inherited defect in a gene (Murphy and Weaver, 2016; Picard *et al.*, 2018). As a result of this gene defect, one or more components of the innate or the adaptive immune system are impaired or can be eliminated (Arason, Jorgensen and Ludviksson, 2010; Murphy and Weaver, 2016). Patients suffering from primary immunodeficiencies can present with a broad spectrum of symptoms, such as an increased susceptibility to infections, malignancy, and inflammation (Arason, Jorgensen and Ludviksson, 2010; Bousfiha *et al.*, 2018), thus IEI are associated with frequent, recurring or persistent infections; however, patients suffering from IEI can also clinically present with signs of autoimmunity, autoinflammation (Arason, Jorgensen and Ludviksson, 2010), or malignancy (Mortaz *et al.*, 2016).

Apart from primary immunodeficiencies, there is also an acquired form of immunodeficiency, known under the term of secondary immunodeficiencies, which are the result of other factors, such as diseases or medication altering the immune system (Murphy and Weaver, 2016).

Generally, IEI represent a large and heterogeneous group which is steadily increasing in number and complexity and currently comprising more than 354 different conditions according to the 2017 Primary Immunodeficiency Diseases Committee Report by the International Union of Immunological Societies (Murphy and Weaver, 2016; Picard *et al.*, 2018). Within this group of disorders, 344 different gene defects have already been discovered (Picard *et al.*, 2018). Moreover, although this group of disorders is continually growing, primary immunodeficiencies are still being underdiagnosed and are occurring more frequently than generally thought (Bousfiha, Jeddane, Ailal, Benhsaien, *et al.*, 2013; Picard *et al.*, 2018), with a varying frequency regarding specific forms of PID depending on the country as well as the population (Notarangelo *et al.*, 2009). As studies suggest, the continually increasing prevalence of IEI could be explained by the growing awareness of

scientists, physicians, and the population as well as by improved forms of diagnostic testing (Kobrynski, Powell and Bowen, 2014).

Back in 1952, Ogden C. Bruton was the first one to officially describe an immunodeficiency disease (Hitzig, 2003). Practicing as a pediatrician at the Walter Reed Army Hospital in Washington, he published a paper accounting his clinical observation of a patient which was completely lacking gamma globulin in the blood, leading to missing antibody production in this patient (Hitzig, 2003; Murphy and Weaver, 2016). Due to Bruton being the first one to describe that condition and the fact that it is inherited X-linked, the first immunodeficiency was called Bruton's X-linked agammaglobulinemia (XLA) (Murphy and Weaver, 2016).

1.1.2 Classification

After the first description of a primary immunodeficiency disease in 1952, being followed by further observations of various different forms of IEI, the World Health Organization (WHO) first met in 1970 in order to conclude the wide range of conditions (Fudenberg *et al.*, 1971, 2010). The result of this committee was the presentation of the knowledge regarding primary immunodeficiencies at that time in the form of a report, which initially described 16 different types and furthermore already contained specific recommendations regarding diagnostic procedures and treatment (Fudenberg *et al.*, 1971).

Later, The International Union of Immunological Societies (IUIS) took the responsibility to publish a report including a classification of primary immunodeficiencies in 1999 following a meeting of the IUIS Scientific Committee in 1998 in Austria. In that classification, five different IEI categories were distinguished. (Rosen, FS; Eibl, M; Roifman, C; Fischer, A; Volanakis, J; Aiuti, F; Notarangelo, L; Kishimoto, T; Resnick, IB; Hammarstrom, L; Seger, R; Chapel, H; Cooper, MD; Geha, RS; Good, RA; Waldmann, TA; Wedgwood, 1999) The latest meeting of the responsible committee was held in February 2017, in London. In each of the committee meetings, there is a vote on whether a new disorder should be included in the classification. In their most recent publication, IEI are classified into 9 different categories based on the molecular defect that is responsible for the disorder. (Picard *et al.*, 2018)

In general, primary immunodeficiencies are classified according to the type of immune mechanism that is affected (Notarangelo, 2010). Thus, IEI can either affect the innate or the adaptive immune system, though defects in one component of the immune system can also affect other components as specific functions of certain components may have an influence on other functions (Notarangelo, 2010; Murphy and Weaver, 2016). IEI that lead to disorders of the adaptive immune system can affect major cells of that system, meaning T-cells, B-cells, or both, leading to combined immunodeficiencies. On the other hand, disorders of the innate immunity include phagocyte and complement defects. (McCusker, Upton and Warrington, 2018)

Disorders of the adaptive immunity can affect various parts. Depending on the cells that are impaired, several forms have been distinguished, such as T-cell (cellular) immunodeficiencies, B-cell (antibody-mediated) immunodeficiencies, combined immunodeficiencies (CID), and severe combined immunodeficiencies (SCID). (McCusker, Upton and Warrington, 2018) In the case that T-cells are affected, either their development, differentiation, or maturation can be impaired and therefore T-cell (cellular) immunodeficiency occurs (McCusker, Upton and Warrington, 2018), with the most severe form known as severe combined immunodeficiency (SCID) which happens when both T- and B-cells are affected (Murphy and Weaver, 2016; McCusker, Upton and Warrington, 2018).
The alteration of T-cells leads to conditions associated with a high susceptibility to various infectious agents which also highlights that T-cells are extremely important in the defense of the adaptive immune system against basically all antigens. Disorders affecting B-cells in their development are characterized by impaired antibody production. Therefore, patients suffering from B-cell defects cannot efficiently cope with infections by pyogenic bacteria as well as some viruses that cannot be neutralized due to missing antibodies. (Murphy and Weaver, 2016)

The innate immunity as the first line of defense against pathogens encompasses cells, such as neutrophils and macrophages, being responsible for phagocytosis and the subsequent elimination of pathogens. Other cells that belong to the innate immune system are dendritic cells, and complement proteins. (Murphy and Weaver, 2016; McCusker, Upton and Warrington, 2018) Disorders of the innate immunity can

affect all of those components, therefore leading to either phagocyte or complement defects (McCusker, Upton and Warrington, 2018).

Currently, besides disorders prone to infections, the heterogeneous group of IEI also comprises a variety of syndromes not mainly being associated with infections but rather with immune dysregulation or autoimmunity (Arason, Jorgensen and Ludviksson, 2010; McCusker, Upton and Warrington, 2018). Some autoimmune diseases are commonly present in patients with IEI (Fischer *et al.*, 2017), including disorders affecting T-regulatory cells, such as the immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome or systemic lupus erythematosus (Arason, Jorgensen and Ludviksson, 2010).

According to the 9 categories published by the IUIS, immunodeficiencies can be classified as immunodeficiencies affecting cellular and humoral immunity, combined immunodeficiencies with associated or syndromic features, predominantly antibody deficiencies, diseases of immune dysregulation, congenital defects of phagocyte number or function, defects in intrinsic and innate immunity, autoinflammatory disorders, complement deficiencies, as well as phenocopies of inborn errors of immunity (Picard *et al.*, 2018).

In the recent IUIS meeting, it was necessary to include two major changes to the existing classification as primary immunodeficiencies have been steadily increasing in number. Firstly, since the last publication of the classification it has been made possible to access the list of disorders on the IUIS website in order to do sorting, and secondly, the term *inborn errors of immunity* was established to describe primary immunodeficiency diseases. The reason for this was that the term *primary immunodeficiency* has some limitations, primarily being referred to as disorders in which infections are the main clinical manifestation. (Picard *et al.*, 2018)

Additionally, since 2013, the IUIS have been publishing another catalogue of IEI that is based on the immunological classification but focuses on the phenotypic features of each immunodeficiency (Bousfiha, Jeddane, Ailal, Al Herz, *et al.*, 2013). As the broad range of IEI can present with a variety of symptoms, the identification of those

disorders is a frequent struggle for medical personal (Bousfiha, Jeddane, Ailal, Al Herz, *et al.*, 2013; Costa-Carvalho *et al.*, 2014).

The newly introduced phenotypic classification facilitates the work of clinicians when they have to diagnose a certain kind of primary immunodeficiency. The main purpose of the classification is to guide physicians through the diagnostic procedure, including clinical features and laboratory results. (Bousfiha, Jeddane, Ailal, Al Herz, *et al.*, 2013)

Currently, the phenotypic classification, which was last published in the year 2017, includes 320 phenotypes commonly being associated with IEI based on the 9 main groups published in the 2017 update of the IUIS classification. Those phenotypes can differ significantly, including infection, malignancy, allergy, autoimmunity, or auto-inflammation. (Bousfiha *et al.*, 2018)

What is more, only recently a smartphone application was developed that provides the phenotypic classification published by the IUIS. Being divided into three sections, the application includes many features, such as classification tables, the possibility to search diseases by names or manifestations as well as guidelines on how to explore IEI by basic laboratory tests. (Jeddane *et al.*, 2017)

As mentioned above, since the diagnosis is still a struggle for non-PID specialists (Bousfiha, Jeddane, Ailal, Al Herz, *et al.*, 2013), the main aim of the application is to facilitate the diagnostic procedure at the bedside (Jeddane *et al.*, 2017).

1.1.3 Clinical presentation

To start with, patients with IEI commonly present with a history of repeated infections in regard to different organs (Costa-Carvalho *et al.*, 2014; Murphy and Weaver, 2016), however; the clinical presentation of IEI can be of a broad range and there are forms that can manifest with a more complex phenotype including various other symptoms besides immunodeficiency (Notarangelo, 2010; McCusker, Upton and Warrington, 2018). In general, a diagnosis of IEI should be considered when patients show one symptom or a combination of symptoms such as recurrent sinus or ear infections, or pneumonias within a period of one year, unusual infections in general, failure to thrive, poor response to prolonged use of antibiotics, persistent thrush or skin abscesses or if there is already another person of the patient's family suffering from IEI (Costa-Carvalho *et al.*, 2014; McCusker, Upton and Warrington, 2018).

Furthermore, a positive family history of recurrent infections may be a strong indicator of an IEI. On the other hand, even the absence of recurrent infections in siblings of a patient may indicate an IEI as environmental factors may not be the causing agents regarding a patient's history of repeated infections. (Costa-Carvalho *et al.*, 2014).

Moreover, as autoimmunity and inflammatory diseases are commonly associated with IEI (Arason, Jorgensen and Ludviksson, 2010; Costa-Carvalho *et al.*, 2014; Fischer *et al.*, 2017; McCusker, Upton and Warrington, 2018) with, as studies showed, the risk of inflammatory bowel disease and autoimmune diseases being 80 and 10 times higher respectively in patients with IEI (Fischer *et al.*, 2017), it should be evaluated in specific cases whether patients with multiple autoimmune or inflammatory diseases may possibly have an immunodeficiency as well (Arason, Jorgensen and Ludviksson, 2010; Costa-Carvalho *et al.*, 2014; Fischer *et al.*, 2017; McCusker, Upton and Warrington, 2018).

Indeed, in many cases patients with IEI simply present with ordinary infections, such as rhinosinusitis, otitis media, or diarrhea and may therefore remain undetected when first being examined by primary-care clinicians (Costa-Carvalho *et al.*, 2014; McCusker, Upton and Warrington, 2018).

According to Prof. Dr. Wahn, there are 12 warning signs regarding the clinical presentation of patients that require the consideration of an IEI and he published a list, stating that in the following situations in young patients, clinicians should consider a primary immunodeficiency (Wahn, 2018):

1.	Positive family history of primary immunodeficiencies
2.	Eight or more purulent otitis media per year
3.	Two or more severe sinusitis per year
4.	Two or more pneumonias within a year
5.	Ineffective calculated therapy with antibiotics within a period of two or more months
6.	Complications associated with live vaccinations (especially with the vaccine against BCG, rotavirus, and polio)
7.	Recurrent or systematic infections with atypical mycobacteria
8.	Recurrent deep skin or organ abscesses
9.	Two or more visceral infections (meningitis, osteomyelitis, septic arthritis, empyema, sepsis)

10.	Persistent candida infections of the skin or mucosa after the first year of life
11.	Unclear erythema or erythroderma in newborn patients or young infants
12.	Failure to thrive in young infants either in combination with or without chronic diarrhea

Table 1: List of 12 warning signs of IEI according to (Wahn, 2018)

According to additional literature on warning signs of primary immunodeficiencies, a specific emphasize is put on the fact that not solely the number of infections but also their severity must be considered when attending patients with possible IEI. Another important factor concerning primary immunodeficiencies is the type of infectious disease. Low pathogens, for instance atypical mycobacteria or toxoplasma, are more likely to cause infections in patients with IEI; thus, infections with those kind of bacteria are possible indicators of an IEI. (Costa-Carvalho *et al.*, 2014)

Furthermore, some infections occur more frequently in specific forms of IEI, for instance, bacterial infections transmitted by the blood are more commonly observed in patients with a primary antibody deficiency, especially in agammaglobulinemia and CVID (Fried and Bonilla, 2009). Concerning other types of infections associated with specific forms of IEI, complement deficiencies show an increased risk of developing infections caused by Neisseria meningitidis, while T cell deficiencies and SCID are more susceptible to infections due to atypical mycobacteria or salmonella (Costa-Carvalho *et al.*, 2014). Moreover, HLH syndrome, both primary and secondary HLH, and XLP syndromes are frequently associated with severe infections from Epstein-Barr virus and T and NK cell deficiencies show an increased risk for infections due to Herpes (Costa-Carvalho *et al.*, 2014; Worth, Houldcroft and Booth, 2016). Finally, chronic granulomatous disease (CGD) and Hyper IgE syndrome (HIES) may present with infections caused by Streptococcus aureus or gram-negative bacteria (Costa-Carvalho *et al.*, 2014).

In relation to pulmonary manifestations, patients with IEI have a high risk of developing pulmonary complications. In fact, infections of the respiratory tract frequently represent the initial clinical presentation and are additionally associated with a high morbidity and mortality in patients with IEI. (Costa-Carvalho *et al.*, 2014; Yazdani *et al.*, 2017)

The spectrum of respiratory infections can be of a broad range and can affect the upper as well as the lower respiratory tract. Manifestations can vary from acute and

chronic infections, such as otitis media or rhinosinusitis, to abnormalities of anatomical structures, allergic reactions, and lymphoproliferative disorders. For instance, laryngeal angioedema, which represents a severe pulmonary complication of the upper respiratory tract due to an obstruction leading to asphyxiation, is commonly observed in patients with an IEI. (Yazdani *et al.*, 2017)

Pneumonia, a pulmonary complication of the lower respiratory tract, is considered as a major warning sign according to the Jeffrey Modell Foundation when occurring in children more frequently than two times a year (Arkwright and Gennery, 2011; Yazdani *et al.*, 2017). Moreover, pneumonia is additionally associated with opportunistic pathogens and can frequently be of a severe character when affecting patients with IEI. Other manifestations of the upper pulmonary tract are bronchitis, bronchiectasis, interstitial lung diseases, or pulmonary adenopathy and malignancies. (Yazdani *et al.*, 2017)

As far as gastroenterological manifestations are concerned, patients with IEI have an increased risk for developing disorders of the gastrointestinal tract, such as acute or chronic diarrhea, malabsorption, atrophic gastritis, pernicious anemia, lymphoid hyperplasia or inflammatory bowel diseases (Wood *et al.*, 2007; Agarwal and Mayer, 2013). The manifestation of gastroenterological disorders in patients with IEI can be explained by the fact that the highest number of lymphocytes can be found in the gastrointestinal tract, displaying the largest lymphoid organ (Agarwal and Mayer, 2013). Primary immunodeficiencies, that are commonly associated with an increased risk for gastrointestinal involvement, comprise CVID, SCID, chronic granulomatous disease (CGD), IPEX syndrome, interleukin-10-receptor deficiency, as well as Wiskott-Aldrich Syndrome (Wood *et al.*, 2007; Agarwal and Mayer, 2013). For instance, according to a review carried out by Agarwal and Mayer, in approximately 50% of cases CGD presents with a disorder of the gastrointestinal tract (Agarwal and Mayer, 2013).

Furthermore, as already mentioned above, autoimmune manifestations are also frequently observed in patients with primary immunodeficiencies, displaying a challenge in diagnosis for rheumatologists (Goyal *et al.*, 2009; Fischer *et al.*, 2017). Omenn Syndrome, for instance, presents with an altered lymphocyte development, and regularly includes autoimmune manifestations, such as lymphadenopathy, splenomegaly, erythroderma, or autoimmune hepatic dysfunction (Goyal *et al.*,

2009). Other primary immunodeficiencies associated with autoimmunity will be explained in more detail in the following section.

1.1.4 Inborn errors of immunity and associated morbidity

In the following section, inborn errors of immunity that are frequently associated with autoimmunity and malignancy will be discussed in more detail.

1.1.4.1 Inborn errors of immunity and autoimmunity

As former research has shown, IEI are frequently not only linked to autoimmunity (Arason, Jorgensen and Ludviksson, 2010; Fischer *et al.*, 2017) but also present for the first time in various cases in the form of autoimmune diseases (Amaya-Uribe *et al.*, 2019).

Since polygenetic IEI represent a quite diverse and complex group of diseases concerning clinical presentation and immunological dysfunction, monogenetic IEI are of greater value for understanding the connection between IEI and autoimmunity. The reason for this is that monogenetic immunodeficiencies, which already exist from birth, are less impacted by environmental factors throughout a patient's lifetime than it is the case with polygenetic immunodeficiencies. Autoimmunity has been observed especially in immunodeficiencies with defects of T-regulatory cells, immunodeficiencies with impaired function of components of the classical pathway of complement as well as in such ones resulting from defects in lymphocyte apoptosis. (Arason, Jorgensen and Ludviksson, 2010)

The development of autoimmune diseases in IEI can be explained by the fact that mutations in specific genes can affect the activity of various cell types or signalling molecules. Furthermore, the clinical presentation of IEI can be similar to that of autoimmune diseases and the distinction between symptoms of those conditions can become difficult. (Amaya-Uribe *et al.*, 2019)

A retrospective study, carried out by the aid of the French national PID registry in 2017, showed that at least one autoimmune or inflammatory manifestation was observed in 26.2 % of explored patients, highlighting the strong link between IEI and autoimmune diseases. For example, in the group of autoimmune diseases, the observed patients with an IEI displayed a risk for autoimmune cytopenia 120 times higher compared to the general population in Western Europe. Furthermore, the relative risks were also found to be higher in children suffering from an IEI compared

to a healthy paediatric control group, especially the risks for inflammatory bowel disease and arthritis. (Fischer et al., 2017)

Various specific and unspecific mechanisms of autoimmunity in IEI were identified and summarized for autoimmune cytopenias (Seidel, 2014) and other autoimmune diseases (Grimbacher *et al.*, 2016).

Due to the help of genetic analysis it could be concluded that specific mutations occurring in IEI genes are crucial in the process of developing various diseases linked to autoimmunity. Some of those mutations occur in genes such as in BTK (Bruton tyrosine kinase), resulting in X-linked agammaglobulinemia, others occur in FOXP3 resulting in X-linked Immune dysregulation polyendocrinopathy-enteropathy, or in AIRE resulting in autoimmune polyendocrinopathy, or in ATM resulting in ataxia-telangiectasia. Other mutations in IEI genes which are linked to autoimmune diseases are observed in WASp, leading to Wiskott-Aldrich syndrome, or in lipopolysaccharide responsive beige-like anchor LRBA. (Amaya-Uribe *et al.*, 2019)

1.1.4.2 Inborn errors of immunity and malignancy

As mentioned earlier, some types of inborn errors of immunity can clinically present with different types of cancer and therefore it can be concluded that some immunodeficiencies show an increased risk of malignancy (Mortaz *et al.*, 2016; McCusker, Upton and Warrington, 2018). On the one hand, one reason for an enhanced risk lies in DNA repair processes that do not work properly in some forms of IEI, on the other hand, there are still mechanisms leading to increased cancer risk that remain unclear (Mortaz *et al.*, 2016). Furthermore, environmental triggers may also play a role concerning the etiological factors of the development of malignancies in some forms of IEI and suggest a multifactorial genesis (Riaz *et al.*, 2019). According to a paper published in 2018, the same cell type or a type with a similar molecular basis as is causing a primary immunodeficiency is also responsible for malignant transformation of cells (Hauck *et al.*, 2018).

In general, patients with an IEI carry a greater risk for developing hematopoietic malignancies instead of solid tumours according to a study carried out by the United States Immune Deficiency Network Registry (Mayor *et al.*, 2018).

In the group of hematopoietic malignancies, lymphomas tend to be the most common type of cancer. Among those, especially B cell lymphomas are majorly

occurring with non-Hodgkin Lymphoma, diffuse large B cell lymphoma, and Hodgkin lymphoma being the most frequent ones. (Riaz *et al.*, 2019)

The most common form of IEI, the common variable immunodeficiency (CVID), shows besides an increased risk for autoimmune diseases a strong link to malignancy with an enhanced risk compared to the general population (Mortaz *et al.*, 2016; McCusker, Upton and Warrington, 2018).

1.1.5 Epidemiology

Since primary immunodeficiencies display a group of disorders that remains underdiagnosed in various countries, the attempt to measure their incidence, prevalence, morbidity, and mortality still displays a struggle and few epidemiological data exists (Gathmann *et al.*, 2009). Additionally, the incidence of IEI is varying between different countries with a higher frequency observed in groups of a certain ethnicity (Notarangelo *et al.*, 2009). For instance, a study carried out in order to evaluate the incidence of all types of typically severe combined immunodeficiencies, revealed a higher incidence of those disorders in a consanguineous compared to a non-consanguineous population (Broides *et al.*, 2017).

Moreover, according to a study carried out in the United States between 2001 and 2007, which represents the largest population-based study of IEI in the US, the estimated prevalence of any diagnosis of an IEI varied between 5.1:10.000 and 3.9:10.000 depending on the database that was used for the analysis, and an increase in prevalence was observed (Kobrynski, Powell and Bowen, 2014). As for Europe, according to the 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity, the prevalence of IEI cannot be specifically estimated since new disorders are rapidly being discovered due to next-generation sequencing and because recently discovered immunodeficiencies have yet only been diagnosed in a small number of patients (Picard *et al.*, 2018).

1.1.6 Diagnosis

To begin with, due to the fact that the number of IEI has been steadily increasing, the diagnostical procedure displays a challenge for many clinicians, and especially for those who are not specialized in those disorders (Bousfiha, Jeddane, Ailal, Al Herz, *et al.*, 2013). According to the Immune Deficiency Foundation, which carried out its first national survey of patients and specialists in 1995, the rate of

hospitalization of patients with IEI after diagnosis dropped from 70% to 48% (Immune Deficiency Foundation, 2001).

1.1.6.1 Comprehensive medical history and physical examination

Generally, if a diagnosis of IEI is suspected in patients presenting warning signs as suggested by the Jeffrey Modell Foundation, the diagnostic procedure should start with a complete medical history of the patient since it may already indicate which mechanisms of immunodeficiency may present the cause of the symptoms of a patient (Notarangelo, 2010; Arkwright and Gennery, 2011; Bonilla *et al.*, 2014). For instance, in the case of infections, taking the medical history needs to encompass the type, the location, the age at onset, as well as the severity of those (Notarangelo, 2010). Moreover, due to the monogenetic character of various forms of IEI, an additional family history can be of a great value (Notarangelo, 2010; Bonilla *et al.*, 2014). More precisely, important factors that need to be evaluated regarding family history are recurrent infections of family members, siblings who diseased in early childhood, or whether there is already a relative with a diagnosed IEI; in fact, even the absence of infections in siblings must be evaluated (Bonilla *et al.*, 2014).

