Event Report: Newborn Screening to Strengthen Early Diagnosis of Primary Immunodeficiencies: Germany as Good-Practice example for Europe?

I. Executive Summary

The digital event *"Newborn screening to strengthen early diagnosis of primary immunodeficiencies: Germany as good practice example for Europe?"* took place on 18 November 2020 online. It was held under the patronage of the German Member of Parliament (MP) Erich Irlstorfer and co-organized by the International Patient Organisation for Primary Immunodeficiencies (IPOPI) and the German patient organisation for congenital immunodeficiencies (dsai e.V.).

In his political preface the patron **MP Erich Irlstorfer** stressed the importance of an early diagnosis of immune defects, such as severe combined immunodeficiencies (SCID). He expressed his wish to remain a key contact person and emphasized his goal to keep in touch with the event organisers and to continue the dialogue after the event in order to move newborn screening (NBS) for these rare conditions forward.

Martine Pergent, President of IPOPI, introduced IPOPI and emphasized that early diagnosis of primary immunodeficiencies is crucial and therefore NBS is of utmost importance. Within the past 10 years, an increasing number of European countries have implemented NBS for SCID. The European initiative Screen4Rare, initiated by IPOPI, the International Society for Neonatal Screening (ISNS) and the European Society for Immunodeficiencies (ESID), aims to promote guidelines and data exchange for NBS in Europe. **Birgit Schlennert**, Managing Director of dsai e.V., described dsai's activities advocating for SCID and NBS, and the needs of patients and their families once they are diagnosed with SCID. Despite the progress made, she also presented current implementation challenges that need to be addressed to cover patients´ needs, such as the request for the introduction of the B-cell defect screening (KREC-screening).

PD Dr. Matthias Perleth and **Dr. Susanne Glodny** from the Federal Joint Committee (*Gemeinsamer Bundesausschuss*, G-BA) presented the current guidelines of NBS in Germany. Dr. Perleth began with a historical overview of the children's guideline (*Kinderrichtlinie*) in Germany before Dr. Glodny specifically addressed the framework conditions of NBS and SCID-screening. According to Dr. Glodny, the introduction of KREC-screening for other immunodeficiencies would generally be feasible to implement, but more evidence is needed to justify an inclusion in the NBS process.

According to the immunologist **Prof. Dr. Horst von Bernuth**, Head of the section Immunology at the Clinic for Pediatrics at Berlin's University Clinic Charité, the early detection of primary immune defects like SCIDs is essential, as these diseases – that affect an average of 25 to 50 patients per year in Germany – remain asymptomatic in the first months of life and success in curing by stem cell transplantation or gene therapy is optimal at an early stage, before any life threatening infection could occur. In his opinion, open challenges that remain are (1) the follow-up of diagnostics, therapy and early diagnosis, and (2) the question of binding demand for treatment, for which guidelines are currently under development.

The **father** of a daughter born in 2019 and diagnosed with SCID, reported on his personal experiences with NBS, diagnosis and treatment. Overall, he expressed his gratitude to the German health care system and the commitment of doctors that made an early diagnosis of his daughter possible. He also highlighted the crucial role of the patient organisation in answering the doubts he and his family had

once the diagnosis was confirmed. As a shortcoming, he pointed out the lack of care for relatives, who are often left alone in this difficult, emotional situation and requested more support.

In the **discussion** that followed, it became clear that the early detection of immunodeficiencies is crucial for the well-being of patients and relatives. Patient organisations such as IPOPI members as dsai e.V. make an important contribution to the support of those affected. The speakers advocated for the introduction of further screenings based on scientific evidence and the exchange of experiences in the European context.

