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Initiation of newborn screening (NBS) programs in Europe dates back to the 1960s. One of the most recent expansions of NBS programs was the addition of severe combined immunodeficiency (SCID) based on detection of T-cell receptor excision circles (TRECs). In this review, we present an overview of the current situation in Europe. To avoid a biased overview based on only published results, a 37-item survey on TREC-based NBS was sent to representatives of 46 European countries. With a response rate of 83%, we collected data of 38 countries. Seventeen of the 38 European countries that have completed the survey have nationally or regionally implemented TREC-based NBS. The survey results emphasize similarities and differences as well as common practices and challenges in TREC-based NBS. Because TRECs are a general surrogate marker for severe T lymphocytopenia, conditions other than SCID are also identified. Therefore, the initial definition of the target disease as "SCID" might need to be reconsidered and extended to "SCID and severe T lymphocytopenia." Even though complete harmonization of TREC-based NBS programs across Europe will remain challenging, collaboration and close partnerships will help in the move toward universal TREC-based screening for all newborns, resulting in more infants with SCID and severe T lymphocytopenia being detected each year. (J Allergy Clin Immunol 2025;155:377-86.)

Key words: *Newborn screening, NBS, severe combined immunodeficiency, SCID, severe T lymphocytopenia, TREC, inborn errors of immunity, IEI, Europe*

Severe combined immunodeficiencies (SCIDs) are inborn errors of immunity (IEI) characterized by absent T lymphocytes, and variably absent B lymphocytes and/or natural killer cells. The classical clinical presentation of SCID includes persistent viral respiratory and/or gastrointestinal infection, respiratory failure, and failure to thrive, leading to death within the first year of life unless treated appropriately at an early age. Variants in around 20 different genes involved in T lymphocyte development have been identified as causes of SCID.[1,2] Additionally, several genetic defects that impair thymic development have been identified, which, although not traditionally considered to be SCID, present with severe congenital T lymphocytopenia, and the same severe immunodeficiency. For the majority of SCID patients, hematopoietic stem cell transplantation (HSCT) is curative, although results are significantly better if the infant is less than 3.5 months old and free of infection.[3-5]

During T lymphocyte development, V, (D), and J receptor gene segments are stochastically rearranged to form unique T lymphocyte receptors; redundant DNA is excised and forms extrachromosomal circular DNA segments, which are not replicated when the T lymphocyte proliferates. It is possible to identify asymptomatic infants with low numbers of newly formed T lymphocytes by quantifying the specific δRec-ψJα excision circle referred to as T lymphocyte receptor excision circles (TRECs) by PCR in dried blood spots obtained for newborn screening (TREC-based NBS).[6] The test is specific for impaired early T lymphocyte development, but low TRECs may also be found in some patients who do not have classic SCID conditions but have other combined immunodeficiencies (eg, DOCK2 and LCK deficiency), or from syndromic disorders associated with impaired T lymphocyte or thymic development (eg, cartilage–hair hypoplasia, 22q11.2 microdeletion, or CHARGE syndrome [coloboma, heart defect, atresia choanae, restricted growth and development, genital abnormality, and ear abnormality/deafness]). There is accumulating evidence that in addition to infants with SCID, these children benefit from early detection via NBS.[7-9] Low TRECs can also be identified in newborns with secondary causes of T lymphopenia (eg, because of profound malformation of lymphatic vessels or maternal immunosuppressant medication).[10] There is accumulating evidence that children with non-SCID

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Abbreviations used

ADA: Adenosine deaminase deficiency
BCG: Bacillus Calmette-Guérin
CHARGE syndrome: Syndrome characterized by coloboma, heart defect, atresia choanae, restricted growth and development, genital abnormality, and ear abnormality/deafness
HSCT: Hematopoietic stem cell transplantation
IEI: Inborn errors of immunity
ITL: Idiopathic T lymphocytopenia
KREC: Kappa-deleting recombination excision circle
NBS: Newborn screening
SCID: Severe combined immunodeficiency
TREC: T-cell receptor excision circle