Additionally to gaining information through medical history as well as family history, performing a physical examination of a patient also has to be included in the diagnostic process (Richardson *et al.*, 2018).

1.1.6.2 Laboratory tests

Regarding laboratory tests, the most useful first-line immunological investigation includes a complete blood count and blood smear, including a differential count of leucocytes and MPV, a lymphocyte subset analysis, and serum immunoglobulin levels. The absolute and relative number of B cells, T cells, T-helper cells, T-cytotoxic cells, NK cells, and activated T cells are measured by the help of antibodies. (Madkaikar, Mishra and Ghosh, 2013; Locke, Dasu and Verbsky, 2014; McCusker, Upton and Warrington, 2018)

Since a broad range of laboratory tests are available, the decision on a specific type of test can be difficult; however, the decision should be guided by the presenting symptoms of a patient (Madkaikar, Mishra and Ghosh, 2013).

Depending on the laboratory results, there may already be clues for certain immunodeficiencies. For instance, combined immunodeficiencies (CID) regularly show low T cells, while predominantly antibody disorders generally present with

normal T cell counts and low or absent B cells. Moreover, an abnormality in neutrophils, either their number of function, indicate a possible diagnosis of a phagocytic disorder. After those initial laboratory results, advanced testing is required. (Madkaikar, Mishra and Ghosh, 2013)

In the case that a disorder of humoral immunity is suspected, screening tests include quantitative analysis of immunoglobulins (IgG, IgA, IgM, IgE) and the results must be adjusted depending on the age of a patient. Moreover, antibody titers need to be evaluated, and concerning results require further testing such as flow cytometry or genetic testing. (Locke, Dasu and Verbsky, 2014)

Suspecting a T cell or combined T/B cell defect, the absolute lymphocyte count is a crucial part of laboratory testing, which must also be adjusted depending on patient age. However, as a low number of T cells can be masked by transplacental transfer of maternal cells, analysis of T markers of cell activation should be done. Following the lymphocyte count, flow cytometry is an important step in the diagnostic procedure. Moreover, immunophenotyping displays an essential part of diagnosis especially for SCID. Furthermore, a possible diagnosis of disorders of neutrophils, after initial laboratory testing, should be further evaluated by morphological analysis of neutrophils and an absolute neutrophil count. Moreover, disorders of the complement system can be detected by two different laboratory tests, evaluating either the function of the classic complement cascade of the alternative pathway. Finally, immune dysregulation disorders require, besides initial complete blood count, the evaluation of immunoglobulins, which generally shows elevated IgE levels. Moreover, flow cytometry may also be valuable for identifying those disorders. (Locke, Dasu and Verbsky, 2014)

1.1.6.3 Flow cytometry

Flow cytometry has evolved as a valuable tool in the diagnosis of primary immunodeficiencies. By flow cytometry, the immune system can be evaluated and certain cell populations, cell membranes, intracellular and intranuclear proteins can be assessed. Since flow cytometry is considerably faster than DNA analysis, it provides clinicians with rapid results in the diagnosis of IEI and therefore displays an alternative to genetic testing. (Kanegane *et al.*, 2018)

Flow cytometry facilitates the diagnosis of various forms of IEI. More precisely, in the group of combined immunodeficiencies, SCID, Omenn syndrome, X-linked hyper-IgM syndrome are, besides others, among the disorders that can be detected

using flow cytometry. As a result of flow cytometry analysis, SCID, for instance, can show an absence of T cells, decreased or absent $CD31^+$ RTE, or perturbations in naïve and memory T cells. Furthermore, there are combined immunodeficiencies with syndromic features, such as Wiskott-Aldrich syndrome or HIES, that can also be detected via flow cytometry. Moreover, antibody deficiencies, that can be detected by flow cytometry, include XLA, CVID, or AR-HIGM. In the group of disorders associated with immune dysregulation, ALPS XLP, IPEX syndrome, LRBA deficiency, and FHLH are candidates for an analysis using flow cytometry. Finally, various specific IEI associated with neutrophil defects, intrinsic and innate immune defects, complement defects as well as phenocopies of IEI can be assessed by the method of flow cytometry. (Knight, 2019)

1.1.6.4 Genetic analyses

Due to the availability of genetic analyses, gene defects that are the cause of a primary immunodeficiency can be detected. To date, there are different forms of genetic analyses in use. Those include targeted gene sequencing, whole exome sequencing, whole genome sequencing or transcriptome analysis. (Richardson *et al.*, 2018)

What is more, since 2011, Next Generation Sequencing (NGS) is available in the diagnostic process of inborn errors of immunity, which displays a fast method of genetic analysis that can sequence an extremely high number of DNA fragments at a time (Meyts *et al.*, 2016).

1.1.6.5 New-born screening for inborn errors of immunity

In the last decades, screening programs in general have evolved drastically and are currently already available for certain inborn errors of immunity in various regions (King and Hammarström, 2018). Early screening methods provide clinicians with the possibility to recognize IEI at an early stage and treatment can be available for patients before complications and long-term effects can occur, especially in the case of SCID which requires timely diagnosis and immediate treatment (Mahlaoui *et al.*, 2017; King and Hammarström, 2018).

SCID can be detected via specific assays using T cell receptor excision circles (TREC) which describe circular pieces of episomal DNA being formed during T cell receptor (TCR) rearrangement in naïve T cells. Therefore, they can indicate recent emigrants of the thymus. In 2008, the first patient was transplanted after a

successful SCID new-born screening had been performed. Besides SCID, other primary immunodeficiencies that can be identified using screening methods include specific forms of congenital B cell deficiency disorders, such as XLA or XLA-like disorders, combined immunodeficiency, ataxia telangiectasia, DOCK 8 deficiency, Nijmegen breakage syndrome, or cartilage hair hypoplasia. (King and Hammarström, 2018)

1.1.7 Treatment

Currently, there are different types of treatment available for patients with primary immunodeficiencies, including immunoglobulin therapy, antibiotics, hematopoietic stem cell transplantation, and gene therapy (Madkaikar, Mishra and Ghosh, 2013; Yarmohammadi, 2014; Mahlaoui *et al.*, 2017).

In the decision on a specific treatment type, clinical presentation, the immune function of a patient, and the underlying genetic defect have to be considered. In many cases, treatment consists of anti-infectious prophylaxis and, in the case that patients are already presenting with infections, the aggressive treatment of those. (Mahlaoui *et al.*, 2017)

For the majority of patients, a replacement therapy with immunoglobulins represents the standard treatment type (Mahlaoui *et al.*, 2017; Marciano and Holland, 2017; McCusker, Upton and Warrington, 2018). Another treatment option is hematopoietic stem cell transplantation (HSCT), requiring an HLA-matching donor which can be a rather successful and curable treatment for patients with SCID, combined defects of T and B lymphocytes, isolated T lymphocyte deficiencies, and patients with disorders of the innate immunity (Gennery, 2014). Moreover, in the past two decades, gene therapy has evolved as a promising treatment type for patients for which no HLA-matching donor can be found (Booth *et al.*, 2019).

1.1.7.1 Immunoglobulin replacement

Immunoglobulin replacement displays the main type of treatment for patients with primary immunodeficiencies (Yarmohammadi, 2014). The first time that an immunoglobulin replacement therapy was applied in the context of primary immunodeficiencies was in 1952, when Bruton discovered the first case of a primary immunodeficiency, which was in fact agammaglobulinemia, treated effectively by the subcutaneous injection of an immunoglobulin and marking the beginning of immunoglobulin replacement therapy (Hitzig, 2003; Yarmohammadi, 2014).

Later, intravenous immunoglobulin therapy also became available. Immunoglobulin replacement aims in patients with primary immunodeficiencies to replace antibody deficiencies and therefore prevent infections and displays a successful type of treatment. Donors of immunoglobulins must be tested for hepatitis B and C, HIV, syphilis, and various other viruses. The dosage of immunoglobulins varies according to the receiving patient and higher doses are necessary in some cases. Generally, patients are receiving infusions every month, though intervals can also vary depending on whether infections continue after administration. Possible adverse effects of immunoglobulin replacement may include mild ones, such as headache, chills, backache, myalgia, fever, nausea, or wheezing. More serious side effects of the therapy are generally uncommon and may include anaphylaxis, thrombosis, myocardial infarction, aseptic meningitis, arrhythmias, and seizure. Regarding monitoring of immunoglobulin therapy, serum levels reach a steady-state after the sixth dose and levels should be assessed every six months. (Yarmohammadi, 2014) For most of the patients, immunoglobulin therapy represents a long-term type of treatment. For this reason, the quality of the used products in the treatment is continuously improving due to a steady advance in production. (Krivan *et al.*, 2017) Moreover, in relation to the route of administration, today immunoglobulin therapy can be administered intravenously or subcutaneously, with the subcutaneous route as a home-bases therapy offering a greater independence and flexibility of patients as well as fewer side effects (Yarmohammadi, 2014; Krivan *et al.*, 2017).

According to a study with IEI patients receiving immunoglobulins conducted in France, replacement therapy in general contributes to a higher quality of live in a considerable manner. Though immunoglobulins can be administered either at home or at a hospital, according to the former mentioned study, quality of live was higher for those patients receiving therapy at home. (Bienvenu *et al.*, 2016)

1.1.7.2 Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation is considered to be a curing and potentially lifesaving type of treatment and is applied to patients with primary immunodeficiencies with the aim of replacing unhealthy stem cells with a genetic defect, for instance malignant, absent, or defective cells, that would further be the cause of an immunodeficiency. The unhealthy stem cells are replaced by healthy cells. (Gennery, 2014)

In order to provide HSCT as a treatment option for a patient, an HLA-identical allogeneic donor must be found, displaying a crucial factor for the performance of HSCT (Gennery, 2014; Kekre and Antin, 2014).

Finding a matching donor is essential; otherwise, the recognition of non-self HLA molecules may result in the rejection of allografts and graft-versus-host disease in immunocompromised patients where T lymphocytes belonging to the donor recognize the recipient as foreign, further rejecting the patient. The source of the healthy pluripotent stem cells can be bone marrow, placental blood from umbilical cord, or peripheral blood after stem cells were mobilized with granulocyte-colony stimulating factor (G-CSF). Subsequently, after developing into erythrocytes or precursors of megakaryocytes or leukocytes, the former pluripotent stem cells are used to replace the unhealthy stem cells in the course of HSCT. (Gennery, 2014)

According to a trial including patients receiving tissue from unrelated donors, no significant difference was found regarding survival rate between peripheral blood and bone marrow recipients (Anasetti *et al.*, 2012).

Regarding the indications of HSCT in patients with an IEI, HSCT is primarily considered in the treatment of SCID, but is also applied to patients with combined defects of T and B lymphocytes, isolated T lymphocyte deficiencies, and patients with disorders of the innate immunity (Gennery, 2014). In fact, for patients with SCID, HSCT displays the most successful type of treatment since it is widely available and potentially curative (Wahlstrom, J.T., Dvorak, C.C. & Cowan, 2015).

A timely indication of HSCT is important since complication rates increase with age and pre-existing infection or damage of organs (Gennery, 2014). Moreover, regarding timing of HSCT, due to new-born screening for SCID, which is recommended in most developed countries, HSCT can be provided at a very early time and increase the survival chances for those patients (Gaspar *et al.*, 2014).

Considering the complications of HSCT, there are certain problems that can arise in the period after transplantation, either in the time period shortly after transplantation, or in the long-term. While GvHD generally represents the most common and most severe complication of HSCT, in the treatment of primary immunodeficiency HSCT is used to restore immune function; thus, the risk of GvHD is generally minimized. Furthermore, marrow aplasia can occur, especially in patients receiving stem cells from umbilical cord, requiring a longer post-transplant erythrocyte and platelet transfusion than in other patients. A potentially life-

threatening complication is a hepatic veno-occlusive disease, leading to hepatomegaly, ascites, fluid retention, gain of weight, and hyperbilirubinemia in the period of one month after transplantation. Other complications include thrombotic microangiopathy, idiopathic pneumonitis, engraftment syndrome, haemorrhagic cystitis, mucositis, and infection. Infection still displays an important complication, contributing frequently to transplant-related mortality. (Gennery, 2014)

1.1.7.3 Gene therapy

Although HSCT is a curative and thus successful type of treatment for patients with primary immunodeficiencies when an HLA-matched donor is available, there are still a certain amount of cases where no suitable donor can be found. In those cases, gene therapy is considered as a valuable form of alternative treatment of a primary immunodeficiency. (Booth *et al.*, 2019)

Moreover, compared to a transplantation with a non-HLA-identical donor, gene therapy has proved to be the more efficient type of treatment (Mukherjee and Thrasher, 2013).

The first time that gene therapy was used in the treatment of an immunodeficiency was already two decades ago in 1990, when two children diagnosed with adenosine deaminase deficiency (ADA-SCID) received gene therapy in the course of a trial. According to the US Food and Drug Administration (FDA), gene therapy is characterized by the effect of transcription and/or translation of transferred genetic material and/or by integrating into the host genome. The administered products can be nucleic acids, viruses, or genetically engineered microorganisms. Furthermore, those products either alter cells in vivo or ex vivo before being administered to a patient. (Wirth, Parker and Ylä-Herttuala, 2013)

Though initially gene therapy was only used in the treatment of ADA-SCID, the range of primary immunodeficiencies that can be considered for gene therapy has widened (Wirth, Parker and Ylä-Herttuala, 2013). Today, gene therapy is used in the treatment of ADA-SCID, X-linked SCID (X-SCID), chronic granulomatous disease (CGD) as well as Wiskott-Aldrich syndrome (WAS) (Booth *et al.*, 2019). In fact, according to a trial, gene therapy proved to be considerably effective in the treatment of ADA-SCID since eight of nine patients in the corresponding trial were able to live without enzyme-replacement therapy after gene therapy treatment (Aiuti *et al.*, 2009). However, though gene therapy proved to be a safe type of treatment for patients with ADA-SCID, concerning the treatment of patients with X-SCID, a risk

for acute leukaemia was revealed in the course of a trial (Aiuti *et al.*, 2009; Hacein-Bey-Abina *et al.*, 2010).

What is more, besides paediatric patients, which were initially the main patient group considered for gene therapy, recently older patients were also treated successfully by gene therapy (Booth *et al.*, 2019).

1.2 The European Society for Immunodeficiencies (ESID) Registry

1.2.1 Introduction

Primary Immunodeficiencies use to be a great challenge in diagnosis for immunologists and doctors as their symptoms can vary in a broad range. Due to this, it is substantial to gather as much information as possible about the different types of immunodeficiencies in order to facilitate physicians in the process of diagnosis and treatment of those disorders. (Kindle, 2007)

Moreover, for a long period of time physicians and scientists caring for patients suffering from immunodeficiencies have highlighted the importance of an international collaboration regarding diagnosis and treatment of immunodeficiencies. Thus, in the 1970s the European Group for Immunodeficiencies was established and since 1994 that collaboration is known as the European Society for Immunodeficiencies (ESID), which contributes as a non-profit organization in order to improve the exchange of information about different aspects concerning immunodeficiencies between medical staff. (Kindle, 2007; Gennery *et al.*, 2018)

Organized in seven working parties, with Inborn Errors, Clinical, Education, Genetics, Registry, ESID Juniors, and PID Care in Development being those parties, ESID has a variety of purposes and aims at creating educational programs for health care staff in order to help them facing the difficulties that come along with the management of primary immunodeficiencies (European Society for Immunodeficiencies, 2019).

Apart from the European Society for Immunodeficiencies, further collaborations with a similar mission have been established by other countries as well (Gennery *et al.*, 2018). For example, North and South America were among the first countries to establish such collaborations with the foundation of the Clinical Immunology Society (CIS) in North America (Fahey, 2011) as well as the Latin American Society for Immunodeficiencies (LASID), being formed in 1993 with the aim of studying the frequency of primary immunodeficiencies and improving knowledge about those diseases (Zelazko *et al.*, 1998).

Additionally, later in 2008, the African Society for Immunodeficiencies (ASID) was created. Finally, the Asian continent joined the nationwide efforts concerning

improvement in the care of immunodeficiencies with the creation of the Asian Pacific Society for Immunodeficiency (APSID) in 2016. Furthermore, in the last period various other groups such as the Arab Society for Primary Immunodeficiencies, the Indian Society for Primary Immunodeficiency (ISPID) and the Japanese Society for Immunodeficiency and Autoinflammatory diseases (JSIAD) have joined the international mission to improve care of immunodeficiencies. (Gennery *et al.*, 2018) Since the establishment of the previously mentioned societies, it has become clear that there exist disparities regarding the level of care of immunodeficiencies within a certain country as well as internationally, highlighting the importance of partnerships (Gennery *et al.*, 2018).

In 2004, The European Society for Immunodeficiencies set up an online registry that should contribute to epidemiological research, which displayed a great struggle due to the diversity of IEI, the great number of different genes involved, as well as the fact that specific forms of IEI are not very common with little existing data (Gathmann *et al.*, 2009). The established registry, the ESID registry, works as an internet-based database with the aim to function as a platform where data on European patients with primary immunodeficiencies including their treatment can be collected (Grimbacher, 2014). Used for long-term documentation, the registry is aimed at improving scientific research (Guzman *et al.*, 2007). Before it was founded, data had only existed in paper-based form (Grimbacher, 2014). Within the constantly updated ESID registry, clinical as well as laboratory patient data can be found (Gathmann *et al.*, 2009). Currently, the ESID registry includes data on more than 25,000 patients with IEI (Seidel *et al.*, 2019). Since the ESID registry was set up in 2004, the number of registered cases has been steadily increasing, from approximately 2400 documented patients according to a first report published in 2006 (Eades-Perner *et al.*, 2007) to approximately 19 400 documented ones in a report of the registry of 2014 (Grimbacher, 2014). Moreover, the ESID registry also comprises data from the United Kingdom Primary Immunodeficiency Network (UKPID) (Edgar *et al.*, 2014).

Moreover, a team responsible for the maintenance and improvement of the ESID registry, the ESID Registry Working Party, has been created. As its main purposes, the working party helps members with technical problems, establishes continuously updated lists of different disorders, provides data analysis, or deals with

documenting centres that encounter problems with ethical issues. (European Society for Immunodeficiencies (ESID), 2019b) One major contribution of the working party to the ESID registry is the establishment of working definitions for clinical diagnosis of IEI, which have been regularly created since 2011 by the corresponding team (Seidel *et al.*, 2019). The criteria can be found on the website of the ESID Registry (ESID Registry Working Party, 2019a).

In July 2019, the ESID online registry[1] contained data on 174 distinct inborn errors of immunity and 309 identified genes can be found in the registry, according to a document containing an updated list of diseases and genes published on the website of the ESID registry (Gathmann, 2019) .

1.2.2 Mission of the ESID registry

The main purpose of the ESID registry is to display a platform that can be accessed easily by physicians and researchers from different countries within Europe as well as some countries from other continents that are taking part in the registry (Grimbacher, 2014; Seidel *et al.*, 2019). The platform should enable its users to access data in order to use it for clinical trials and research projects (Seidel *et al.*, 2019). By doing so, ESID aims at answering questions concerning the epidemiology of IEI that have been considered as being a great challenge by clinicians and researchers. The broad range of different forms of IEI as well as the constantly evolving new disorders demand for a platform where data can be collected and being updated constantly in order to enable long-term documentation of patients, displaying one of the main missions of the ESID registry. (Gathmann *et al.*, 2009) Moreover, the registry helps to connect various centers caring for patients with inborn errors of immunity, enabling researchers to perform multi-centric trials (Gathmann *et al.*, 2009; Seidel *et al.*, 2019).

1.2.3 Participating countries

Regarding the countries that are currently participating in the ESID registry, the website of the registry provides a complete list of countries with documenting centres. Currently, 31 countries have been already documenting to the ESID registry. More specifically, the participating countries include, in alphabetical order, Austria, Belarus, Belgium, Croatia, Czech Republic, Egypt, Estonia, France, Germany, Greece, Hungary, the Islamic Republic of Iran, Ireland, Israel, Italy,

[1] https://cci-esid-reg.uniklinik-freiburg.de/EERS

Lithuania, Netherlands, Norway, Poland, Portugal, Romania, the Russian Federation, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, and finally the United Kingdom. (European Society for Immunodeficiencies (ESID), 2019c)

1.2.4 Structure of the registry

The storage of the patient data of the ESID registry happens in Freiburg, Germany (Kindle, 2007). Although there is the possibility to access a certain amount of data publicly at the web page of the ESID registry, gaining more detailed information is limited to ESID registry members owning a password and a username. Moreover, ESID registry members have as well the possibility to analyze data of the ESID database using their login. Additionally, it is also possible for third parties doing research to access the data. In order to get access, researchers must submit a proposal to the ESID registry working party, or a contract can be set up with the ESID allowing researchers to get access to the registry. (Seidel *et al.*, 2019)

The database was primarily structured according to the existing categories of immunodeficiencies, currently being 7 different categories. Each IEI diagnosis has its own sub-registry where a patient is documented with his main disease. Generally, in all those sub-registries exist the same fields for entering data. Those fields include information on diagnosis, gender, and age of a patient at the time of diagnosis. Additionally, there are fields about whether a case is sporadic or familial, about current medication, treatment side effects, basic laboratory values, and genetic data. (Kindle, 2007)

Moreover, there are different disease-specific registries included in the ESID online database, which all share a common dataset (Guzman *et al.*, 2007).

In 2014, the registry was restructured in order to provide higher quality and completeness of the collected data. In the new database, there are three levels of data collection with different information fields. Data fields which are part of level one must be filled out for all patients included in the registry; thus, that kind of data is important for carrying out epidemiological studies since it is available for all patients. Fields that are part of level two and level three are not mandatory for all patients. Level two includes more detailed information on diagnosis and follow-up data of patients suffering from specific diseases, while the purpose of level three is to be used for projects during a certain amount of time in which data can be collected for research and studies. (Grimbacher, 2014)

1.2.5 Parallel registries

Besides the ESID registry, there are various other national registries existing in parallel within European borders, such as the German National Registry of Primary Immunodeficiencies (El-Helou *et al.*, 2019), the French National Registry of Primary Immunodeficiencies (CEREDIH: The French PID study group, 2010), The United Kingdom Primary Immune Deficiency (UKPID) Registry (Edgar *et al.*, 2014), or The Swiss National Registry for Primary Immunodeficiencies (Marschall *et al.*, 2015). The mentioned national registries have in common that they use the ESID database platform for their performance and are co-ordinated at the Centre for Chronic Immunodeficiency (CCI) belonging to the University Medical Centre in Freiburg, Germany (Gathmann *et al.*, 2013).

The national registry in Germany was set up in 2009 in order to facilitate the analysis of data such as the diagnostic delay, factors regarding clinical course, therapeutic measures, or epidemiological data. Its data, which up to date comprises more data on approximately 2500 patients, is based on the data set of the ESID registry with the main advantage that the data can also be used in international research (Gathmann *et al.*, 2013; El-Helou *et al.*, 2019).