II. Detailed Content Report

POLITICAL STATEMENT BY THE PATRONAGE MP ERICH IRLSTORFER

- The patron of the event, MP Erich Irlstorfer, has been a member of the German Parliament (*Bundestag*) for the CDU/CSU parliamentary group since 2013. In Parliament, he is a member of the Health Committee and rapporteur for the areas of child and youth medicine.
- In his political foreword, MP Irlstorfer emphasized that primary immunodeficiencies often lead to death if left untreated and that early detection is of utmost importance. Currently, NBS in Germany covers 14 diseases, which also include the screening for severe combined immunodeficiency (SCID).
- MP Irlstorfer was shocked about the fact that only a fraction of immunodeficiencies are currently detected at an early stage. He stressed the importance of high-quality diagnosis and treatment. Both the diagnosis and the treatment process are associated with almost unbearable psychological pressure and uncertainty for the families – a situation that – in his view – is unacceptable in Europe. For this reason, he feels the urge to politically engage in this topic.
- He expressed his wish to remain a key contact person and emphasized his goal to keep in touch with the event organizers and to continue the dialogue after the event in order to move newborn screening (NBS) forward.

KEYNOTE: IPOPI & DSAI E.V. MARTINE PERGENT & BIRGIT SCHLENNERT

- **Martine Pergent**, President of IPOPI, introduced the international organisation for primary immunodeficiencies, and explained that primary immunodeficiencies cover 430 rare diseases. She stressed that early diagnosis is crucial and that NBS is of utmost importance.
- In her overview of recent NBS developments, she explained that in 2009, no country tested for SCID. However, a lot has changed in the past 10 years. The PID Life Index developed by IPOPI provides an overview of the global and European situation. In 2019, Germany, Sweden and Switzerland introduced screening for SCIDs as part of their NBS programs. Together with the European Society for Immunodeficiencies (ESID) and the International Society for Neonatal Screening (ISNS), IPOPI launched Screen4Rare. The aim of this initiative is to promote guidelines for NBS in Europe and to enable an exchange of screening methods and data collection, in which Member States can rely when considering the update of their newborn screening programs.
- **Birgit Schlennert**, Managing Director of dsai e.V., described the year 2019 as an important milestone for SCID patients and their families in Germany. In her presentation, she quoted from the book *„Isoliert – Mein Kind hat kein Immunsystem“* (translated: Isolated – My Child has no immune system) by Stephanie Geffert. The book was published before screening for SCIDs was introduced in Germany. The excerpt described that SCIDs can only be cured by stem cell

transplantation – a therapy that was already available in Germany before SCIDs were included in the NBS. However, without NBS, the diagnosis and therapy often started too late.

- dsai was invited to participate in the process of introducing SCID to the NBS, and hence had its voice heard during the benefit assessment and the decision-making process in the G-BA.
- Despite these successes, Ms. Schlennert also discussed practical challenges in the screening process. Above all, she highlighted that fears of affected families must be taken more seriously. Through specialized clinics, SCID-patients' medical needs are taken care of very well in Germany. However, long term competent psychological care, counselling, and an exchange with other affected families is similarly important and oftentimes lacking.
- NBS for SCIDs saves lives. Nevertheless, there are still more than 430 immune defects that impact the lives of patient families and are currently not covered in the NBS. Next to the screening for T-cell defects, it was originally planned to include screening for B-cell defects in the NBS guidelines as well. However, screening for B-cell defects has not been implemented yet, and dsai e.V. continues to advocate for its inclusion in the NBS.