Furthermore, another country that established a national registry on primary immunodeficiencies was France. Its national registry was set up in 2005, including data on approximately 3000 mainly paediatric but also adult patients in 2010. Moreover, the corresponding French PID study group estimated the overall prevalence of primary immunodeficiencies by the aid of the national registry. According to a report published in 2010, the prevalence in France was estimated at 4.4:100.000. (CEREDIH: The French PID study group, 2010)

Moreover, The United Kingdom Primary Immune Deficiency (UKPID) Registry was set up in 2008 by the UK Primary Immunodeficiency Network (UKPIN), consisting of 38 immunology centres within the UK. As a great for the ESID registry, the UKPID registry transfers its patient data twice per year to the ESID registry in those cases where patients have given their full consent to the transfer of data. In a paper published in 2012, the UKPIN reported on 2229 patients that had been documented in the national registry up to that date. (Edgar *et al.*, 2014)

Finally, The Swiss National Registry for Primary Immunodeficiencies represents another national registry on primary immunodeficiencies, which was initialized in 2008. It constitutes of 17 medical centres within Switzerland attending to patients

with primary immunodeficiencies and is hosted on the same platform as the ESID registry. According to a report of 2015, in the time period between 2008 and 2014, 348 patients had been included into the national registry in Switzerland. Of those patients, it was reported that eight patients had been deceased, while two were lost to follow-up. (Marschall *et al.*, 2015)

1.2.6 ESID registry publications

A list of publications which are associated with the ESID registry as they are based on registry data can be found on the webpage of the European Society for Immunodeficiencies (European Society for Immunodeficiencies (ESID), 2019a).

For instance, according to a recent publication, the genetic diagnosis status of French patients could be determined by the help of the French national PID registry. According to their analysis, genetic testing was performed in 51.6% of patients, while 48.4% were not genetically tested or their status remained unknown. (Mahlaoui *et al.*, 2019)

Moreover, in a rather large study, comprising data on 2700 patients with CVID from 23 different countries, the ESID registry helped to analyse the general burden of CVID and comorbidities of those patients, including, besides others, associations between comorbidities and years of life lost to disability or premature death. For instance, the study showed that almost half of CVID patients' burden (44%) could be associated with infections or bronchiectasis. (Odnoletkova *et al.*, 2018) Furthermore, The PedPAD study also used data of the ESID registry in order to perform a comprehensive analysis of more than 2000 patients with hypogammaglobulinemia, identified Turkey, Germany, and Spain as the countries with most registered patients suffering from that disorder, regarding age at diagnosis, found statistically significant but still small differences between countries, and finally, and, finally, identified a strong male dominance in patients with hypogammaglobulinemia (Schatorjé *et al.*, 2014).

1.2.7 Austrian participation in the ESID registry

The Austrian participation in the ESID registry was primarily initiated at St. Anna Children's Hospital, Vienna, early in 2009, according to a documenting containing a

vote of the ethics commission of the St. Anna Children's Hospital in Vienna [2] (Lavaulx-Vrécourt, 2009) and soon supported by the newly founded Working Group for Paediatric Immunology of the Austrian Society for Paediatrics (Arbeitsgruppe für Pädiatrische Immunologie der Österreichischen Gesellschaft für Kinder- und Jugendheilkunde, AGPI-ÖGKJ) according to a protocol of its founding meeting in Salzburg[3] (Förster-Waldl, Seidel and Wintergerst, 2010). The founding members of the AGPI included Univ. Doz. Dr. Andreas Heitger, a.o. Univ. Prof. Dr. Elisabeth Förster-Waldl, Dr. med.-univ. PD Markus Seidel, and Prof. Prim. Uwe Wintergerst. The AGPI was designed in order to facilitate the networking of paediatricians in Austria, to enable national as well as international research projects, and to improve cooperation and support between Austrian paediatricians in the context of diagnostical procedures and treatment measures regarding patients with inborn errors of immunity. Another major purpose of the AGPI was to work on the establishment of shared guidelines and standard operating procedures (SOPs) to be used during the diagnostic process in the case of a suspected immunodeficiency in paediatric patients. (Förster-Waldl, Seidel and Wintergerst, 2010)

The working group designed various projects within the course of the founding meeting in January 2010, where 20 members participated. Those founding projects included, firstly, the nationwide participation in the ESID registry and the establishment of algorithms for the diagnostical procedures regarding patients with inborn errors of immunity as well as for the evaluation of periodical fever and autoinflammatory diseases. For this purpose, in the context of the founding meeting, a presentation about ESID including a list of possibly interested institutions in Austria regarding a participation in the ESID registry was held by Dr. med.-univ. PD Markus Seidel in order to inform participating members about the mission and structure of the ESID registry. Within this presentation, a shared access to the ESID database was discussed. Secondly, another project to be defined by the founding members of the AGPI was the establishment of a complete list of laboratories responsible for the performing of special immunological evaluations. Thirdly, the implementation of

[2] Document provided by Dr. med.-univ. PD Markus Seidel, containing the protocol of a vote of the ethics commission of the St. Anna Children's Hospital of Vienna in favour of the storage of patient data within the ESID registry and its usage for research, signed on the 3rd of June, 2009, by Dr. Roland Lavaulx-Vrécourt

[3] Document provided by Dr. med.-univ. PD Markus Seidel, containing the protocol of the founding meeting of the Working Group for Paediatric Immunology of the Austrian Society for Paediatrics in Salzburg in January 2010

primary immunodeficiencies of a severe character to new-born screening was discussed during the founding meeting. (Förster-Waldl, Seidel and Wintergerst, 2010)

Initially, 31 participants demonstrated their interest in participating in the ESID registry according to a document containing an inquiry from the founding meeting of the Working Group for Paediatric Immunology of the Austrian Society for Paediatrics [4] (AGPI Österreich, 2010); however, only four documenting centres have yet been established besides the two former mentioned centres in Vienna according to the ESID Registry.

[4] Document provided by Dr. Seidel, containing an inquiry with a list of persons interested in participating in the ESID registry, which was conducted at the founding meeting of the Working Group for Paediatric Immunology of the Austrian Society for Paediatrics in Salzburg in January 2010

1.2.8 Purpose of this study

1.2.8.1 Cross-sectional study – ESID registry Austria

The main purpose of this thesis is to collect data from patients with inborn errors of immunity from all currently documenting centres in Austria in order to provide, for the first time in Austria, a nation-wide, multi-centric, and cross-sectional study regarding patients with IEI. Though there is a variety of literature concerning the ESID registry in general and national participations in the registry as well as national registries existing in parallel, few data can be found regarding Austrian patients with inborn errors of immunity documented in the ESID registry. This thesis should help in expanding that kind of data and contribute to increasing the literature of national participations in the ESID registry.

By performing a cross-sectional study, the prevalence of certain kind of inborn errors of immunity in Austria as well as in the specific documenting centres will be analysed, the frequency by which certain diagnostical procedures and treatment options were used will be evaluated, including the frequency of HSCT and immunoglobulin therapy, and finally, the diagnostic delay will be explored. Moreover, the clinical manifestation of patients with IEI, including symptoms of onset and the time of the initial manifestation of those symptoms, as well as the age distribution of patients regarding time of clinical or genetic diagnosis will be investigated. The former mentioned parameters should contribute to presenting a comprehensive view of the current situation of Austrian patients suffering from primary immunodeficiencies.

1.2.8.2 A decade of Austrian participation in the ESID registry – the search for strengths and weaknesses

Since the ESID registry was established in Austria ten years ago, the study carried out in this thesis aims to provide a comprehensive analysis of the first decade of Austrian participation. In addition, by the help of a survey conducted at the documenting centres as well as at various medical centres in the care of patients with primary immunodeficiencies, benefits as well as barriers of the ESID registry ten years after its establishment will be explored. Results will contribute to presenting to which extent the ESID registry is currently used by documenting centres and to providing a view about the current knowledge of the ESID registry as the main documenting database for patients with IEI in Austria.

2 Patients and Methods

2.1 Patients

The data used for the analysis corresponds to patients with inborn errors of immunity documented in the ESID Registry.

At the time of the data collection, the ESID online database comprised information about 181 patients diagnosed with an inborn error of immunity. The youngest patient was 2 years old; the oldest patient was 79 years old at the time of the data extraction. All those patients were similarly included in the collection as well as the analysis of data and there was no limitation regarding age or gender.

The number of documented patients, the range of ages per documenting centre as well as the median age of patients are presented in Table 2.

Documenting centre	Number of documented patients	Range of ages	Median age
Department of Paediatrics, Medical University of Graz	53	2 – 38 years	14 years
Department of Internal Medicine, Medical University of Graz	52	22 – 79 years	56.5 years
St. Anna Children's Hospital, Vienna	34	10 – 30 years	14.5 years
Hospital of Klagenfurt	17	2 – 33 years	11 years
Medical University of Vienna	13	7 – 53 years	11 years
Children's and Women's Hospital, Linz	12	2 – 23 years	9.5 years

Table 2: Number of patients per documenting centre, age distribution, and median age

2.2 Methods

For the analysis within the cross-sectional study patient data was extracted from the online database of the ESID Registry for inborn errors of immunity in the period between April and May 2019. For the data collection, a specific login was created which permitted Austrian wide access to patient information belonging to six documenting centres. Those centres were the St. Anna Children's Hospital in Vienna, the Medical University of Vienna, the Women's and Children's Hospital in Linz, the Hospital in Klagenfurt, and the Paediatric Unit as well as the Internal Unit of the Medical University of Graz.

Within the online database, the possibility to export some of the patients' information into an excel-file was used to create a base document which already contained some patient data including the ESID ID, the documenting centre, the year of birth, the living status, the sex, the PID diagnosis, the affected gene, information about hematopoietic stem cell transplantation, whether level 1 documentation has been completed, and the dates of the last documentation. That base document was then subsequently expanded with the following parameters

- Month of birth
- Current age
- Information about whether it is a familial case, whether the patient is a twin, or if there is evidence for consanguinity of parents
- Laboratory for genetic analysis
- Information about whether genetic tests have been performed
- Sequencing methods
- Reason for genetic analysis
- First PID-related symptoms
- Information about whether diagnosis was made by lab abnormalities only
- Date of onset of symptoms
- Date of first clinical diagnosis
- Date of genetic diagnosis
- Information about therapy: gene therapy, Ig replacement therapy, splenectomy
- Hematopoietic stem cell transplantation:
    - Date of transplantation

    - Type of donor
    - Source of CD34 stem cells
- Ig replacement therapy:
    - Date of first Ig replacement
    - Current brand name
    - Current routine of administration
    - Current place of administration
    - Current weight (kg)
    - Current dose (mg/kg body weight)
    - Dose per month
    - Current dose (total amount)
    - Interval for current dose
    - Current side effects

The extracted patient data did not include names, and only the ESID ID was subsequently used in the analysis of data.

Not all patient files included information on all former mentioned parameters, some patient files missed information in some fields. However, those patients were still included in the data collection as well as the analysis, but the fields that did not contain information remained empty in the excel file. Therefore, for the cross-sectional study, the total amount of patients used for specific analyses is not consistent and is indicated below.

For the analysis of sequencing methods, patients whose ESID entries contained any form of information in the sequencing method input field, were included, in total 114 patients.

For the analysis of the reasons for genetic analysis, patients whose ESID entries contained any form of information in the corresponding input field, were included, in total 114 patients.

For the diagnostic delay, patients whose ESID entries contained information on a specific time point regarding age at manifestation, age at clinical diagnosis as well as age at genetic diagnosis, were included in the analysis. Specifically, 47 patients had information in all the mentioned input fields entered and were therefore included in the analysis of the diagnostic delay.

2.3 Prevalence analysis

After the data collection was finalised, prevalence calculations and diagrams for the cross-sectional study were made by the aid of the excel programme. For the study, the analysis included:

1. General characteristics of the ESID registry
    a. Prevalence of the main categories of IEI in Austria and in each documenting centre
    b. Prevalence of female and male patients in Austria
    c. Prevalence of IEI among documenting centres in Austria
    d. Prevalence of analysing laboratories
    e. Prevalence of sequencing methods
    f. Prevalence of each reason for genetic analysis
    g. Prevalence of familial cases
    h. Prevalence of patients with level 1 completed

2. Patient characteristics
    a. Prevalence of first IEI-related symptoms
    b. Prevalence of patients which were either clinically, only genetically, or clinically and genetically diagnosed
    c. Duration of time passed between onset of symptoms, clinical diagnosis and genetic diagnosis (diagnostic delay)
    d. Prevalence of patients with consanguinity of parents
    e. Prevalence of patients alive / deceased

3. Treatment characteristics
    a. Frequency of Ig replacement therapy, hematopoietic stem cell transplantation, gene therapy, and splenectomy
    b. Hematopoietic stem cell transplantation: frequency of certain donor types and sources
    c. Immunoglobulin replacement therapy: frequency of certain routines and places of administration

For the analysis of the registered patients per 100.000 inhabitants in European participating countries, data on the numbers of registered patients was derived from the ESID Reporting Tool.

Regarding the ethics commission, an approval in favour of the utilization of the ESID registry for research purposes had already existed before work in the course of the diploma thesis began. Thus, for the thesis, no application to the corresponding ethics commission had to be submitted.

2.4 Survey

As another part of the thesis, a survey, which was aimed at clinicians and physicians in Austria currently attending to patients with inborn errors of immunity, was conducted during May and July 2019. The purpose of the survey was to investigate not only the benefits of an online registry such as the ESID registry, but also to reveal the barriers that come with it and that still make the work with the registry in some cases difficult. The survey consisted of 19 questions which were designed either in the style of yes or no answer, multiple-answer, or short-answer questions. For further information, the survey can be found in the annex. The questionnaire was initially created as a Word-document and later implemented into a PDF-document which was finally sent out to 18 persons working either in one of the Austrian documenting centres or in a hospital which is independent from the registry but is yet receiving patients with inborn errors of immunity.

By the 22th of August 2019, ten questionnaires were returned either by postal way or by means of fax and were subsequently analysed. It was agreed to focus on the issues that delivered the most interesting information and on topics that had either quite similar or quite diverse answers. The results of the survey are discussed in detail in the following section.

3 Results

3.1 General characteristics of the ESID registry

In the first chapter regarding study results, there will be information on the general characteristics of patients registered in the European Society for Immunodeficiencies Registry, which were revealed during the cross-sectional study. This information comprises not solely characteristics of the Austrian participation but also certain facts that were retrieved from the ESID Reporting Tool, such as the registered patients per country or the current coverage of IEI in Europe. The former mentioned general characteristics will be presented in various figures as well as in textual form in the following sections.

3.1.1 Main categories of inborn errors of immunity in Austria

The presentation of study data starts with an analysis of the main categories of IEI to be found in the Austrian part of the ESID Registry and their frequency within the country. To begin with, of 181 Austrian patients that were reported in the ESID Registry by May 2019, 180 patients were found to include a current diagnosis in the registry, while one patient remained without a diagnosis in the ESID registry at the time of analysis.

Regarding specific categories of IEI, the highest number of patients, more specifically 76 patients (42%), was found in the group of predominantly antibody disorders which therefore represents the most common IEI category in the Austrian part of the ESID Registry, as is demonstrated in Figure 1. Within this group of disorders, common variable immunodeficiency (CVID) was found to be the most frequent one with 26 patients diagnosed. Following that disorder, in the group of predominantly antibody disorders, in decreasing order of frequency, 25 patients were diagnosed with an unclassified antibody deficiency, 7 patients with IgA deficiency and 5 patients were diagnosed with IgG subclass deficiency. One patient was diagnosed with each of the following disorders, including selective IgA deficiency, IgA with IgG subclass deficiency, and Hyper-IgM Syndrome.

The second largest group of IEI is represented by a group of disorders summarized under the term of “other well defined PIDs”, with 42 patients in total documented in the registry, corresponding to 23% of patients as seen in Figure 1. DiGeorge Syndrome (DGS) was the most common type of disorder found in that group; 20

patients with DGS were documented. Other disorders of that category documented in the registry were Ataxia-telangiectasia (8 patients), Nijmegen breakage syndrome (5 patients), Wiskott–Aldrich syndrome (2 patients), Cartilage hair hypoplasia (2 patients), and X linked thrombocytopenia (2 patients). Netherton syndrome, Hyper IgE Syndrome, as well as WIP deficiency was represented by one patient each.

Autoinflammatory disorders, including 16 patients (9%), constitute the third largest group of disorders found in the Austrian participation of the ESID Registry, as can be seen in Figure 1. Unclassified antibody deficiency was the most common autoinflammatory disorder with 25 documented patients. Moreover, Familial Mediterranean fever had been diagnosed in six patients, followed by two patients with Hyper IgD Syndrome (MVK). Muckle-Wells syndrome and TRAPS syndrome had been observed in one patient each.

Furthermore, phagocytic disorders were found in 14 patients (8%), representing the fourth largest group of disorders as demonstrated in Figure 1. In this group, chronic granulomatous disease (CGD) constitutes for the most common type; it was found in the entry of five patients. Continuing, three patients were diagnosed with cyclic neutropenia, two patients with congenital neutropenia, another two patients with Glycogen storage disease type I (GSD I). Finally, one patient had been diagnosed with leukocyte adhesion deficiency (LAD), while another patient was diagnosed with Shwachman-Diamond-syndrome.

The fifth largest group of IEI was found to be diseases of immune dysregulation with eleven patients (6%) diagnosed, which can be seen in Figure 1. Most patients, four patients to be more precise, were affected by autoimmune lymphoproliferative syndrome (ALPS). In addition, two patients had been diagnosed with immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX). Besides that, early-onset multi-organ autoimmune disease, familial hemophagocytic lymphohistiocytosis (FHLH), X-linked lymphoproliferative disease (XLP), RAS-associated autoimmune leukoproliferative disease (RALD), as well as Autoimmune polyendocrine syndrome type 1 (APECED) was observed in one patient each.

Moreover, there are nine patients, corresponding to 5% of patients, with an unclassified immunodeficiency, while seven patients (4%) had a complement disorder. Combined immunodeficiencies were found in a small number of patients (four patients, 2%). Finally, only one patient, accounting for 0,5% of cases, was documented with a defect in innate immunity. The previously mentioned data can be seen in Figure 1.

As is demonstrated in the pie chart of Figure 1, predominantly antibody disorders represent the category of IEI to be diagnosed in the greatest number of patient cases, followed by “other well defined PIDs”, which were diagnosed in a quarter of patients in the ESID Registry in Austria. Combining the remaining less frequent diagnoses of patients (unclassified immunodeficiencies, defects in innate immunity, autoinflammatory disorders, complement disorders, diseases of immune dysregulation, phagocytic disorders, and combined immunodeficiencies), predominantly antibody disorders still reaches a higher percentage (42%) compared to the total sum of less frequent diagnoses (34.5%) (Figure 1).

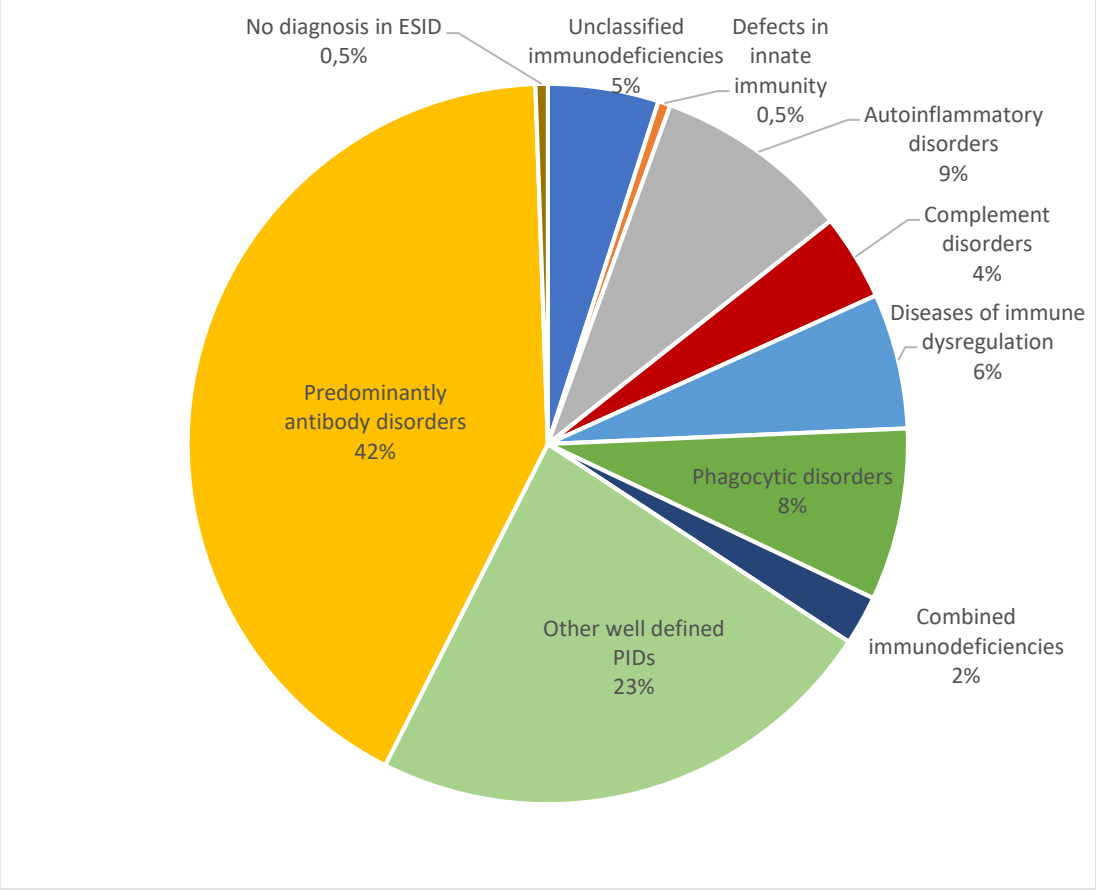

Figure 1: Main categories of inborn errors of immunity in Austria (n=181)

3.1.2 Main IEI categories in Austrian patients per documenting centres

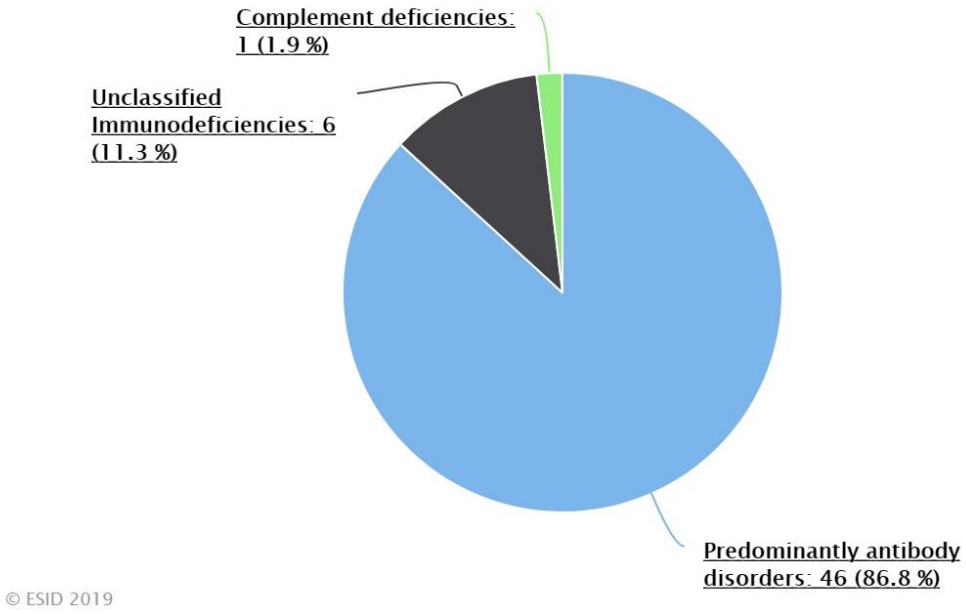

Figure 2: Main categories, Department of Internal Medicine, Medical University of Graz (ESID, 2019)

The prevalence of the main IEI categories in the documenting centre of the Department of Internal Medicine of the Medical University of Graz is represented in Figure 2, which shows a clear dominance of predominantly antibody disorders. More precisely, 46 patients, accounting for 86.8% of patients in that centre, are diagnosed with predominantly antibody disorders. Besides that, two other categories of primary immunodeficiencies were found in that centre, namely unclassified immunodeficiencies (six patients, corresponding to 11.3% of patients) and complement deficiencies (one patient, corresponding to 1.9% of all patients) as can be seen in Figure 2.

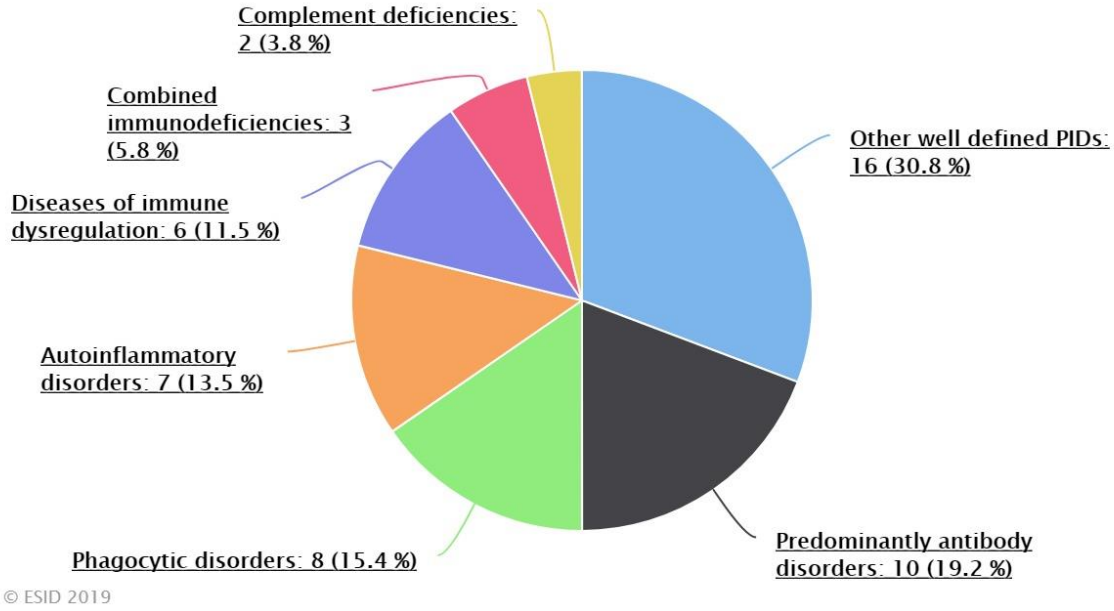

Figure 3: Main categories, Department of Paediatrics, Medical University of Graz (ESID, 2019)

Figure 3 represents the distribution of main categories in the Department of Paediatrics of the Medical University of Graz, where patients could be divided into seven IEI categories. The largest proportion of patients had been diagnosed with a disorder out of the group of “other well defined PIDs” (16 patients, 30.8%) (Figure 3). Predominantly antibody disorders represented the second largest group of disorders in that centre; in fact, ten patients (19.2%, as can be seen in Figure 3) were documented with a predominantly antibody disorder in contrast to the previously mentioned centre where those disorders made up more than three thirds of patients. Besides that, phagocytic disorders, autoinflammatory disorders and diseases of immune dysregulation can be found with similar frequencies; 8 patients (15.4%) are diagnosed with a phagocytic disorder, 7 patients (13.5%) with an autoinflammatory disorder and 6 patients (11.5%) with a disease of immune dysregulation (Figure 3). The smallest number of patients suffers from a combined immunodeficiency (3 patients, 5.8%) or a complement deficiency (2 patients, 3.8%) (Figure 3).

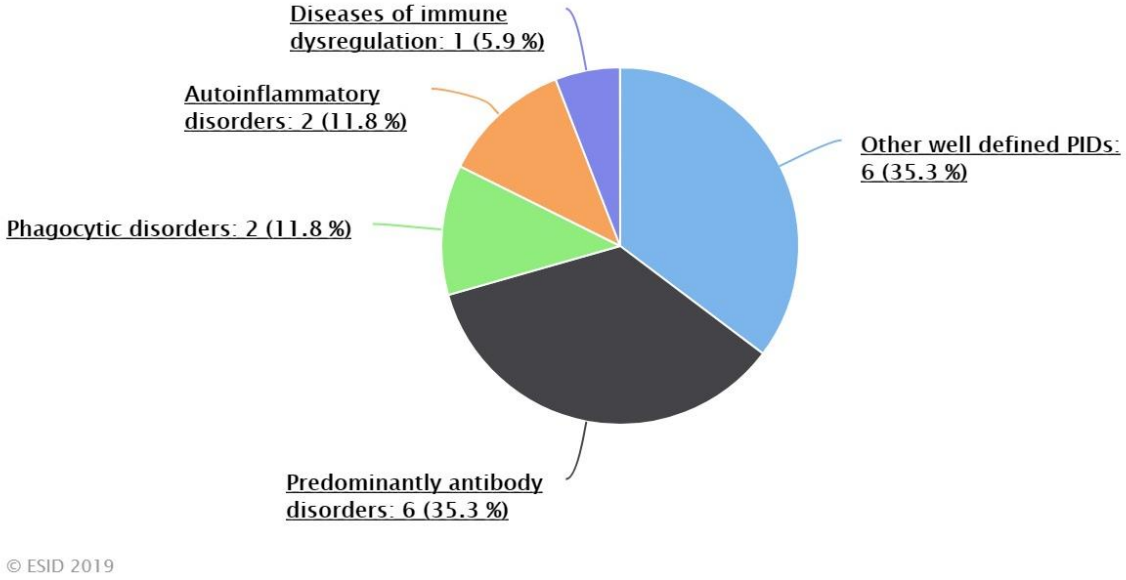

Figure 4: Main categories, Hospital of Klagenfurt (ESID, 2019)

The prevalence of IEI main categories in the next documenting centre, the Hospital of Klagenfurt, is presented in Figure 4 and shows a similar distribution as in the Paediatrics Department in Graz. The group of disorders with “other well defined PIDs” as well as predominantly antibody disorders each include six patients (35.3%) as can be seen in Figure 4. Both groups combined constitute more than two thirds of documented patients in the centre in Klagenfurt. Following those disorders, phagocytic disorders had been diagnosed in two patients, corresponding to 11.8% of patients (Figure 4). Furthermore, autoinflammatory disorders had equally been observed in two patients, corresponding to the same percentage of patients as phagocytic disorders (Figure 4). According to the entries in the online ESID database, only one patient (5.9%) in Klagenfurt had been diagnosed with a disease of immune dysregulation (Figure 4).

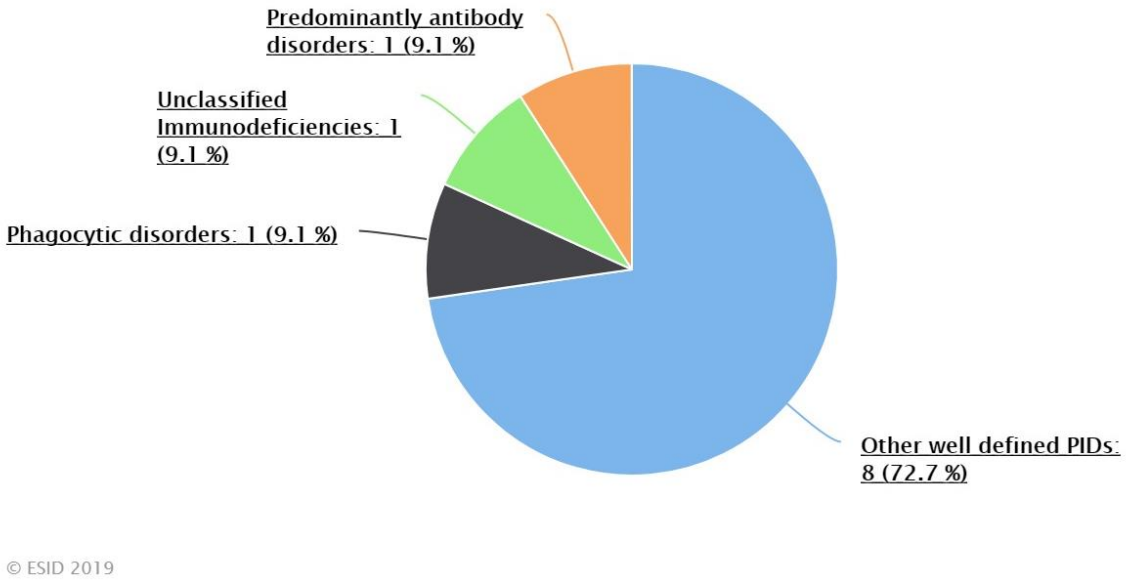

Figure 5: Main categories, Children's and Women's Hospital, Linz (ESID, 2019)

Figure 5 displays the distribution of the main IEI categories in the Children's and Women's Hospital in Linz. There, the prevalence of IEI diagnoses differs from other documenting centres in Austria. To be more precise, "other well defined PIDs" seem to be by far the most documented group of disorders. Of eleven patients already documented in the ESID registry by that centre, eight patients (72.7%) carry the diagnosis of "other well defined PIDs" in their entries, as demonstrated in Figure 5, and from the remaining three patients, each patient is either diagnosed with a phagocytic disorder, an unclassified immunodeficiency, or a predominantly antibody disorder.

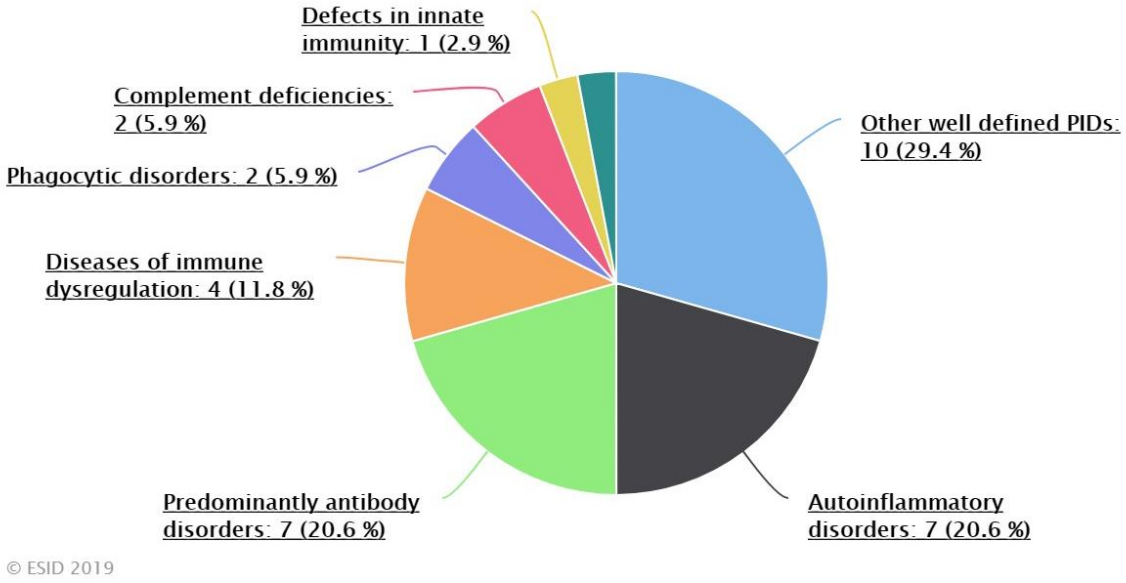

Figure 6: Main categories, St. Anna Children's Hospital, Vienna (ESID, 2019)

Figure 6 represents the distribution of IEI among patients of the St. Anna Children's Hospital in Vienna. In the documenting centre of the St. Anna Children's Hospital in Vienna, "other well defined PIDs", similar as in five of the other Austrian documenting centres, represented the largest patient group with ten patients included, corresponding to 29.4% of patients as can be seen in Figure 6. Autoinflammatory disorders were found in the entries of seven patients (20.6%) (Figure 6). Furthermore, predominantly antibody disorders, equally to autoinflammatory disorders, had been diagnosed in seven patients (20.6%) (Figure 6). Diseases of immune dysregulation were documented in four patient cases (11.8%), while phagocytic disorders and complement deficiencies were found in two patients each (5.9%) (Figure 6). In the St. Anna Children's Hospital in Vienna, only one patient (2.9%) was documented with a defect in innate immunity (Figure 6).

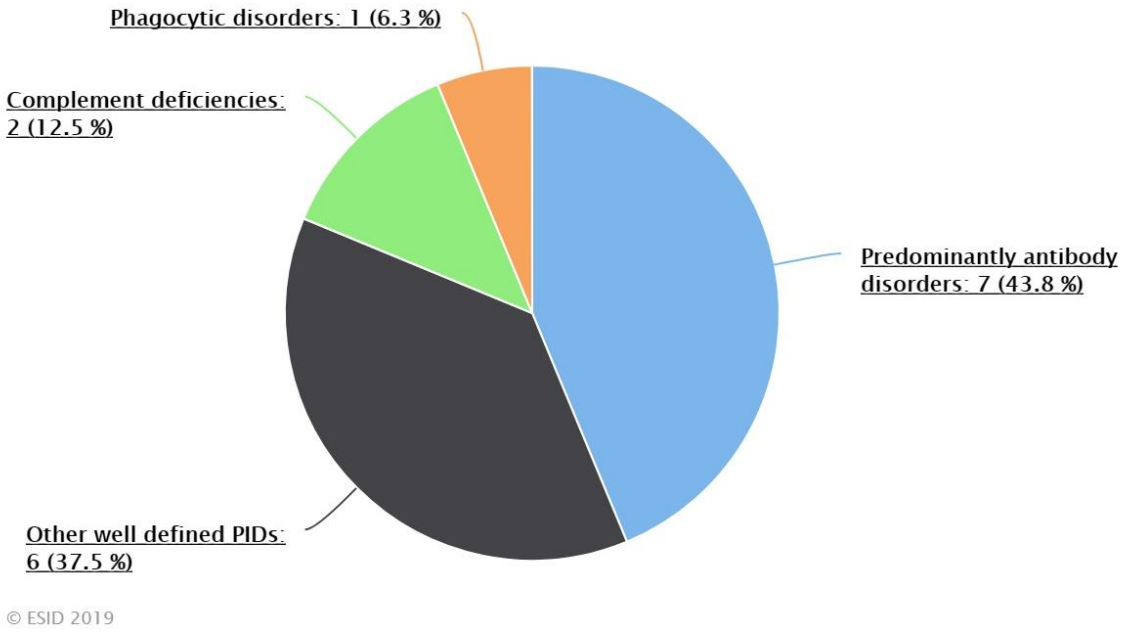

Figure 7: Main categories, Medical University, Vienna (ESID, 2019)

Figure 7 displays the main categories of patients documented by the Medical University of Vienna. As can be seen, predominantly antibody disorders constitute the largest category with seven documented patients (43.8%), followed by "other well defined PIDs" with six registered ones (37.5%) (Figure 7). Complement deficiencies affected two patients (12.5%), and finally, one patient had been diagnosed with a phagocytic disorder (6.3%) (Figure 7).

3.1.3 Sex distribution of patients with IEI in Austria

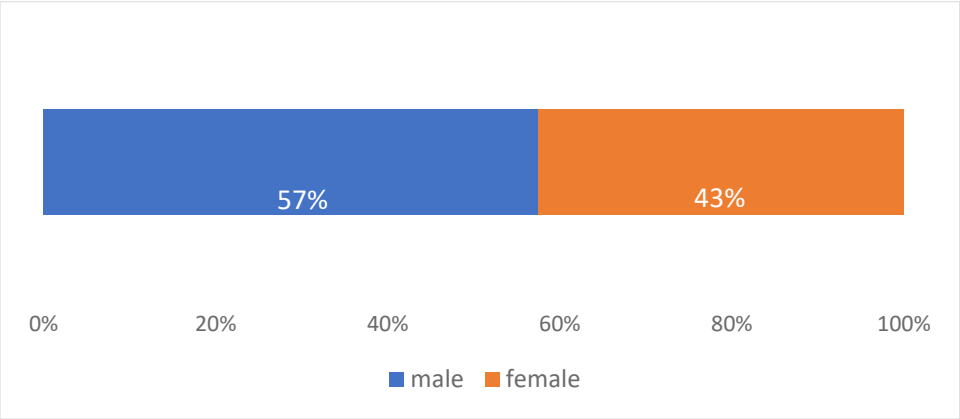

Figure 8: Sex distribution of patients with IEI in Austria (n=181)

Regarding the sex distribution of IEI in Austria, at the time of analysis, 104 male and 77 female patients were documented in the registry. Therefore, male patients constituted 57% of entries in the ESID online database, while female patients made up 43% of entries, which can be seen in Figure 8, providing a visual presentation of the sex distribution of Austrian IEI patients documented in the ESID registry.

3.1.4 Registered patients per country

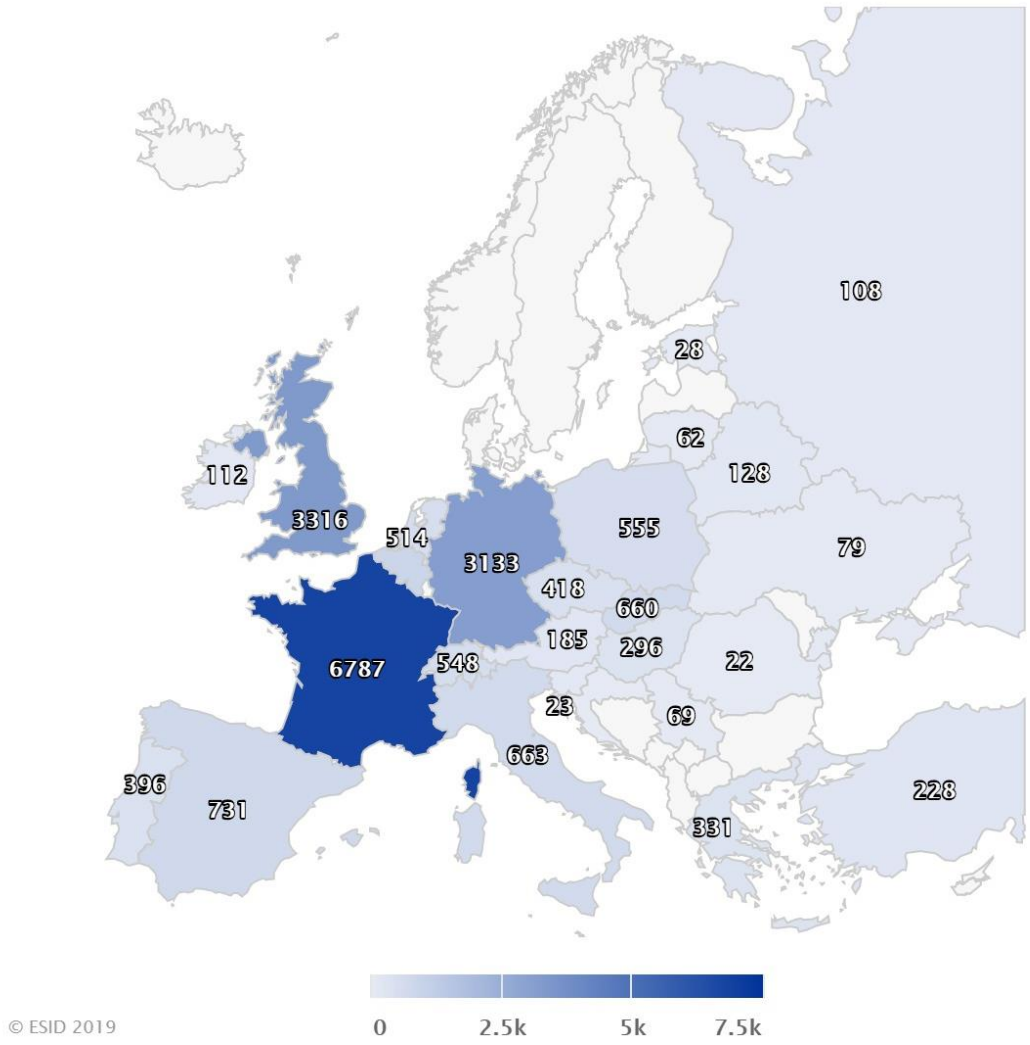

Figure 9: Registered patients per country in Europe (ESID, 2019)

In Figure 9, a map of Europe extracted from the ESID Reporting Tool represents the number of patients which are registered in the ESID online database by the European participating countries. The countries are represented in different shades of blue depending on the total number of documented patients per country, as is further demonstrated in the scale at the bottom of the map. Countries coloured in ivory, namely Iceland, Norway, Scotland, Finland, Latvia, Denmark, Bosnia and Herzegovina, Montenegro, Albania, Kosovo, North Macedonia, Moldova, and Bulgaria are currently not part of the participating countries. In Figure 9, Austria is represented by 185 documented patients, already more patients than included in the study carried out within this thesis due to the map having been extracted from the ESID Reporting Tool at a later date (July, 2019).

In July 2019, France, the United Kingdom, and Germany are among the first three countries with the highest number of registered patients. By far, France is responsible for the highest number of registered patients, more precisely 6787 patients, while Romania has the smallest number of documented patients, namely 22 patients in one documenting centre which can be seen in Figure 9. The United Kingdom represents the country with the second largest number of documented patients; in fact, by July 2019, 3316 patients had already been documented by 37 centres in the ESID online database (Figure 9). Germany, with 3133 registered patients in 40 centres, occupied the third place regarding the number of registered patients (Figure 9).

Concerning the number of documenting centres, Germany has the highest number (40 centres), followed by the United Kingdom with 37 centres, Italy with 14 centres, Spain with 11 centres, and Switzerland with 10 centres documenting patients with an IEI. In the remaining participating countries in Europe, seven or less documenting centres are currently existing.

Country	Registered patients	Registered patient(s) per 100.000 inhabitants
Austria	185	2
Belarus	128	1
Croatia	23	1
Czech Republic	418	4
Estonia	28	2
France	6787	10
Germany	3133	4
Greece	331	3
Hungary	296	3
Republic of Ireland	112	2
Italy	663	1
Lithuania	62	2
Netherlands	514	3
Poland	555	1
Portugal	396	4
Romania	22	0
Russia	108	0
Serbia	69	1
Slovakia	660	12
Slovenia	121	6
Spain	731	2
Turkey	228	2
Ukraine	79	0
United Kingdom	3316	5

Table 3: Registered patient(s) of European participating countries per 100.000 inhabitants

In the course of this study, the number of registered patients of European participating countries, according to the map seen in Figure 9, was assessed in relation to the countries' inhabitants. Table 3 provides the corresponding data. According to the analysis, Slovakia (12 patients), France (10 patients), and Slovenia (6 patients) show the most documented patients per 100.000 inhabitants (Table 3).