KEYNOTE: G-BA PD DR. MATTHIAS PERLETH & DR. SUSANNE GLODNY

- PD Dr. Matthias Perleth and Dr. Susanne Glodny from the Department of Medical Advice of the Joint Federal Committee (G-BA) presented the current NBS guidelines in Germany.
- **Dr. Perleth** started with an introduction to the children's guideline (*Kinderrichtlinie*), which is one of the oldest guidelines of the G-BA, launched in 1971 to identify and treat developmental disorders at an early stage. Since the introduction of the German Genetic Diagnostics Act (*Gendiagnostikgesetz*) in 2010, in order to add new diseases to the NBS list, (1) genetic diagnostic procedures must be in place to determine the defect, and (2) a therapeutic option must be available.
- **Dr. Susanne Glodny** presented the specific regulations for NBS. The extended NBS consists of the general provisions (parental consent), the procedure, approval, and quality assurance for laboratory services. Currently, there are 11 approved laboratories and 2 approved centres in Germany that meet the quality assurance criteria.
- The current target diseases of NBS in Germany mainly entail metabolic diseases. In 2014, the GKV-Spitzenverband (the nationwide association of health insurance companies in Germany) submitted an application for the evaluation of SCID screening. The benefit assessment was performed by the Institute for Quality and Efficiency in Health Care (IQWiG) and then forwarded to the G-BA, where physicians, professional associations, laboratories and patient organisations were involved in the decision-making process. Screening processes in other countries were also observed in order to define false-positive findings and decide which diseases to include in the NBS. Overall, four years have passed between the application and the implementation of the SCID-screening.
- According to Dr. Glodny, the introduction of a KREC-screening for further immunodeficiencies would generally be feasible for the laboratories. However, more evidence would be needed to include it in the NBS. In addition, she pointed out that false-positive diagnoses put a high burden on parents and relatives. It is therefore a challenge to find all positive cases while avoiding false-positive test results.

KEYNOTE: CHARITÉ PROF. DR. HORST VON BERNUTH

- **Prof. Dr. Horst von Bernuth,** Head of the section Immunology at the Clinic for Pediatrics at Berlin's University Clinic Charité, highlighted the medical perspectives of NBS.
- He pointed out that the main challenge of SCID is that the disease develops in an asymptomatic stage first, which is why early detection is essential. He also mentioned that there are several treatment options as of today which are under review and optimisation and that the disease is a very rare, usually a second diagnosis. On average, 25-50 patients per year are currently estimated to be diagnosed with SCID in Germany.
- Prior to the launch of the SCID-screening as part of the NBS, so-called CID clinics and CID centres – that specialise on newborn screening – were assessed for quality assurance. 18 clinics and 11 centres were eventually selected across Germany. As opposed to France and Great Britain, where centres are mostly located in the capitals, Germany took a regional approach in order to ensure equal access to medical care in cities and rural areas alike.
- At the Charité in Berlin, the NBS for SCIDs proceeds as follows. Immediately after birth, all parents sign a document, stating that they want to be informed about the results of the 14 NBS diseases. If the results are positive, the laboratory manager reports them to Prof. Dr. Bernuth and his team. The parents and relatives are informed about the results immediately. On the following day, the first appointment is made for a blood test, the results of which are available after four hours. Within 24 hours after the screening, the parents receive the diagnosis. If the SCID diagnosis is confirmed, the appointment for a stem cell transplantation usually takes place after another 24 hours.
- Since the introduction of the SCID screening in 2019, three SCID cases have been diagnosed in Berlin and received a stem cell transplant. In Germany, 15 out of 17 positively tested newborns have survived so far. The two deceased babies suffered from an additional autoimmune disease that was not detected. Another 21 combined immunodeficiencies were diagnosed and treated.
- Prof. von Bernuth identified quality assurance as one of the main tasks to increase the survival rate of SCID-newborns to 100%. He highlighted that the mandatory reporting to the SCID registry is already at 100%. Open challenges, in his view, are (1) the follow-up of the diagnosis, therapy and early diagnosis and (2) the obligation for treatment according to guidelines.

PATIENT STORY

- The father of a daughter born in October 2019, who was one of the first newborns tested positive for the newly introduced SCID-screening, reported on his personal experiences with the screening, diagnosis, and treatment of his daughter.
- He described that the first abnormalities were already noticed during an ultrasound examination, before the NBS results indicated further issues. After a gene analysis, his daughter was diagnosed with the gene defect cartilage-hair hypoplasia. She was also screened for SCID and consequently positively diagnosed with it in addition to her other gene defect. Due to Covid-19 restrictions, the stem cell transplantation was delayed for 7 months, and the parents were not allowed to visit their daughter at the same time or stay overnight. In total, their daughter spent several months in the clinic.
- Overall, the treatment methods have worked well. The father described the regional setup in Germany as excellent and a great relief for affected families. He expressed his gratitude towards

the German health care system and for the early detection and treatment of his daughter's disease. He also referred to elements that should be improved, including the lack of psychological support, and more explanations on technical terms and medical abbreviations that could be solved by modifying the information provided to the families.