3.1.5 Coverage of patients with inborn errors of immunity

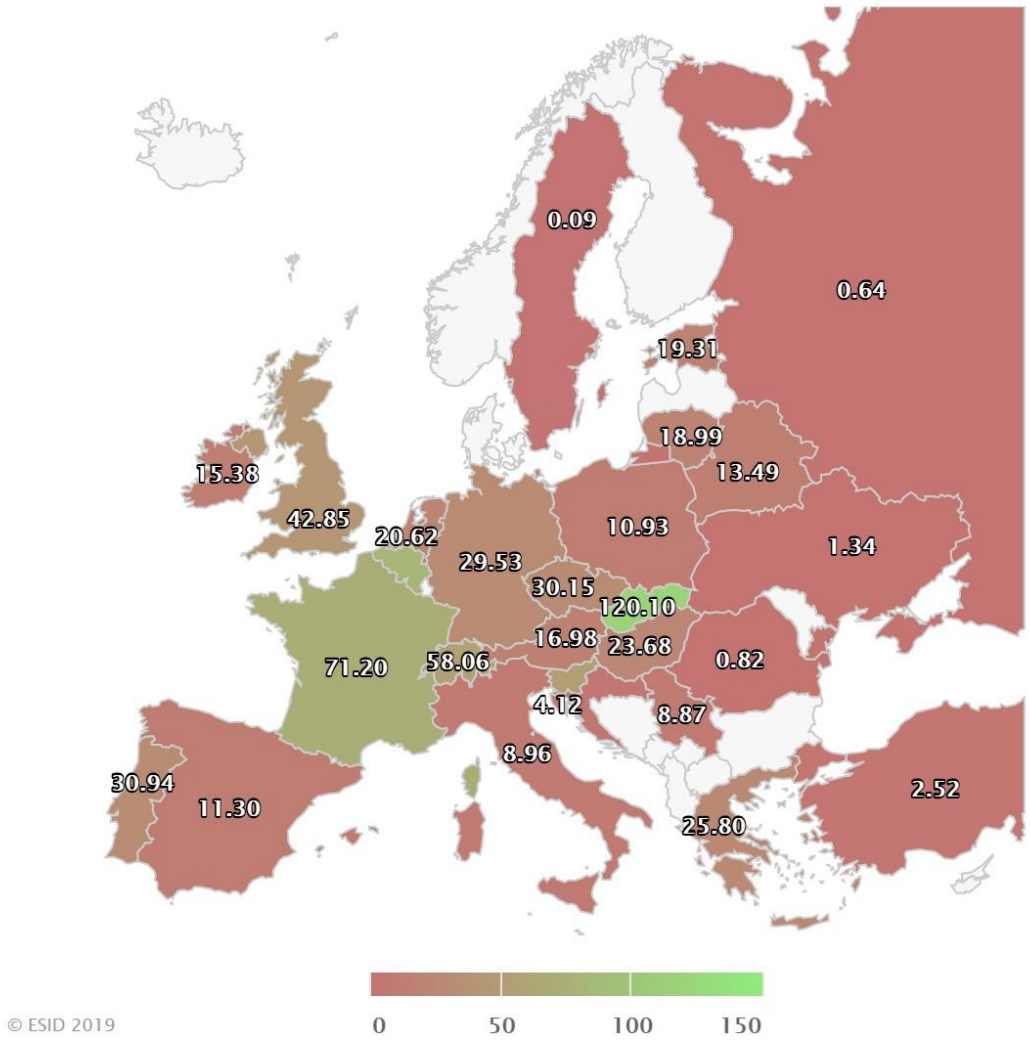

Figure 10: Coverage of patients with IEI within European participating countries (ESID, 2019)

This section will present the coverage of patients with IEI within Europe by the help of the data from the ESID Registry Reporting Tool. The coverage is visualised in Figure 10. The term coverage describes the percentage of reported alive patients from estimated alive patients. As can be seen in the European map in Figure 10, in Austria, 16.98% of estimated patients are currently covered according to the data from 2019 from the ESID Registry Reporting Tool. More precisely, in the current population of 8.725.931 people living in Austria, it is estimated that 960 people are indeed suffering from an inborn error of immunity while at the same time there are only 163 patients documented[5].

[5] Number of documented patients differs from study data extracted from the ESID registry (May 2019) due to possibly outdated data in the ESID Reporting Tool.

3.1.6 Distribution of patients with IEI between documenting centres

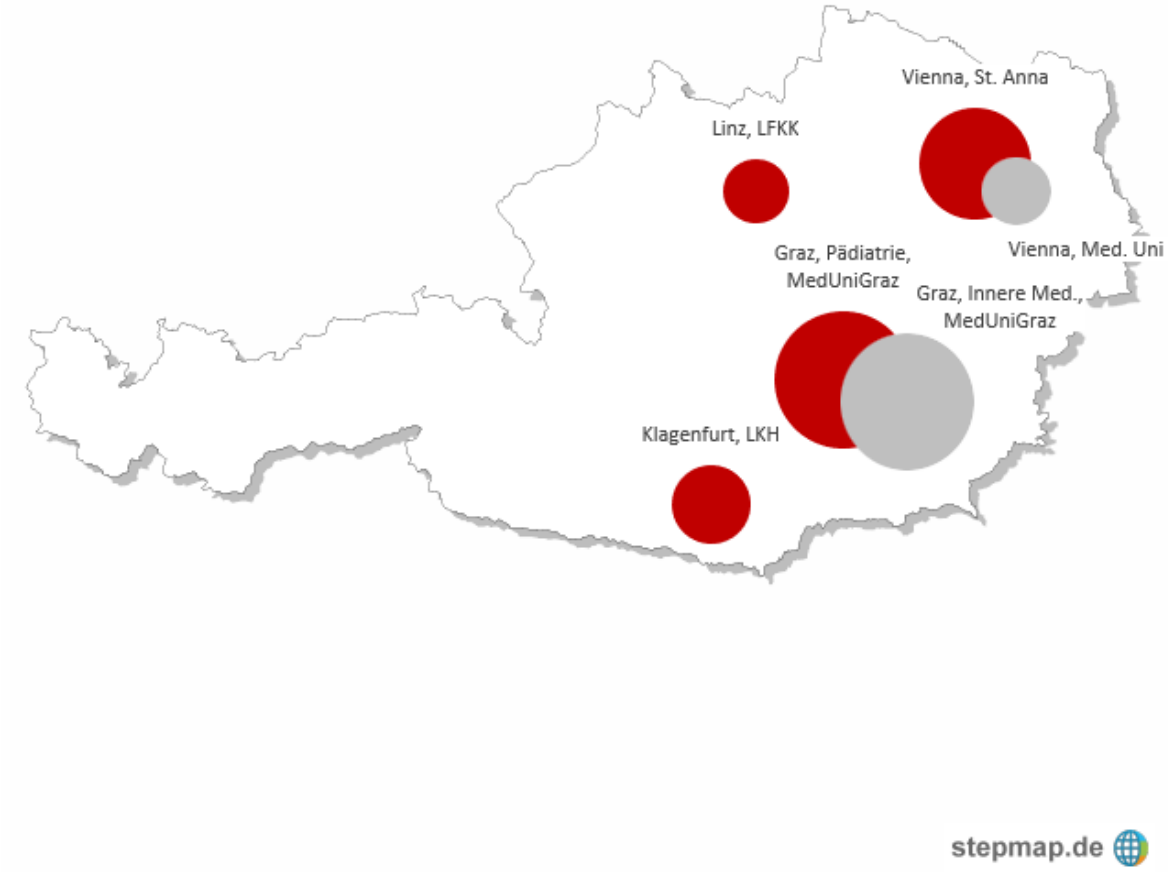

Figure 11: Distribution of IEI among documenting centres in Austria (StepMap, 2019)

As another part of the thesis, it was investigated in what manner patients with IEI are distributed among the various documenting centres in Austria. Figure 11 demonstrates the distribution of patients by the aid of bubbles varying in size within a map showing the Austrian boundaries. The sizes of the bubbles correspond to the number of patients with an IEI that had been registered in the ESID online database by the different documenting centres. As the study revealed, the highest number of patients was documented to the database by the Paediatrics Department of the University of Graz. In fact, the ESID Registry contained 53 patients of that documenting centre at the time of data analysis. Almost reaching the number of the Paediatrics Department, the Department of Internal Medicine of the University of Graz had already reported 52 patients to the ESID Registry. Therefore, the bubbles in Figure 11 corresponding to the two documenting centres in Graz are of a similar

size in order to demonstrate that patients with IEI were distributed equally among the Paediatrics Department and the Department of Internal Medicine of the University of Graz.

In addition, the St. Anna Children's Hospital of Vienna was responsible for the third highest number of patients being documented, 34 patients had been documented by that centre. On the other hand, the second documenting centre in Vienna, which belongs to the Medical University of Vienna, was only responsible for the documentation of 13 patients, which corresponds to the fifth highest number of documented patients in the Austrian part of the ESID registry. Thus, the Medical University of Vienna is demonstrated by a bubble of a rather smaller size than that of the St. Anna Children's Hospital as demonstrated in Figure 11.

Furthermore, the Hospital of Klagenfurt documented 17 patients, and finally, the smallest number of patients, precisely 12 patients, were registered by the Children's and Women's Hospital of Linz.

To sum up, the documenting centres located in Graz and Vienna are represented by a high number of patients except for the Medical University of Vienna, which had only documented 13 patients. The documenting centres located in Linz and Klagenfurt were accountable for a rather smaller number of patients than the centres in Graz and the St. Anna Children's Hospital of Vienna; thus, smaller bubbles are shown in Linz and Klagenfurt in the Austrian map.

3.1.7 Laboratories for genetic analyses

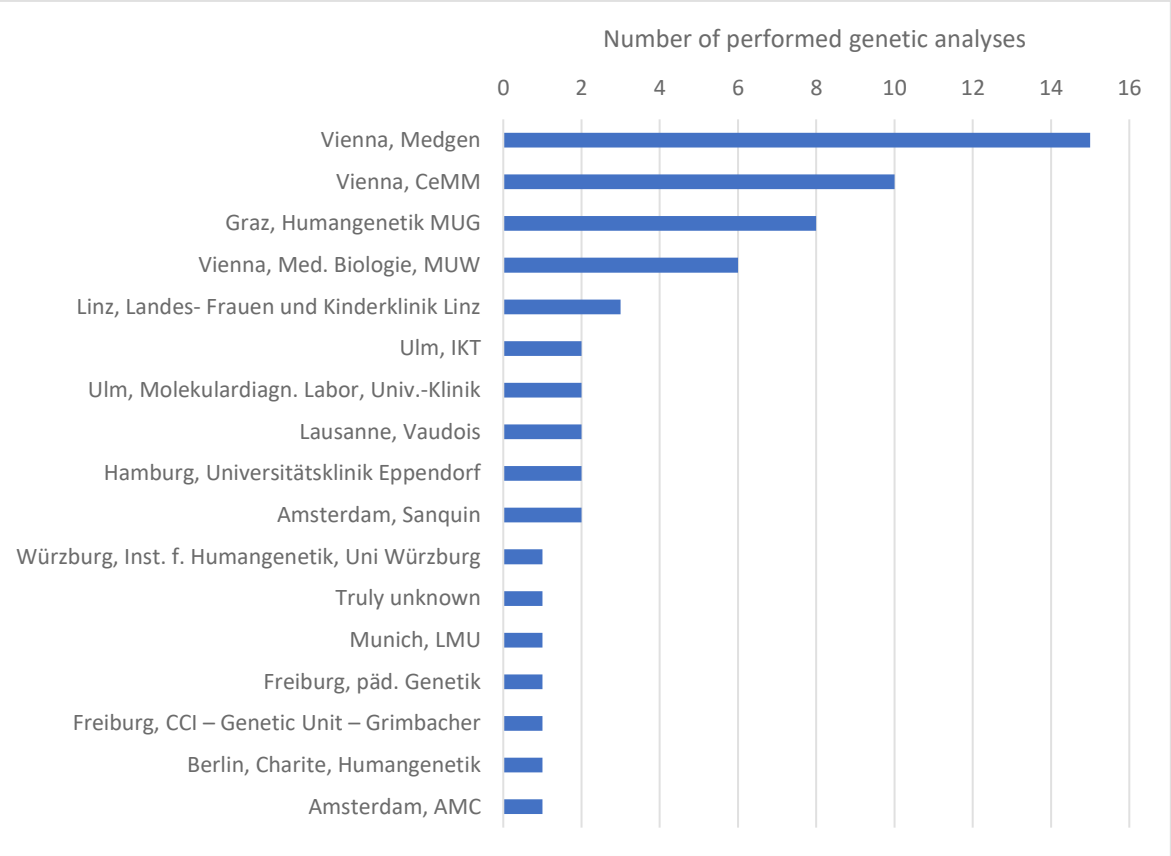

Figure 12: Laboratories for genetic analyses

Figure 12 demonstrates the frequency, according to the entries in the ESID online database, by which certain laboratories within Europe were used for the performance of genetic analyses in Austria in order to prove or refute a diagnosis in patients with a clinically suspected IEI. Of 181 registered Austrian patients, the patient files of 56 individuals provided information on the laboratory that had been used for the genetic analysis. In total, 16 different genetic laboratories were identified, which are represented in Figure 12 in descending order of frequency. In one specific patient case, the laboratory which had performed the genetic analysis was indicated as being truly unknown, which means that the responsible documenting centre has in fact no information on the laboratory although there is evidence that a genetic analysis had been performed.

According to the explored data in this study, the genetic laboratory that performed most of the genetic analysis for registered patients in Austria was the Medgen laboratory in Vienna. Medgen was responsible for the genetic analyses in 25% of

all patients' entries containing information on a laboratory, corresponding to 15 patients (Figure 12). The genetic laboratory which is responsible for the second largest number of genetic analyses in the Austrian ESID online database is the Research Centre for Molecular Medicine of the Austrian Academy of Sciences laboratory (CeMM). This laboratory, which is also located in Vienna, performed the genetic analyses of ten patients (Figure 12). Following the CeMM, the Institute for Human Genetics, belonging to the Medical University of Graz, carried out the genetic testing in eight patients with an inborn error of immunity, which corresponds to 14% of cases in which a laboratory is given (Figure 12). The Institute for Biology of the Medical University of Graz was in charge of genetic testing in six patients, which means in 10% of cases, and the Women's and Children's Hospital of Linz performed the analysis in three cases of a suspected inborn error of immunity, which corresponds to 5% of cases (Figure 12).

Two institutes in Ulm had already been assigned for the task of genetic testing, each institute in two patient cases. Therefore, each institute was responsible for the testing in 3% of patient cases and those laboratories are the Institute for Clinical Transfusion Medication and Immunological Genetics (IKT) and the Laboratory for Molecular Diagnostics belonging to the University of Ulm (Figure 12). Equally, one genetic laboratory in Lausanne, one of the Medical University of Eppendorf in Hamburg, and the Sanquin laboratory in Amsterdam were each also in charge of the analysis in two patients (3%) (Figure 12).

The subsequent genetic institutes were rarely found in the patient files of the Austrian ESID online database; however, each performed the genetic testing in one patient. Those laboratories were the Institute for Human Genetics of the University of Würzburg, the Ludwig Maximilian University of Munich (LMU), the Institute for Paediatric Genetics in Freiburg, the Genetic Unit (CCI, Grimbacher) in Freiburg, the Institute of Human Genetics belonging to the Charité in Berlin, and finally the Academic Medical Centre in Amsterdam (Figure 12).

3.1.8 Sequencing methods

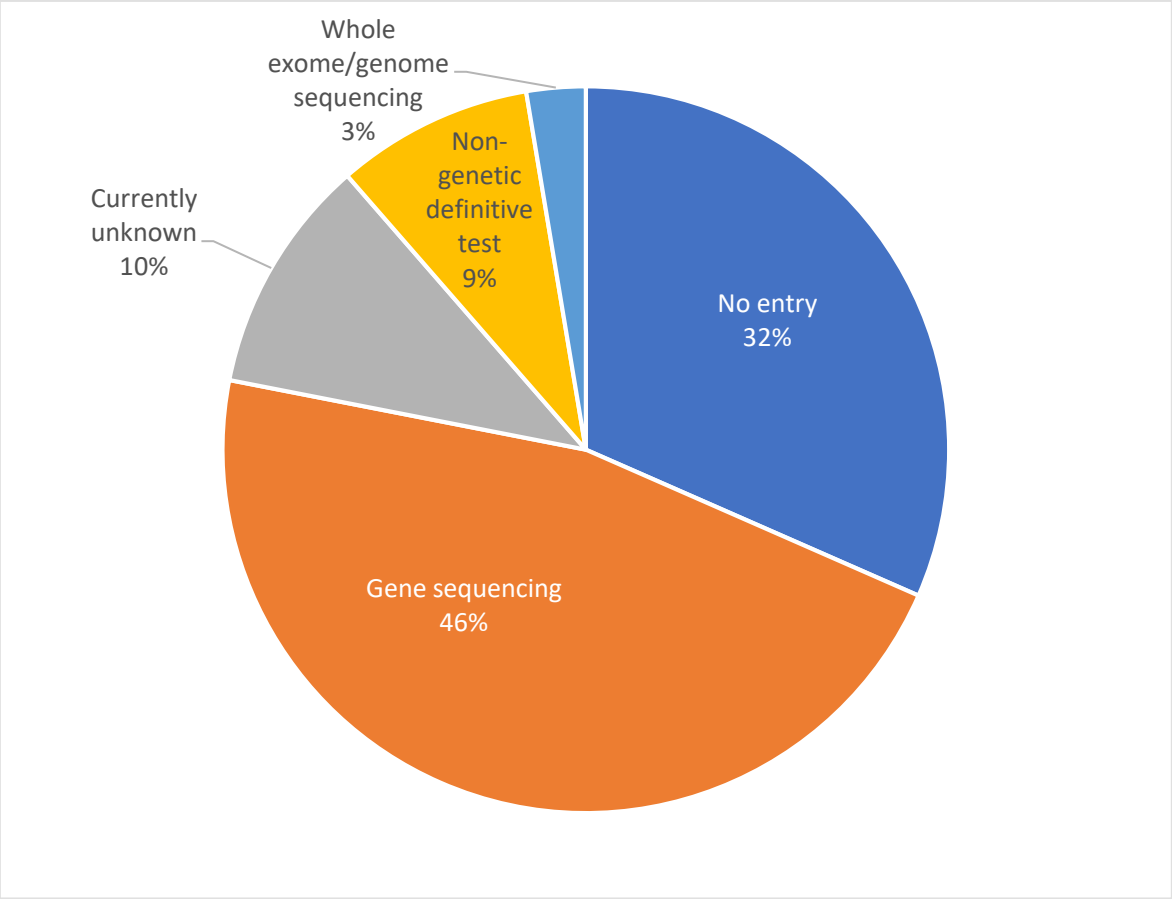

Figure 13: Sequencing methods used in genetic analyses (n=114)

In the process of this study, not solely the various laboratories responsible for genetic testing were explored, but also the sequencing methods that were used in those analyses and their frequency was examined. Figure 13 represents the frequency of sequencing methods according to the ESID registry; patients that were not genetically tested are excluded.

Of 181 Austrian patients documented in the ESID registry, 67 patients (37%) were not genetically tested; thus, their corresponding input file for sequencing methods remained empty. Those patients are not represented in Figure 13. Patient files of 66 patients revealed information on a specific sequencing method that was used in the diagnosis. Patient files of 36 patients (32%) did not contain any form of information on sequencing methods; the corresponding input fields remained empty (Figure 13). However, in 12 patient cases (10%), the type of sequencing was indicated as being currently unknown (Figure 13), which means that though the information is not

presented in the online database, it can be retrieved from the documenting centre that is responsible for those specific patients.

According to the information provided by the ESID online database, three different methods were used in the testing of documented patients. Those methods include, in descending order of frequency, gene sequencing, non-genetic definitive tests, and whole exome/genome sequencing.

The genetic material of the highest number of patients, more specifically of 53 patients, was analysed using gene sequencing, which equals to 46% of patients whose entries in the ESID online database provided information on a specific sequencing method (Figure 13).

Moreover, non-genetic definitive test was used in a rare number of patients; however, it is still the method that was performed in the second highest number of patients. In fact, the diagnosis of ten patients, which corresponds to 9%, could be verified by that form of sequencing method (Figure 13).

Whole exome/genome sequencing was solely performed in three patients, according to the entries in the ESID online database, which equals to 3% of documented patients with given information on sequencing methods (Figure 13).

3.1.9 Reason for genetic analyses

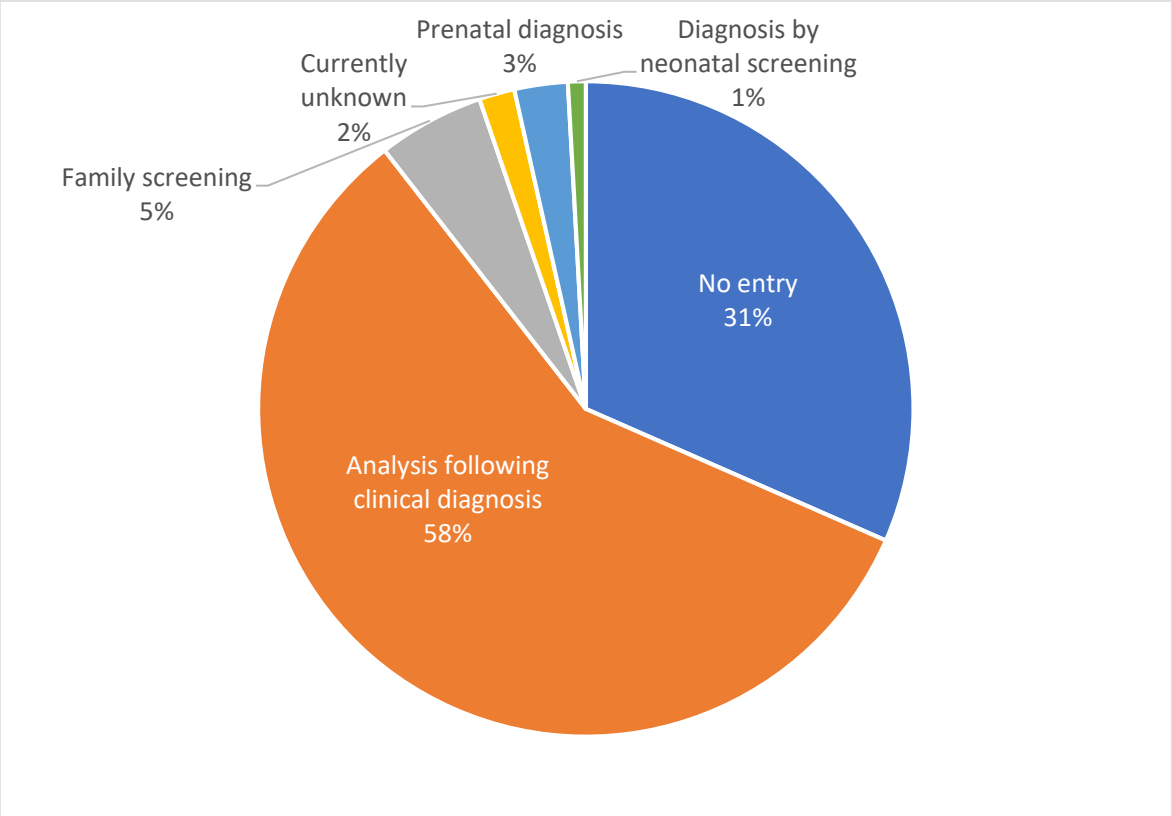

Figure 14: Reason for genetic analyses (n=114)

Another aspect concerning the process of genetic testing is the reason that led physicians and clinicians to the decision to request genetic analysis, which is demonstrated in Figure 14. In fact, study data revealed information concerning the reason for the performance of genetic analyses of 114 patients. 67 patients were not genetically tested and therefore showed no reason concerning genetic testing; they are not represented in Figure 14.

The input fields of 36 patients contained no information on a specific reason, which equals to 31% of patients, and in two patient cases (2%) the reason for genetic analysis is indicated as being currently unknown, which can be seen in Figure 14.

According to the information of those patients that contained a specific reason for analysis in the ESID registry, four different aspects could be identified. In the highest number of patients, more precisely in 66 patients (58%), clinical diagnosis led to the performance of genetic testing (Figure 14). Continuing, family screening detected an inborn error of immunity in six patient cases (5%) and can be seen in Figure 14. Prenatal diagnosis could be accomplished in three patients (3%), while neonatal screening identified an inborn error of immunity in one patient (1%) (Figure 14).

3.1.10 Familial cases

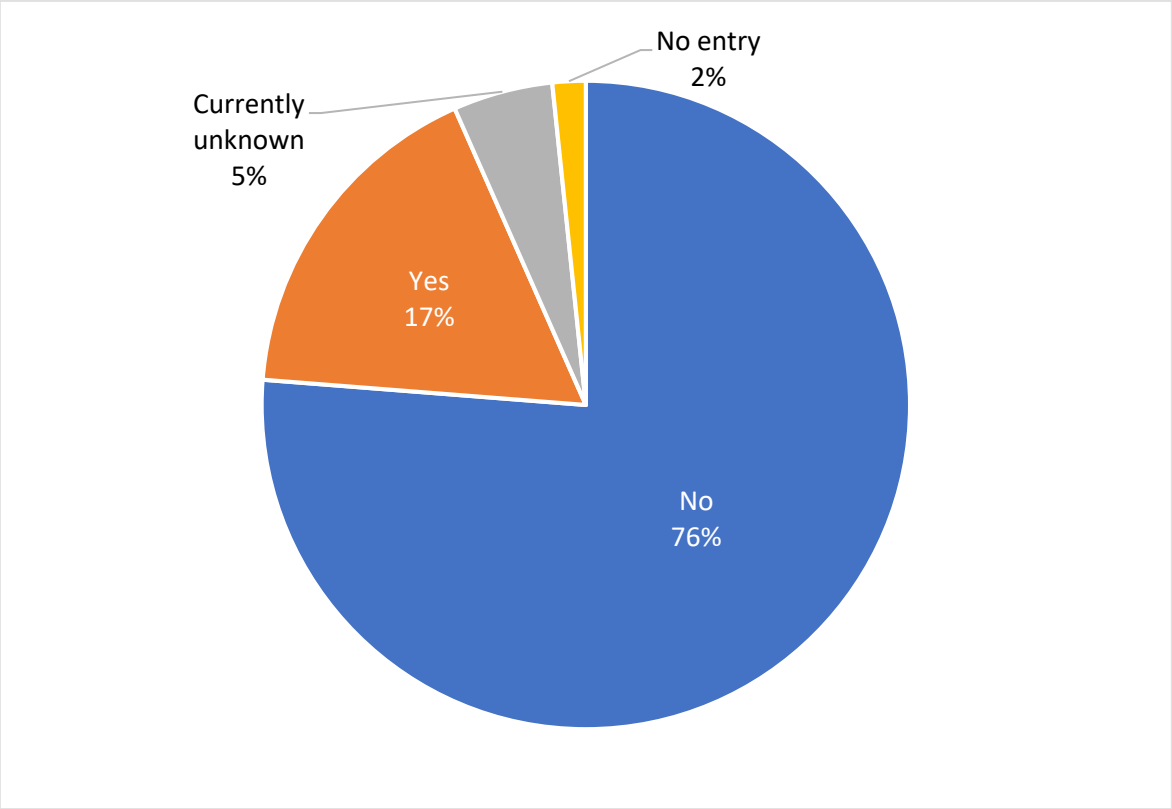

Figure 15: Percentage of familial cases among patients with IEI in Austria (n=181)

The ESID online database provides information on whether a certain patient case is a familial case, which means that either a parent or a sibling had already been diagnosed with a certain kind of inborn error of immunity. Figure 15 shows the prevalence of familial cases in the Austrian ESID registry.

To start with, of all 181 patients documented in the Austrian ESID online database, 169 patient files contained specific information on whether a patient case is a familial case. In the case of 12 patients, corresponding to 5% of documented patients, the patient files provided insufficient information regarding familial cases, that is it was either currently unknown whether those patients had affected relatives or the corresponding input fields remained entirely empty (Figure 15). However, the study revealed that 31 patients had at least one other person in their family already diagnosed with an IEI; therefore, those patient cases represented a familial case. To put it differently, 17% of all documented patient cases in Austria were familial cases (Figure 15).

Furthermore, Figure 16 demonstrates the percentages of familial cases with identified and not identified index patients. Due to the option to indicate index patients in the case of a positive history of IEI of a patient, it could be concluded that in 17 patient cases there had already been an index patient identified. This made up to 55% of all familial cases in the Austrian ESID online database, shown in Figure 16. Nevertheless, in 45% of all familial cases, corresponding to 14 patients, the index patient remained unknown (Figure 16).

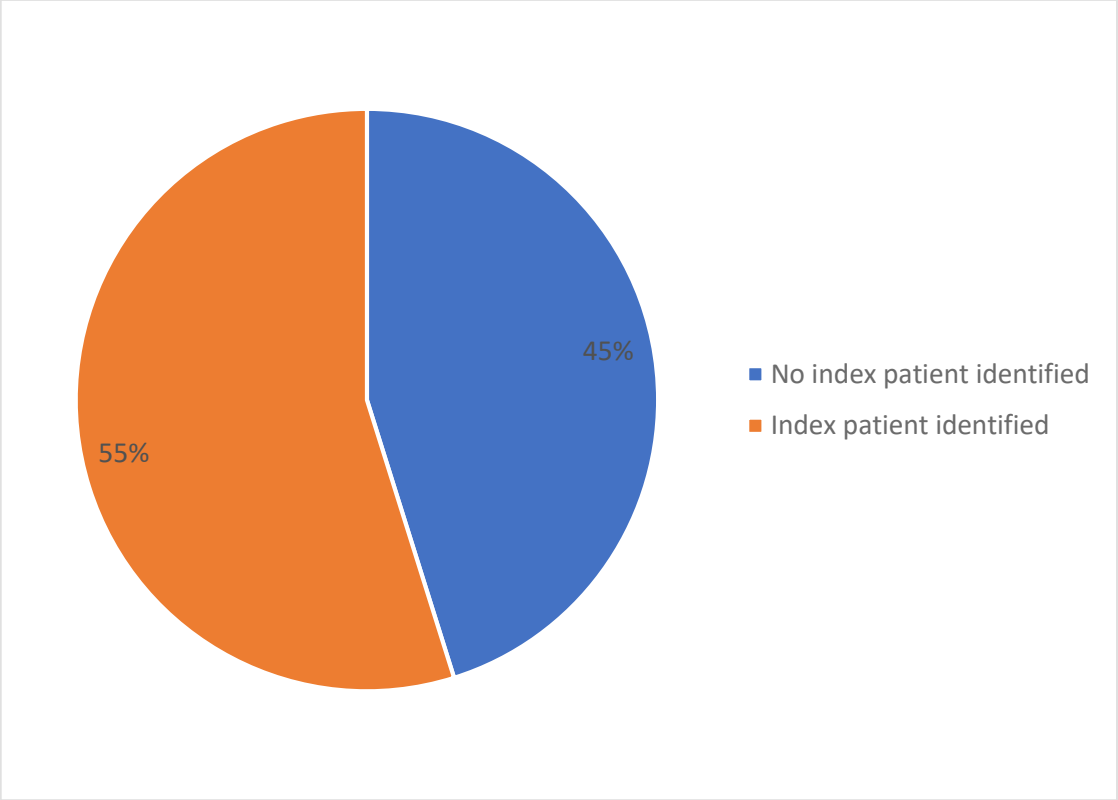

Figure 16: Percentage of identified index patients in familial cases (n=31)

3.1.11 Patients with level 1 documentation

Regarding the percentage of patients with completed level 1 documentation in the online database, of all 181 registered patients in Austria, level 1 had already been completed in the files of 141 patients (78%). On the other hand, in the files of 35 patients, corresponding to 19% of patients, there was still missing information in order to accomplish an entire level 1 documentation. Besides that, in the files of five patients, in 3% of patients to put it differently, it was not indicated whether level 1 documentation has already been accomplished.

3.2 Patient characteristics

In the following chapter, various results regarding patient characteristics will be presented. Those results will more closely give an insight into different aspects of the registered patients' histories, such as symptoms, timepoints of manifestation and diagnosis, consanguinity of parents, or living status.

3.2.1 Presenting symptoms

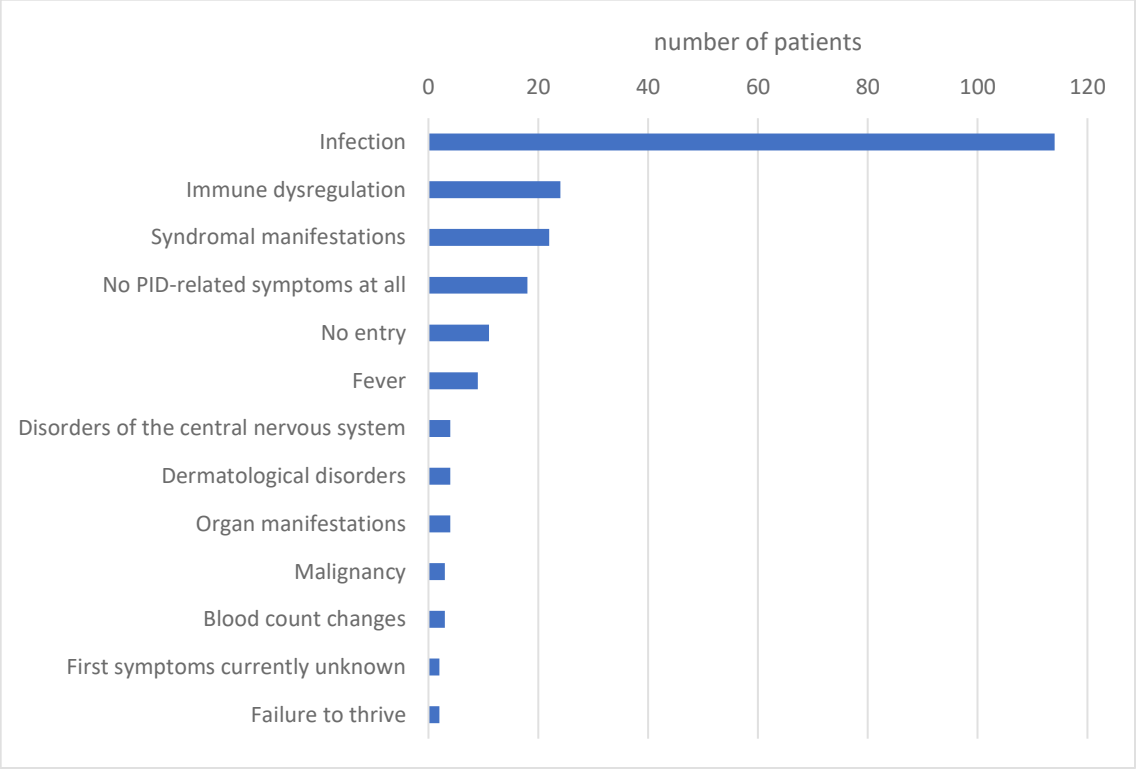

Figure 17: First IEI-related symptoms

After the extraction of data from the 181 patients from the Austrian ESID online database, the wide range of symptoms that patients showed at the onset of their disorder and which were associated with IEI were examined. Figure 17 provides a presentation of the prevalence of the presenting onset symptoms. Various patients manifested with multiple symptoms; therefore, the total number of observed symptoms is higher than the number of patients.

To start with, infection was the most common IEI-related symptom to be observed in documented patients in Austria. In other words, of 181 patients, 63% of patients manifested with infection, corresponding to 114 patients as demonstrated in Figure 17.

However, in 13% of patients, immune dysregulation was indicated as having been the first symptom associated with an IEI. In fact, immune dysregulation was the symptom of onset in 24 patients according to the Austrian ESID online database (Figure 17).

In the files of 22 patients, which corresponds to 12% of patients, an inborn error of immunity initially showed syndromic manifestations (Figure 17).

Quite contrary to the former mentioned syndromic manifestation, another initial symptom was fever, which was observed in 9 patients (5%) of the 181 documented patients (Figure 17). In detail, fever as the first IEI-related symptom was observed in the form of recurrent as well as periodic fever attacks.

Moreover, the study additionally revealed that an IEI initially manifested also by disorders of the central nervous system, as they were observed in four patients (Figure 17). Those disorders comprised ataxia, which could be observed in three patients, and microcephaly, having been detected in at least one patient of the Austrian ESID registry.

Dermatological disorders as first IEI-related symptoms were present in four documented patients in the Austrian ESID online database, as can be seen in Figure 17. More precisely, dermatological disorders comprised cutaneous lupus erythematosus, skin rashes in combination with increased inflammation values, dystrophy in combination with dermatitis and ichthyosis, as well as multiple cutaneous abscesses. Those former mentioned dermatological disorders were detected in one patient each.

Besides skin affection, inner organs were equally observed to be the cause of manifestation of an IEI. Those organ manifestations, which were found to be the symptom of onset in four patients (Figure 17), comprised hepatosplenomegaly, compression of the oesophagus after lymphadenitis, arthralgia, and adenopathy. Each organ manifestation was observed in one patient.

Additionally, blood count changes were observed in three patients (Figure 17). In detail, neutropenia, thrombocytopenia, or unclear pancytopenia were observed in one patient each.

Moreover, three patients manifested due to malignancy (Figure 17).

Finally, failure to thrive was observed in two patients and responsible for their inborn error of immunity to become clinically present (Figure 17).

However, although the first IEI-related symptoms were seen to be of a broad range, in 18 patients still no IEI-related symptoms were observed at all, adding up to a total of 10% of patients. Furthermore, in two patients the first symptoms were indicated as being currently unknown according to the entry in the ESID registry. Unfortunately, the files of 11 patients provided no information regarding first IEI-related symptoms.

3.2.2 Quality of diagnosis

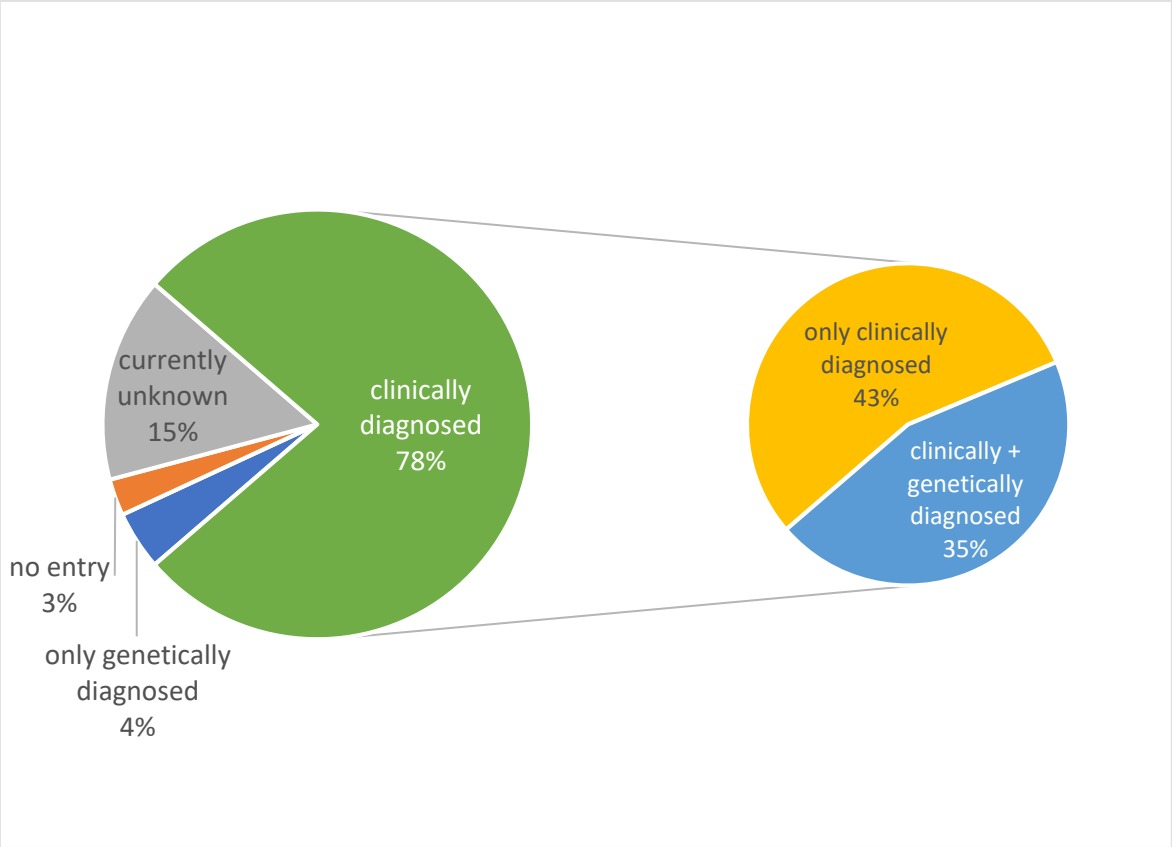

Figure 18: Quality of diagnosis

Figure 18 displays a presentation of the quality of diagnosis in Austrian patients from the ESID Registry. The term quality of diagnosis is used to describe different portions of patients regarding the level of diagnosis that had been accomplished in those patients. As demonstrated in the pie chart on the left side of Figure 18, the percentage of patients that had been clinically diagnosed is visible. In the smaller pie chart on the right side of Figure 18, the portion of patients clinically diagnosed is further divided into those patients that had only been clinically diagnosed and those patients with a clinical as well as a genetic diagnosis.

Of 181 documented patients, 78% contained at least a clinical diagnosis in their ESID files, which means that the date of a clinical diagnosis is available in the patients' entries (Figure 18). That percentage corresponds to 140 patients out of a total of 181 patients. 78 patients (43%) were genetically diagnosed.
On the other hand, 4% of patients did not have a clinical but solely a genetic diagnosis; thus, eight patients were only genetically diagnosed (Figure 18).

Moreover, in 15% of all registered patients, corresponding to 28 patients, it cannot be concluded, according to the ESID registry, whether those patients did have a clinical diagnosis since the corresponding input fields indicated that the information had been currently unknown (Figure 18). As mentioned in the former sections, that information could be retrieved from the physicians and clinicians responsible for those patients; however, it cannot be retrieved from the stored information in the ESID online database directly. Unfortunately, in 3% of cases, corresponding to five patients, no information was given regarding a clinical diagnosis; the input fields remained entirely empty (Figure 18).

Examining those patients with a clinical diagnosis in more detail, the files of 63 patients additionally contained a genetic diagnosis in the ESID online database. Thus, 35% of clinically diagnosed patients had additionally also been genetically diagnosed (Figure 18). Therefore, those patients show a rather high quality of diagnosis as their diagnosis of an IEI had not only been clinically but also genetically verified. Still, 43% of patients do have a clinical diagnosis, but are still missing a genetic diagnosis, which equals to 77 patients (Figure 18).

3.2.3 Age at diagnosis

In this section, there will be a presentation of the age of patients regarding diagnosis. Generally, regarding the age at clinical diagnosis of Austrian patients in the ESID registry, the average age at diagnosis was 15.04 years, while the median age at diagnosis was found to be 6.17 years. According to the analysis carried out in this study, of 140 clinically diagnosed patients, 61 patients were aged five or younger than that when their clinical diagnosis was made. Almost half of those patients, more precisely 32 patients, were aged one or younger at the time of their clinical diagnosis, which corresponds to 23% of the 140 clinically diagnosed patients. Of those below the age of one year, study data revealed that 22 patients had their clinical diagnosis within the first six months after birth, while another ten patients were clinically diagnosed during the second half of their first year of life. Furthermore, eleven patients were older than one year, but below the age of two years at the time of their clinical diagnosis. Nine patients were aged over two but younger than three years when clinical diagnosis was made, five patients older than three and younger than four years, and finally, four patients were aged over four and younger than five years.

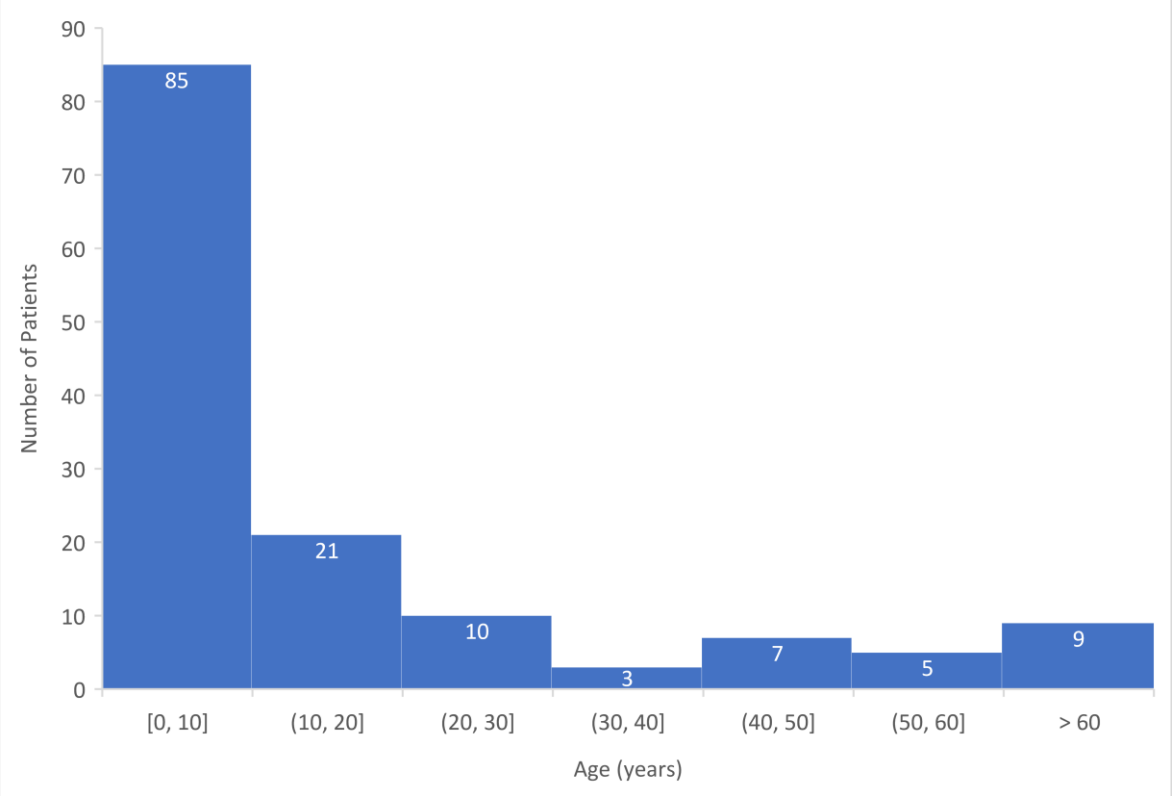

Figure 19: Age at clinical diagnosis in different decades of life

As Figure 19 demonstrates the number of patients clinically diagnosed in different decades of life, the highest number of patients can be found in the age group between birth and ten years of age. In fact, 85 out of 140 clinically diagnosed patients were aged under ten at the time of clinical verification of an inborn error of immunity (Figure 19). After ten years of age, the number of patients to be clinically diagnosed with an IEI decreases to 21 patients in the age group from 10 to 20 years, further decreasing in the age group from 20 to 30 years to 10 patients (Figure 19). Moreover, though the patient numbers are quite small, a slight peak was observed in the age group from 40 to 50 years. During that period, to be more precise, seven patients were clinically diagnosed in contrast to three clinically diagnosed patients in the age group from 30 to 40 years (Figure 19).