DISCUSSION

The main questions asked during the event were the following:

- What roles do patient organisations like dsai e.V. play for relatives?
    - The father answered that the family was in contact with dsai e.V. and the Deutsche Knochenmarkspenderdatei (DKMS; a non-profit bone marrow donor centre based in Germany). Through dsai they were able get informed about the screening process and the chances of recovery at an early stage. All in all, the patient organisations were very helpful, as they are available as a point of contact for affected families.
- What kind of political actions would dsai e.V. appreciate?
    - Birgit Schlennert replied that patients' voices should not only be heard, but they should also be given the right to vote and continue to be involved in decision-making processes. Particularly with regards to B-cell defects NBS, dsai e.V. would like to see the patient's perspective integrated more strongly.
- How could Germany support other European countries in their regulatory framework for NBS and SCID-screening?
    - According to Dr. Perleth, there are registration initiatives, in which German data is made available. The G-BA is often in contact with foreign institutions, so there is certainly a multilateral exchange at European level. Compared to other countries, the barriers to access the health care system in Germany are very low. There are direct cost transfer regulations in the pharmaceutical and inpatient care sectors. In the outpatient sector, there is the hurdle that the G-BA must include the applicant in the consultation. This system is often criticized because the procedure is quite bureaucratic and takes a long time. Nevertheless, an acceleration has been observed in recent years. Applications and assessments must now be carried out within 2 years.
- Why is Germany a good practice example in newborn screening?
    - Martine Pergent answered that experts such as immunologists and representatives of patient organisations are convinced of the necessity of NBS for SCIDs. To establish NBS for SCIDs more broadly in Europe, there is a need for more data and an exchange on logistical experiences. Germany has already established an effective NBS process and is therefore a good practice example. IPOPI believes that ensuring an effective exchange of data and guidelines from the European countries who have put in place NBS for SCIDs will lead to better and more informed assessments and help new countries in engaging in screening for rare diseases like SCIDs when they are curable.
- What other screenings could be introduced in Germany?
    - Prof. Dr. von Bernuth explained that it is very important to act along the guidelines of the screening criteria. In his opinion, B-cell defect screening (KREC-screening) is very important. His team is currently supporting KREC-screening in Szczecin in cooperation with Poland. In his experience, false-positive results do not put an unbearable burden on parents. It is rather a political decision whether it is financially viable to accept further screenings.

- Dr. Perleth made it clear that the G-BA acts based upon application initiatives. These applications must be submitted by organizations such as the *GKV-Spitzenverband*. If the literature suggests that a new screening should be introduced, one should contact one of these organizations that can submit the application. In the case of SCIDs, the evidence base is good, there are reliable testing procedures and there is a therapeutic option without which the newborn child will die or suffer severe conditions. The G-BA therefore has an obligation to deal with SCIDs. A statement can also be published to advocate for the introduction of a new screening, but this does not guarantee a panel assessment.

CLOSING REMARKS LUTZ DOMMEL

- As seen and heard from the panellists and during the discussion, for conditions such as SCIDs timely referral to diagnosis can lead to effective treatments and even cure, which is fundamental for patients, their families and society. It is now of utmost importance to keep improving the bridge between the screening, diagnosis and treatment. The composition of the audience of the discussion shows the interest of sharing the German example as well as that of other screening European countries.
- Germany is one of the first countries in the European Union that has implemented SCID at a nation-wide level. These practices and the lessons learned from the journey of including SCIDs in the list of conditions that can be screened can certainly help other countries when assessing the inclusion of SCIDs within the panel of diseases newborns are screened for and contribute to construct an EU-wide database.
- In this sense the role of patient organisations is crucial, for which the dsai's contribution to the development of the topic in Germany and IPOPI´s Screen4Rare campaign at EU level are excellent examples. Both groups have helped in understanding the importance for patients and their families of a timely diagnosis and the right process from screening to treatment as well as for the benefit of the whole society. Hopefully, these precedents can help countries where NBS for SCIDs is yet to be considered or achieved.

III. Agenda

Time	Agenda	Speaker
12:00 – 12:05	**Welcome**	Lutz Dommel (RPP, Moderator) Birgit Schlennert (dsai e.V.) Martine Pergent (IPOPI)
12:05– 12:10	**Political Statement by the patronage**	MP Erich Irlstorfer
12:10 – 12:30	**Keynote: IPOPI & dsai e.V.** Patient perspectives on Newborn-Screening (NBS) and the Severe Combined Immunodeficiency (SCID) in Germany and the EU	Martine Pergent (IPOPI) Birgit Schlennert (dsai e.V.)
12:30 – 12:40	**Keynote: G-BA** Current NBS and SCID regulations in Germany	PD Dr. Matthias Perleth (G-BA) Dr. Susanne Glodny (G-BA)
12:40 – 12:50	**Keynote: Charité** Medical perspectives on NBS and SCID in Germany	Prof. Dr. Horst von Bernuth (Charité)
12:50 – 13:00	**Patient Story** Personal experiences with the SCID screening process, the early diagnosis, and the treatment	Father of a daughter born and diagnosed with SCID in 2019
13:00 – 13:25	**Discussion**	Lutz Dommel (RPP, Moderator) Participants
13:25 – 13:30	**Closing remarks**	Lutz Dommel (RPP, Moderator)

IV. List of Participants

Name	Institution
Speakers	
Erich Irlstorfer	Member of the German Parliament
Martine Pergent	IPOPI
Birgit Schlennert	Dsai e.V.
PD Dr. Matthias Perleth	G-BA
Dr. Susanne Glodny	G-BA
Prof. Dr. Horst von Bernuth	Charité – Berlin University of Medicine (Charité – Universitätsmedizin Berlin)
Anonymous	Father of a patient
Lutz Dommel *(Moderator)*	RPP
Participants	
Yordan Aleksandrov	RPP
Kerstin Angler	Takeda
Steffen Ball	Dsai e.V.
James Bonham	NHS
Martin Büchler	ELA e.V.
PD Dr. Fabian Hauck	LMU Klinikum der Universität München
Rüdiger Gatermann	CSL Behring
Natalie Helena	IPOPI
Kathrin Holm	RPP
Reyhan Kalayci	Bundesärztekammer (German Medical Association)
Gunda Kohlke	CSL Behring
Natalie Kohzer	BKK Dachverband
Jakob Kühler	RPP
Magda Lourenco	IPOPI
Michelle Maibaum	RPP
Andrea Maier-Neuner	Dsai e.V.

Karin Modl	Österreichische Selbsthilfegruppe für primäre Immundefekte (ÖSPID) (Austrian self-help group for primary immunodeficiencies)
Carsten Mohr	Presence Group
Christine Mundlos	ACHSE e.V.
Julia Nordin	IPOPI
Johan Prevot	IPOPI
Elke Radermacher	Takeda
Dr. Andreas Reimann	Admedicum
Sára Ritter	RPP
Michael Scholz	ELA e.V.
Pascale Schroeder	Presence Group
Prof. Dr. Catharina Schütz	Uniklinikum Carl Gustav Carus, Dresden
Leire Solis	IPOPI
PD Dr. Carsten Speckmann	Universitätsklinikum Freiburg
Ulrike Stamm	Dsai e.V.
Gaby Strotmann	LMU Klinikum der Universität München
Johannes Sturm	RPP
Elliot Tricot	RPP
Marie-Sophie Wenzel	Office of Manuela Ripa, Member of European Parliament
Frank Willersinn	Alpha-1 plus
Markus Wörz	G-BA