3.2.4 Diagnostic delay

Figure 20: Age at diagnosis and diagnostic delay of patients with initial manifestation between birth and the age of five years (n=39)

In this section, the term *diagnostic delay* will be introduced and explained in more detail in the following lines. For the analysis of the diagnostic delay in this study, data of 47 patients whose ESID entries contained information on the age at manifestation and the age at clinical as well as genetic diagnosis was used. Figure 20 represents the diagnostic delay of patients with initial manifestation between birth and the age of five years. In Figure 20, the age of a patient at the time of the onset of the first IEI-related symptoms is shown on the X-axis. On the Y-axis, the age of the same patient at the time of clinical diagnosis is demonstrated. Patients between birth and the age of five years are included in the presentation to focus on the diagnostic process in that life period. Furthermore, by the aid of vertical lines, the chart demonstrates the diagnostic delay which is used to describe the time period that had passed between the clinical and the genetic diagnosis of a patient. The median diagnostic delay in Austrian patients with IEI was 0.25 years.

Basically, under the condition that a patient is clinically diagnosed shortly after the development of the first symptoms, the graph in Figure 20 and Figure 21 would be of a linear character. Thus, outliers in Figure 20 and Figure 21, which deviate from the estimated linear graph, suggest that there was a delay regarding the clinical diagnosis after the initial onset.

The greatest so-called diagnostic delay can be seen in the middle of Figure 20. The corresponding patient developed symptoms associated with an inborn error of immunity at the age of two and was clinically diagnosed four years after at the age of six; however, another twelve years had passed until a genetic diagnosis of an IEI could be accomplished in that patient (Figure 20). Therefore, this demonstrates the greatest diagnostic delay that could be found in the ESID online database of Austrian patients.

Generally, regarding the diagram presented in Figure 20, it becomes evident that specific patient cases are associated with a diagnostic delay. 28 patients had their diagnosis verified by genetic testing within one year after onset of symptoms, which equals to 59% of analysed patients. The longest diagnostic delay was twelve years. Seven patients remained without a definitive genetic diagnosis for three years after manifestation. In eight patients, including the patient case mentioned above, a genetic diagnosis could only be verified one or more years after the clinical diagnosis was made. Still, the fact that there is a great amount of cases with no or a short vertical line represented in Figure 20, demonstrates that in a high proportion of cases there is a minimal time delay between the clinical and the genetic diagnosis.

Moreover, as can additionally be seen in Figure 20, the greatest proportion of patients develop IEI-related symptoms for the first time up to the end of their first year of life. Indeed, there is a high density of patients within the first six months after birth, indicating that most of the patients develop symptoms quite early in their lives.

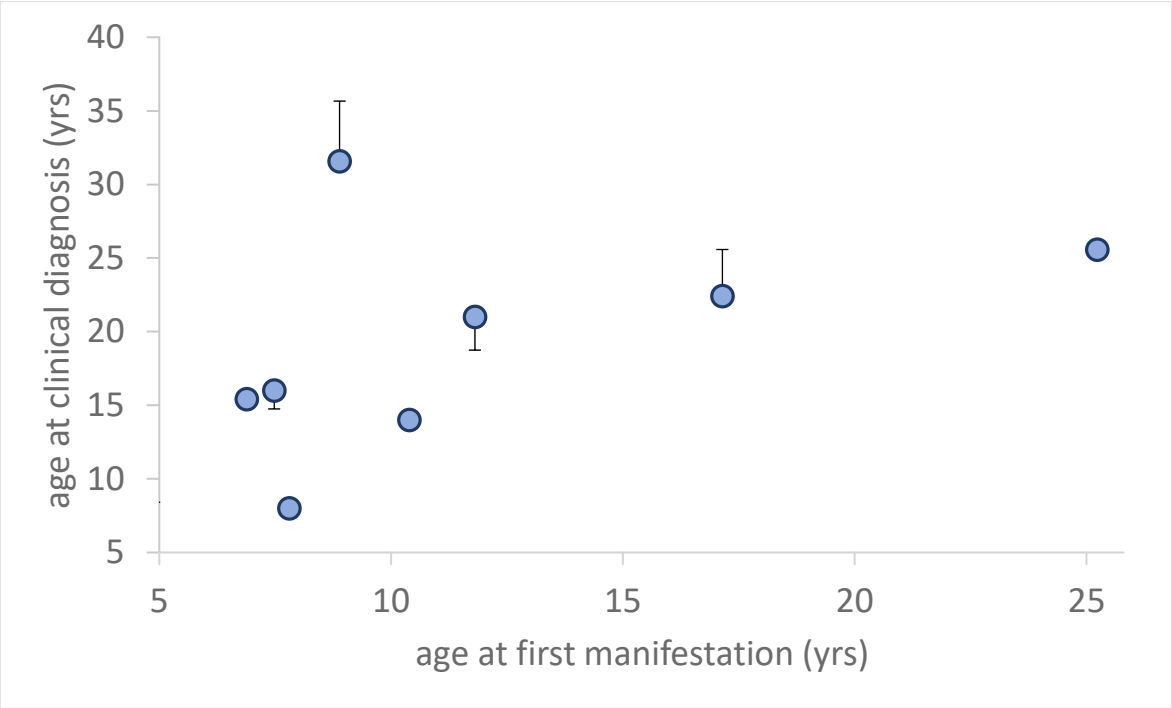

Figure 21: Age at diagnosis and diagnostic delay of patients with initial manifestation between the age of 5 and 25 years (n=8)

Figure 21 represents the diagnostic delay of patients with initial manifestation between the age of five and 25 years. Eight patients, whose ESID entries contained specific time points regarding manifestation, clinical, and genetic diagnosis, were found in that age group and are represented in Figure 21. According to the ESID registry, in two patients genetic testing was performed prior to a clinical diagnosis; in fact, one patient was genetically diagnosed at the age of 18, but clinically diagnosed at the age of 21, and another patient was genetically diagnosed at the age of 14, while clinical diagnosis followed two years later at the age of 16. In five patients, a genetic diagnosis was made within one year after manifestation. In two patients, a diagnostic delay of three and four years respectively was observed.

3.2.5 Further findings

In this section, further findings regarding patient characteristics will be presented in textual form.

Regarding the living status of documented patients in the ESID online database in Austria, 173 patients out of a total number of 181 patients were alive at the time of data analysis in May 2019, which equates to 96% of patients. Nevertheless, eight patients (4%) were documented as being deceased.

Moreover, another information that the ESID online database provides about its documented patients is whether the parents of a patient with an inborn error of immunity were found to be in a relationship of consanguinity. During the process of data analysis, the frequency of parental consanguinity was investigated. In the cases of seven patients, consanguinity of parents could indeed be found, which corresponds to 4% of all documented patients in the Austrian ESID online database. However, in 14 patient entries (8%) there was either no information given or the information on consanguinity of parents was currently unknown, which means that the only possibility to gain further information is through the contact of the physicians or clinicians responsible for those specific patients.

3.3 Treatment

In this chapter, study results regarding therapeutic measures will be demonstrated, such as the results concerning the assessed treatment types in general as well as findings about the various types of treatment of inborn errors of immunity and their characteristics.

3.3.1 Treatment types

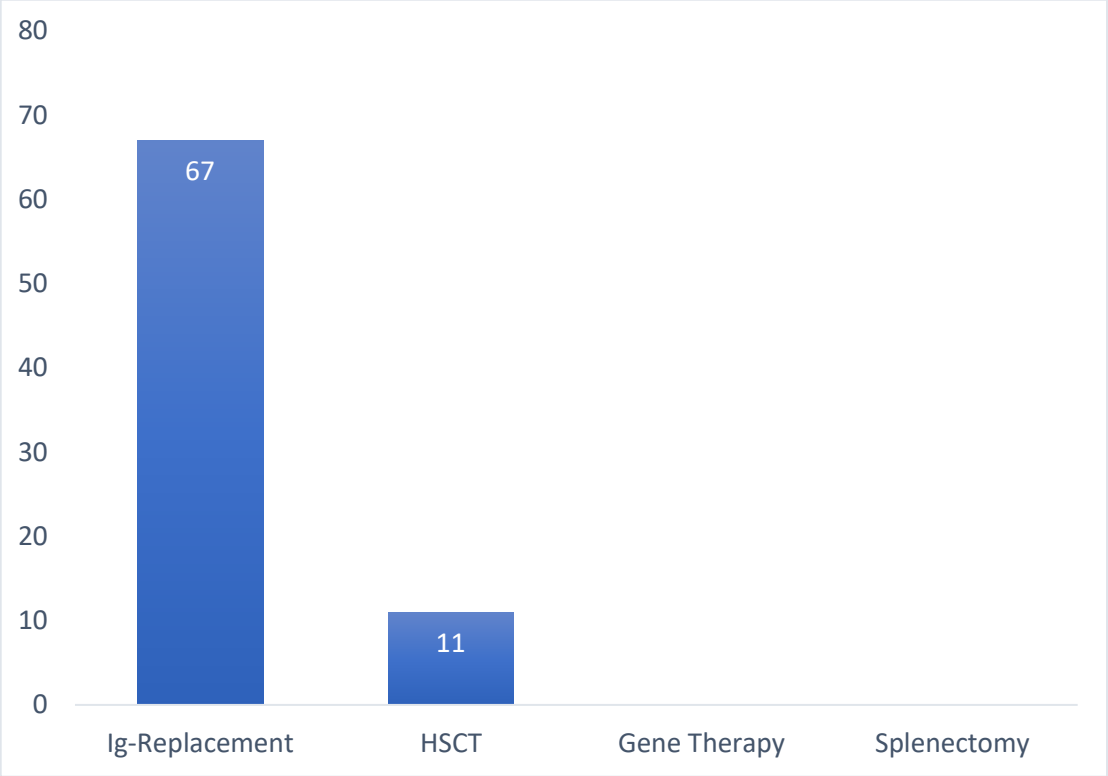

Figure 22: Treatment types assessed in ESID registry (n=78)

At the time of data analysis, the ESID registry only contained the possibility to select a treatment type out of four options. More precisely, the assessed treatment types to be selected from were immunoglobulin replacement therapy, hematopoietic stem cell transplantation, gene therapy, and splenectomy. The ESID registry contained no possibility to select any form of antibiotics or other therapy types. Figure 22 represents data on treatment of all patients whose ESID entries contained information on a specific treatment type, specifically of 78 patients, more precisely, it shows the frequency by which the former mentioned treatments were performed in Austrian patients.

According to the data extracted from the ESID registry, 67 patients out of a total number of 181 patients had been receiving immunoglobulin replacement therapy (Figure 22). To put it differently, 37% of all patients were under the treatment of immunoglobulin replacement therapy.

Furthermore, HSCT was performed in eleven patients, as can be seen in Figure 22, which corresponds to 6% of all documented patients.

As reported in the ESID registry, no patient had yet received gene therapy or splenectomy in Austria.

3.3.2 Hematopoietic stem cell transplantation

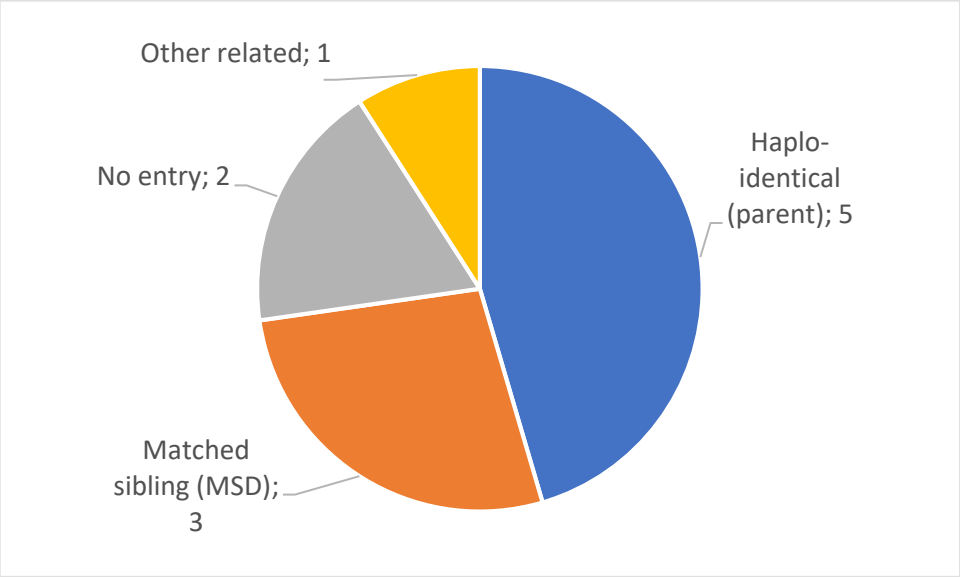

Figure 23: HSCT, type of donor (n=11)

In the case of hematopoietic stem cell transplantation in a patient, the ESID online database provides the opportunity to indicate the type of donor that was selected for the transplantation. As mentioned earlier and displayed in Figure 22, HSCT could be performed in eleven individuals. Figure 23 represents various types of donor in patients undergoing HSCT. Of those eleven patients, in five cases the type of donor was found to be haplo-identical, that is it was a parent of the patient (Figure 23). Moreover, in three transplantations a matched sibling served as the donor of stem cells while in one case of HSCT a person indicated in the ESID database as “other related” donated the corresponding tissue or blood to a recipient (Figure 23). Unfortunately, in two cases of HSCT, no information was given concerning the type of donor that was used (Figure 23).

Regarding the source of tissue CD34 stem cells were derived from for the transplantation, according to the ESID registry, peripheral blood was used in seven patient cases, whereas bone marrow was selected for two patients as the source of stem cells. However, the selected tissue to be used for the transplantation remained unclear in two cases of HSCT.

3.3.3 Immunoglobulin therapy

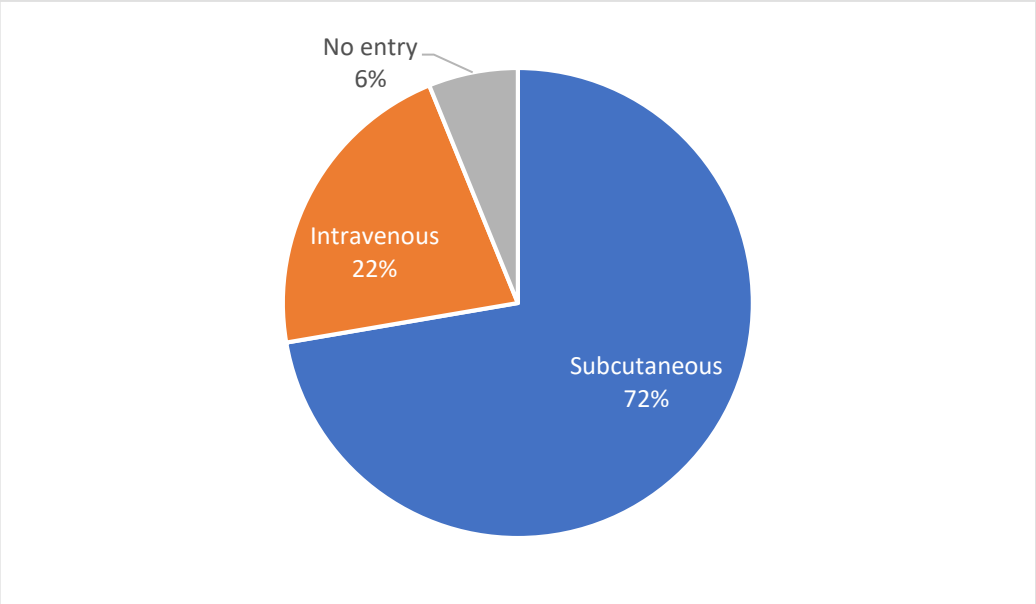

Figure 24: Immunoglobulin therapy, routine of administration (n=67)

As pointed out in Figure 22 from the preceding section, immunoglobulin therapy was performed in 67 Austrian patients documented in the ESID registry. In order to provide more information on the characteristics of the performed immunoglobulin replacements, Figure 24 illustrates the routine administration in the case of 67 patients with replacement therapy. In the ESID registry, a selection between intravenous or subcutaneous administration can be made. The analysis of data revealed that immunoglobulin therapy was subcutaneously administered in 47 patients (72%), shown in Figure 24, marking that form of administration as the most commonly used administration routine in Austrian patients. In 14 cases, corresponding to 22% of immunoglobulin therapy cases, intravenous administration was used (Figure 24). Finally, in 6% of cases no information was provided regarding the routine of administration by the ESID online database (Figure 24).

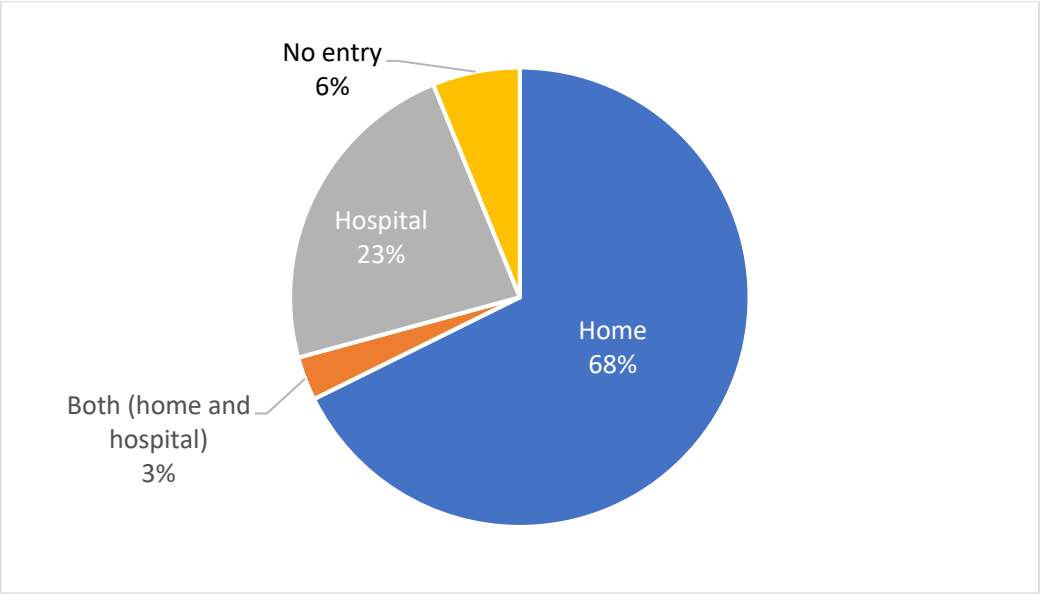

Figure 25: Immunoglobulin therapy, place of administration (n=67)

Moreover, Figure 25 gives a visual presentation of the place of administration for immunoglobulin replacement therapy. 44 patients received therapy at home, corresponding to 68% of performed immunoglobulin replacement therapies, which can be seen in Figure 25. In 23% of cases, immunoglobulin therapy was performed in the hospital while in 3% of cases both a hospital as well as the home of patients served as the place for administration (Figure 25). Unfortunately, in 6% of immunoglobulin replacements the ESID registry provided no specific information on a certain place of administration (Figure 25).

3.4 Survey Findings

In this part, there will be a presentation of the main findings of the questionnaire which was sent out to and answered by clinicians in the care of patients with inborn errors of immunity. The information in this section primarily presents the key results from the survey; however, it will not include all data by covering all answers but highlight specific results that seem to be of high significance. The full questionnaire can be found in German in the appendix section. Moreover, the findings will be presented anonymously.

Table 4 presents survey questions and the answers of participants in keywords.

Question (keywords)	Answer	
Number of treated IEI patients at medical centres participating in survey	Range: 0 – 312 patients Median: 53 patients	
Establishment of ESID registry at medical centre of survey participants	Already established	8 centres
	In planning	1 centre
	Not planned	1 centre
Survey participant is main responsible person at his/her medical centre regarding ESID registry	Yes	7 times
	No	3 times
Knowledge concerning ESID registry	Medical staff has full knowledge	1 time
	Medical staff knows only parts	1 time
	Specific people with detailed knowledge	8 times
Number of people with access to ESID online database	Range: 0 – 4 people Median: 1 person	
One person is primarily responsible for entering data	Yes	7 times
	No	3 times
Persons entering data into the registry	One defined person	6 times
	Medical specialists	1 time
	Research staff	3 times
	Nurses	1 time
Need of assistance in entering data (multiple answers were selected)	Yes	8 times
	No	4 times
	Uncertain	1 time
Problems encountered in the process of entering data into the registry	Yes	2 times
	No	4 times
	Uncertain. / Not specified.	2 times
Opinions on whether the registry's restructure led to improvement of the registry during clinical routine	Yes	5 times
	No awareness of registry before restructure	4 times
	No answer	1 time
Opinions on specific changes of the registry after its restructure (multiple answers were selected)	Data entry simpler	5 times
	Increased usability in clinical routine	4 times
	Increased comparability of data	1 time

	No changes observed	4 times
Frequency of data updates in ESID registry	< 1 time/month	5 times
	1 time/month	1 time
	Sporadically	2 times
Usage of parallel registries besides ESID registry to document patients with IEI	No	9 times
	Yes	1 time
Greatest benefits of ESID registry (multiple answers were selected)	Contributes to maintain overview of IEI patients	7 times
	Contributes to research	5 times
	Valuable tool in patient management	6 times
Disadvantages of ESID registry (multiple answers were selected)	Low information content	1 time
	Divergence of data	1 time
	Access limited to own centre	2 times
	Others. / Not specified.	5 times
Awareness of IEI working definitions by clinicians	Yes	8 times
	No	2 times
Usage of ESID registry for national or international research purposes or project applications	Yes	1 time
	No	9 times
Reasons for incomplete data entry (not answered by all participants)	Shortage of time besides clinical routine	6 times
	Insufficient knowledge of registry	1 time
	Insufficient training	1 time
Wishes regarding ESID registry	Documentation of malignancy incidences per year	
	Documentation of biological usage	
	More medical staff needed	

Table 4: Survey results

Initially, it is important to mention that the ESID Registry had already been established in the medical centres of eight out of ten questioned participants. One participant indicated that its establishment was already planned, while another participant communicated that the ESID Registry would not be of use at the participant's centre since patients would normally be transferred for a final diagnosis and subsequent treatment to another medical centre already documenting patients to the ESID online database.

At first, regarding the number of patients with inborn errors of immunity, that were treated in a specific documenting centre at the time of the survey, in three out of five questionnaires from centres that are steadily reporting their patients to the ESID online database, the number of treated patients would differ significantly from the

documented ones in the ESID Registry. For instance, in one specific documenting centre, the number of treated patients in contrast to the documented ones was found to be 18 times higher, which in the questionnaire demonstrated the greatest deviation between treated and documented patients. Moreover, another documenting hospital claimed to have 8.3 times more patients currently being treated than registered, while in a third centre, where there was also a difference between the two corresponding numbers, the number of treated patients was found to be only 2.9 times higher. In the questionnaires of three documenting centres, no correlation between treated and registered patients could be made since those centres had not yet been documenting their patients to the ESID Registry. One questionnaire, being answered by a corresponding person of a documenting centre, revealed no information regarding treated patients as the person indicated the question could not be answered. One participant claimed to have no patients with inborn errors of immunity.

Regarding the restructuring of the ESID Registry, all of those who had already known and been in contact with the online database before believed that the process of restructure facilitated the usage of the registry in clinical practice. There were several reasons given for this. First and foremost, in five out of ten times it was indicated that the data entry was made increasingly easier by the restructure. Moreover, one questioned person believed that the better usability is due to the fact that the data stored in the ESID Registry was made more comparable after restructuring the registry. However, though in general it was agreed on the restructure having a positive impact on the registry, in three times either no change was noted by users of the registry or no details were provided regarding that specific question. One participant did not answer that question.

Furthermore, another aspect of the survey findings was the fact that a great number of questioned persons, eight out of ten, mentioned that up to the time of the survey they did not have any kind of educational training regarding the online database of the ESID Registry. Regarding the preferred type of orientation, which should help documenting centres become more familiar with the online database and the data entry, in five times it was mentioned that a personal contact via telephone or mail including the possibility to state questions would be most helpful. Following that, in

two times it was stated that a visit by a training person at documenting centres would indeed be welcomed, while in another two times survey participants would prefer an instruction in the course of the ÖGKJ or during another form of meeting or conference. Nevertheless, in four times no instruction at all was desired since participants indicated that they would be well informed regarding data entry and usage of the online database.

Moreover, when being interviewed about the main advantages of the ESID Registry, more than two thirds, actually seven out of ten survey participants, considered the online database as a useful tool in order to maintain a better overall view of the patients currently being treated in the corresponding documenting centres of the participants. Half of the participants, five out of ten to be more precise, additionally believed that the ESID Registry would be of a great value for its usage in research, especially when being used in epidemiological studies. Moreover, another aspect regarding the greatest benefit of the registry, considered to be true by five participants, was that the registry would improve the management of patients with inborn errors of immunity since it would serve as a valuable instrument in diagnostics and treatment and contribute to a better networking between documenting centres in the case of more complex questions concerning specific patient histories.

On the one hand, survey participants generally agreed on the benefits of the ESID registry, as similar answers received a similar number of votes, on the other hand, in relation to the main disadvantages of the registry there was no consensus. While one participant considered the low information content of the registry as the main disadvantage, in another case it was stated that the main disadvantages was due to the patient data lacking in consistency. However, in two times it was agreed upon that the limitation of primarily solely gaining access to the data of patients belonging to the documenting centre in which participants are currently working at represents one of the greatest drawbacks of the ESID Registry.

In addition, as response to the reasons beyond a possible insufficient entry of patient data by certain documenting centres, the sparse time besides clinical practice was mentioned in six out of nine times. In addition, insufficient knowledge of as well as

inadequate instruction into the ESID online database were believed by one survey participant each, for their part, to be responsible for an incomplete data entry.

In relation to the usage of the ESID Registry in the context of research, survey participants were interviewed whether they had already used the database for national or international research purposes or project applications. Concerning that question, survey data showed a quite uniform picture as eight out of ten participants had not yet used the registry for research or project purposes. However, one participant indeed had already accomplished research or projects by the aid of the ESID Registry and additionally indicated to be aware of the various possibilities that the database provided in order to conduct research.

Finally, regarding the working definitions for clinical diagnosis of inborn error of immunity, that were established by the ESID Registry Working Party in order to improve the quality of clinical diagnosis (ESID Registry Working Party, 2019b; Seidel *et al.*, 2019), eight participants claimed to be aware of that list and four of them would additionally use the diagnostic criteria in their daily clinical routine. Still, in two out of ten times survey participants indicated that the working definitions for clinical diagnosis would be unfamiliar for them.

4 Discussion

Ten years after its establishment in Austria, the ESID registry is used by six medical centres for the documentation of their patients with IEI and currently comprises data on 181 Austrian patients. For clinicians which regularly document patients to the registry, its establishment has facilitated the management of patients and aided in gaining a better overview on them since survey results showed a general agreement concerning those aspects.

4.1 General findings and comparison of Austrian results to European ESID findings

Firstly, though the distribution of IEI main categories displays a clear dominance of predominantly antibody disorders when the entirety of Austria is considered, the distribution in the documenting centres shows a different image. According to the study data, a clear dominance of “other well defined IEI” was observed regarding the patients documented by the Children’s and Women’s Hospital in Linz since more than three thirds of patients (72.2%) were documented with that IEI category. This contrasts with the distribution of IEI in other documenting centres in Austria where “other well defined IEI” reach the highest prevalence in the Hospital of Klagenfurt (35.3%); still, this corresponds solely to half of the prevalence documented by the documenting centre of Linz. Moreover, the Department of Internal Medicine of the University of Graz further differs from other documenting centres regarding the main categories of IEI as predominantly antibody disorders reach a high percentage. In fact, 86.8% of patients are documented with a predominantly antibody disorder, while those disorders solely constitute 42% of patient cases when considering the entirety of Austrian patients in the ESID registry. However, this discrepancy is expectable, because it is the only centre with mainly adult patients so far, with an inherent higher proportion of patients with CVID. Still, previously mentioned aspects may raise the question whether there is a prevalence of some centres for primarily documenting certain kinds of IEI categories. Moreover, regarding the main categories, Austrian results are in accordance with certain international findings since similar results were found by other European countries using ESID registry data, with predominantly antibody disorders as the leading IEI category in, for instance, Germany, Switzerland, France, and the United Kingdom (CEREDIH: The French PID study group, 2010; Edgar *et al.*, 2014; Marschall *et al.*, 2015; El-Helou *et al.*, 2019). Across European borders, data derived from the Iranian Primary

Immunodeficiency Registry equally identified predominantly antibody disorders as the main IEI category in Iranian patients (Aghamohammadi *et al.*, 2014). However, the prevalence of predominantly antibody disorders in Austria was found to be higher compared to results of Kuwaiti patients published in a recent paper, which showed that in Kuwait patients were only diagnosed with that group of disorders in 17.8% of IEI cases, compared to the 42% of Austrian patients, and mainly diagnosed with immunodeficiencies affecting cellular and humoral immunity (Al-Herz *et al.*, 2019).

Regarding the number of registered patients per country, it became evident that fewer patients have already been documented in the eastern than in the western part of Europe and the number of documented patients per country varies to a great degree. France, Slovakia, and Slovenia currently have ten, twelve, and six documented patients respectively per 100.000 inhabitants, therefore displaying the European countries with most registered patients per 100.000 inhabitants. Compared to Austria with two documented patients per 100.000 inhabitants, their registration rate in relation to their inhabitants was observed to be quite higher. Additionally, in Austria, an uneven geographical distribution regarding documented patients can as well be seen since all documenting centres are in the middle and eastern part of Austria. In fact, no patients from the western part of Austria are yet included in the ESID registry; thus, data from the ESID registry currently fails to represent characteristics of patients from all Austrian regions.

In line, in relation to the coverage of European patients with IEI, it became evident that the Austrian rate (16.98%) can be considered rather low when compared to that of its neighbouring states, especially that of Germany (29.53%), Hungary (23.68%), Czech Republic (30.15%), Slovakia (120.10%), Slovenia (53.30%), and Switzerland (58.06%); only Italy has a lower rate than Austria (Italy: 8.96%). This may suggest that, firstly, special efforts need to be taken to increase the awareness of Austrian doctors regarding primary immunodeficiencies and their clinical presentation, and secondly, information about the existence of the ESID registry and the modality of entering patients into it need to be communicated more efficiently. Further, potential obstacles or reasons for the low participation need to be identified.

Moreover, regarding onset symptoms, results represent infection as the most common initial symptom of manifestation in Austrian patients, according to the ESID registry. However, while infection displays the symptom of onset in more than half of documented patients, it became evident that the first clinical presentation of IEI can be quite diverse. This implies that; besides infection, other presenting symptoms equally require special attention and must be considered as a potential form of manifestation of an IEI, such as immune dysregulation or syndromic manifestations.

Regarding diagnostic delay, of 47 patients whose ESID entries contained specific information on the time of onset and the time of clinical, as well as genetic diagnosis, 28 patients had their diagnosis verified by genetic testing within one year after clinical diagnosis. Thus, the diagnostic delay can be regarded as being minimal in more than half of the patients considered for the analysis. However, a greater diagnostic delay, for instance up to twelve years, could be still observed. This highlights the importance of comprehensive clinical patient evaluation and genetic testing in order to provide patients earlier with appropriate therapy according to their underlying genetic defect.

4.2 Benefits and barriers of the ESID registry and survey results

Additionally, in the course of this thesis, a special emphasize was put on investigating the benefits and barriers that are associated with the ESID registry and its online database. Basically, as one of its greatest expected advantages, the ESID online database was found in our survey to be a valuable and practical tool for the analysis of centre-oriented as well as national data of patients with IEI. Since the database is easily accessible from any kind of device under the sole condition that a user-login and a password is provided, analysis can be done from various places and at any kind of desired time. Thus, the database is not limited to the usage during clinical hours. Moreover, as it is not solely possible to access patient data belonging to the clinicians' own documenting centres, but also to further gain access to nationwide data of patients, it enables clinicians to include a higher number of patients in projects or analyses. Therefore, this contributes to statistically more significant results, further highlighting a great benefit of the ESID registry in terms of research and projects. This kind of transparency about the number and distribution of Austrian patients with IEI could facilitate the feasibility assessment of national studies, increase the cooperation levels of the Austrian network for clinical

immunologists, and even, on the centre-level, enable maintaining a GDPR-conform real-time list of IEI patients, including their current treatment etc. Internationally, a high number of registered patients may be crucial for the participation in studies, which may be highlighted by the fact that Austrian data was excluded from analysis in a comprehensive study on hypogammaglobulinemia due to a low number of registered Austrian patients according to a paper (Schatorjé *et al.*, 2014).

Moreover, as the ESID database enables extracting certain patient data automatically to offline documents, such as excel or pdf sheets, clinicians or researcher can immediately initiate analysis, therefore facilitating the working process. However, though certain patient data can be extracted, there is still a great amount of data that is not included in the extracted file, which can be regarded as a drawback of that database function.

As far as barriers of the ESID registry are concerned, one of the main aspects that must be mentioned is that, currently, all the patient data is derived from few documenting centres in the middle and eastern part of Austria, as mentioned above, limiting the epidemiologically representative character. Thus, when patient data is used in analyses, results fail to represent the entirety of Austrians patients with IEI. Furthermore, as has been revealed by the help of the questionnaire within this thesis, a great number of patients currently being treated in Austrian centres have not yet been documented to the ESID registry, even though the corresponding medical centres are already participating. This was evident by the discrepancy between the actual number of treated patients indicated in the questionnaires by various documenting centres and the number of already registered patients in the ESID online database. This implies that the ESID registry currently fails to represent data of all treated IEI patients, highlighting the importance to encourage and support a more comprehensive data entry.

What is more, another factor that may be complicating data analyses is the inconsistency of patient data in the online database. Some entry fields in the patient tabs provide database users with a variety of selectable input data possibilities. For instance, regarding the date of onset of symptoms, it is either possible to select a specific data, a specific year, or a time period that can range from one to five years.

Indeed, for various patients it is not possible to indicate a specific month of onset; however, for the analysis of patient data the diversity of entry information represents a complicating factor.

Additionally, since the process of restructure of the ESID registry in 2014, which was necessary to improve data quality and stringency by reducing the number of obligatory items and details (Grimbacher, 2014), thereby cutting the average time needed for an entry to a fraction of few (5-15) minutes per patient, the online database contains fewer information. Consequently, fewer information is available in level 1 datasets for research as well as for clinicians to compare their own patients to those of other documenting centres. However, the fact that level 1 datasets are mandatory for all documented patients (Grimbacher, 2014) may suggest that those fields are of special importance for feasibility and epidemiological studies, further displaying a major basis for clinical studies of pharmaceutical companies. This additionally implies that a complete level 1 documentation, which so far could not be accomplished in 19% of documented cases in Austria, is crucially important, otherwise Austrian patients may not benefit from clinical trials by international pharmaceuticals.

Furthermore, a major disadvantage of the ESID registry is the current limitation in selectable options since a selection can solely be made between immunoglobulin therapy, HSCT, gene therapy, and splenectomy. Important other treatment options, such as the use of antibiotics in the prevention and treatment of infections, or on biologicals to treat manifestations of immune dysregulation, are missing and therefore cannot be included in statistical analyses using the registry data. Moreover, regarding the frequency of certain types of treatment assessed in the registry, it needs to be stated, that some part of the data is additionally prone to be under-representative for one main reason. The main proportion of IEI patients in need of transplantation are new-borns or infants with SCID who are likely to be admitted to a transplant unit without ever seeing the immunodeficiency outpatient clinic. Thus, they are very likely to be registered in the EBMT and SCETIDE databases (pendants to the ESID registry for patients undergoing HSCT and suffering from a primary immunodeficiency) and seen in HSCT follow-up clinics only, therefore escaping a second time the ESID registration.

4.3 Conclusions

Finally, it needs to be stated that all centre-specific analyses carried out within this study, either the analyses of diagnostic procedures or treatment options, still represent regional or local conditions and the total number of patients per documenting centre may be too low to perform epidemiological extrapolations. In order to do so, it would be important to include more Austrian departments of Internal Medicine in the care of adult patients with IEI as well as to increase the number of registered patients nationwide. Still, it needs to be highlighted that the ESID registry represents an important database since it is the only multi-centric platform for the documentation of patients with IEI in Austria. Thus, it is of great significance as a basis for considerations and decisions in terms of public health. Clinicians are enabled to perform centre oriented as well as nation-wide analyses and, internationally, comparisons between participating countries are facilitated due to the registry. However, certain barriers cannot be ignored, such as the insufficient data entry by documenting centres, the incompleteness of specific data, the unequal geographic distribution of Austrian documenting centres or the fact that certain medical centres caring for patients with IEI are still not represented in the ESID registry. Thus, awareness for the diverse clinical manifestation of IEI as well as for the importance of the ESID registry in terms of epidemiological research must be raised in Austria.

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Appendix – Questionnaire

Fragebogen – Multizentrische österreichweite Querschnittsanalyse der Inzidenz und Betreuung von Patienten/Innen mit primären Immundefekten anhand des Registers der Europäischen Gesellschaft für Primäre Immundefekte (ESID)

Univ.-Klinik für Pädiatrische Hämato-Onkologie, LKH Graz

Im Rahmen meiner Diplomarbeit, einer Analyse der österreichischen Teilnahme am ESID Register, 10 Jahre nach Aufnahme des Registers, führe ich eine Umfrage bezüglich des Registers an den teilnehmenden Zentren in Österreich durch. Aus diesem Grund bitte ich Sie, den nachfolgenden Fragebogen auszufüllen und an mich zu retournieren. Die Beantwortung sollte nicht länger als 5-7 Minuten dauern. VIELEN DANK !

1. Wie hoch ist derzeit die (ungefähre) Anzahl der Patienten/Innen mit primären Immundefekten, die Sie an Ihrer Klinik betreuen?

   _____ Patienten mit primären Immundefekten sind derzeit an meiner Klinik in Betreuung, davon ca. ____ % Kinder < 18 Jahre.

2. Ist die regelmäßige Registrierung von Patienten/Innen mit angeborenen Störungen des Immunsystems in das ESID Register, das derzeit Daten von > 25.000 Patienten/Innen umfasst, an Ihrer Abteilung etabliert?

   ☐ Ja.

   ☐ Nein

   ☐ in Vorbereitung ☐ nicht geplant

   warum nicht: _____

   im Fall „nicht geplant“, bitte springen Sie zu Frage 13.

3. Sind Sie der / die Hauptverantwortliche für das ESID-Register an Ihrer Abteilung?

   ☐ Ja.

   ☐ Nein.

4. Wie gut ist das ärztliche Personal Ihrer Abteilung über das ESID-Register informiert?

   ☐ Alle Personen des ärztlichen Personals sind ausreichend sowohl über Struktur als auch über die Dateneingabe informiert.

   ☐ Alle Personen des ärztlichen Personals kennen das Register, wissen jedoch nicht über genaue Strukturen Bescheid.

   ☐ Nur vereinzelte Personen wissen über das ESID-Register im Detail Bescheid.

5. Ist Ihnen bekannt, wie viele Personen an Ihrer Abteilung einen Zugang inkl. Benutzername und Passwort zur Online-Datenbank des ESID-Registers haben?

   ☐ Ja, _____ Personen haben einen Zugang; ☐ es ist mir nicht bekannt.

6. Gibt es in Ihrer Abteilung eine definierte Person, die für die Eintragung der Daten von Patienten/Innen in das ESID-Register zuständig ist?

   ☐ Ja.

   ☐ Nein.

7. Welche Personen tragen an Ihrer Abteilung regelmäßig Patientendaten in das Register ein? (mehrere Antworten möglich)

   ☐ An meiner Abteilung gibt es nur definierte Personen, die dafür zuständig sind.

   ☐ Fachärzte/innen

   ☐ Assistenzärzte/innen

   ☐ Turnusärzte/innen, Ärzte/innen in Basisausbildung

   ☐ Wissenschaftliche oder Dokumentations-Mitarbeiter/innen

   ☐ Dipl. Gesundheits- und Krankenpfleger/innen

8. Sind Sie der Meinung, dass Sie unterstützende Hilfestellung bei der Eintragung der Daten in das Register benötigen könnten?

   ☐ Ja, ich hatte noch keinerlei Einführung, eine Schulung würde mir bei der Eintragung helfen. Wenn ja, welche Art von Schulung würden Sie bevorzugen:

      ☐ es kommt jemand an mein Zentrum

      ☐ Persönlicher Kontakt und Frage/Antwort-Möglichkeit telefonisch oder per Email

      ☐ Eine regelmäßige Skype- oder Telekonferenz

      ☐ Einweisung im Rahmen der ÖGKJ (oder anderer) Tagung oder einer AG-Sitzung

   ☐ Ich weiß zwar prinzipiell Bescheid, bin mir bezüglich einiger Felder aber noch unsicher. Welche ? _____

   ☐ Nein, ich bin bestens informiert.

9. Waren Sie schon einmal mit Problemen bei der Dateneingabe konfrontiert?

   ☐ Ja.
   Falls ja, welche? _____
   _____

   ☐ Nein.

   ☐ Weiß nicht. / Keine Angabe.

10. Sind Sie der Meinung, dass die Umstrukturierung des Registers 2014 zu einer Verbesserung geführt hat?

☐ Ja, es ist nun einfacher im klinischen Alltag zu verwenden.

☐ Nein, früher hat es mir im klinischen Alltag mehr geholfen.

☐ Ich kannte das ESID-Register vor der Umstrukturierung noch nicht.

11. Inwiefern hat sich das Register nach der Umstrukturierung für Sie verändert? (mehrere Antworten möglich)

☐ Einfachere Dateneintragung.

☐ Bessere Nutzbarkeit im klinischen Alltag.

☐ Bessere Vergleichbarkeit der Daten.

☐ Größerer Nutzen in der Forschung.

☐ Keine Änderung bemerkt / keine Angabe.

12. Wie häufig werden die Daten der Patienten/innen Ihres Zentrums im Register aktualisiert?

☐ Nach jedem Patientenkontakt (klinische Vorstellung, Kontakt über Telefon/Brief/EMail).

☐ Nicht nach jedem Patientenkontakt, jedoch mindestens einmal im Monat.

☐ Seltener als einmal pro Monat.

☐ Sporadisch oder seltener als einmal pro Jahr.

13. Führen Sie oder andere Personen in Ihrer Institution ein anderes Register über Patienten/Innen mit primären Immundefekten?

☐ nein

☐ ja. Wenn ja, bitte um kurze Beschreibung von Grund und Struktur, und ob parallel oder anstelle _____
_____

Ist dieses Register oder die Liste GCP- und DSGVO-konform?

☐ Ja ☐ nein

14. Wo liegen Ihrer Meinung nach die größten Vorteile eines Registers, wie dem des ESID-Registers? (mehrere Antworten möglich)

☐ Hilfreiches Tool im Patientenmanagement (Diagnostik, Therapie, Vernetzung bei komplexen Fragen, andere_____).

☐ Hilfreiche für den Überblick über die an meinem Zentrum betreuten Patienten/Innen.

☐ Gute Verwendbarkeit für Forschung (z. B. epidemiologische Studien).

☐ Andere Vorteile: _____

15. Ist Ihnen die Liste der „klinischen diagnostischen Kriterien“ des ESID Registers bekannt? (Katalog zum Download auf der Webseite der ESID Registry Working Party bzw. Pop-up bei neuer Patienteneingabe zur Verifikation der Diagnose bei fehlender genetischer Ursache)

☐ Nein.

☐ Ja. Wenn ja, verwenden Sie diese im klinischen Alltag, z.B. für Management-Entscheidungen bei Patienten ohne genetische Diagnose oder bei Detektion einer VUS?

☐ Ja ☐ nein

16. Wo liegen Ihrer Meinung nach die Nachteile des ESID-Registers?

☐ Zu wenig Informationsgehalt.

☐ Patienten/Innendaten zu uneinheitlich.

☐ Primärer Zugriff auf eigenes Zentrum beschränkt.

☐ Ich liefere Daten aber weiß nicht, wofür.

☐ Andere Nachteile: _____

17. Haben Sie selbst schon einmal das ESID-Register für nationale oder internationale Forschungszwecke oder Projektanträge verwendet?

☐ Ja. ☐ Nein.

Ich kenne die Möglichkeiten

☐ Reporting Tool (vorgefertigte, real-time Auswertungen und Graphiken)

☐ Umfrage in allen ESID Register Zentren weltweit

☐ Projektantrag für gezielte Forschungsfrage an Registerleitung

18. Falls zutreffend: Welchen Grund würden Sie für eine etwaige mangelnde Dateneintragung Ihrerseits nennen? (mehrere Antworten möglich)

☐ Zu wenig Zeit neben dem klinischen Alltag.

☐ Mangelnder Nutzen für den klinischen Alltag.

☐ Unzureichende Kenntnis des Registers.

☐ Mangelnde Einschulung.

19. Was würden Sie sich selbst bezüglich des ESID-Registers wünschen?

_____
_____
_____
_____
_____

Vielen Dank für Ihre Informationen! *Sabrina Taucher und Markus Seidel, im Mai 2019.*

Optional: Ihr Name: _____