T lymphocytopenia also benefit from specific treatments and/or prophylactic measures.[8,9] Therefore, there is an ongoing discussion in several European countries to redefine the name of the screening target disease to "SCID and severe T lymphocytopenia." This seemingly small change of definition can have a considerable effect in individual screening programs because patients with (non-SCID) severe T lymphocytopenia are considered to have false-positive results in some countries or screening programs. It should be noted that opinions on the target definition and what to define as a truly or falsely positive scan even differ between involved screening professionals and health care providers in the same country. Nevertheless, as long as screening remains based on quantification of TRECs, all programs will identify newborns with all forms of severe T lymphocytopenia, who can benefit from the appropriate treatment depending on their diagnosis.

MULTIFACETED APPROACH TO SCREENING FOR SCID AND SEVERE T LYMPHOCYTOPENIA IN EUROPE

Neonatal screening programs provide countries with an important tool to improve public health by identifying and treating severe congenital disorders early, thereby reducing morbidity, mortality, and health care costs. In Europe, the history of neonatal screening dates back to the 1960s, with various countries gradually implementing programs tailored to their specific health care system and population needs.[11] The most recent major expansion of screening in many European countries was the addition of SCID/spinal muscular atrophy screening to NBS programs. The first pilot studies for NBS for SCID and severe T-lymphocyte deficiencies were performed in the United States more than 15 years ago. The first statewide SCID screening pilot study commenced in Wisconsin in 2008.[12] Subsequently, the addition of SCID to the Recommended Uniform Screening Panel resulted in an acceleration in the number of states screening for SCID.[13] By the end of 2018, NBS for SCID had been adopted by public health programs in all 50 states, the Navajo Nation, and Puerto Rico.[14] Pilot and proof-of principle studies in European countries such as Sweden, the United Kingdom, France, Italy, the Netherlands, and Spain followed some years later after the first pilot studies in the United States.[15-22] However, Europe has a more conservative and heterogenous approach when it comes to population screening programs.[23] Health care has always been left to the own responsibility of the individual countries, allowing each country to make its own decision with regard to conditions that should be included in NBS programs.[24] NBS is typically funded by national health care services or health insurance, making NBS free of charge for parents. This often results in complex, time-consuming governmental and financial decision-making processes when expansion and inclusion of new conditions are considered.[25] Implementation of new conditions such as SCID in European countries can vary widely as a result of considerations:

- *Policy landscape:* National health care policies, legal frameworks, and funding structures significantly influence the decision-making process.
- *Resource availability:* Variable access to specialized screening and diagnostic laboratories as well as trained personnel and access to HSCT programs can impact the feasibility of implementing SCID NBS in a particular country.
- *Cost-effectiveness analysis:* National decision-makers weigh the financial benefits of early intervention against program implementation costs.
- *Societal impact:* Potential improvements in public health and reduced long-term health care needs are crucial considerations.
- *Effects on other public programs:* Vaccination schedules might need adjusting in countries—for example, in countries where bacillus Calmette-Guérin (BCG) or rotavirus vaccines are administered relatively early.
- *Ethical considerations:* Including genetic testing within SCID NBS raises ethical questions that need to be addressed within local cultural contexts.

The above-listed specificities of the neonatal screening programs reflect the diversity of the situation in Europe. Complete harmonization across Europe might be difficult to achieve, but NBS programs will benefit many infants across the continent. In this review article, we map the current situation of SCID NBS in Europe as it stands in 2024.

CURRENT SITUATION FOR NBS FOR SCID AND SEVERE T LYMPHOCYTOPENIA IN EUROPE

Many countries in Europe have now instituted population-wide TREC-based NBS, whereas others offer screening in certain regions or have published preimplementation analyses and pilot studies. An updated overview of all published European studies has been included in Table E1 in the Online Repository available at www.jacionline.org. Including only published results can lead to a biased overview of the current situation in Europe. Therefore, in preparation of this review, a questionnaire on NBS for SCID and severe T-lymphocyte deficiencies was sent out to representatives of TREC-based NBS programs in 46 European countries. The 37-item questionnaire included general information about the NBS program and more detailed questions on NBS for SCID and severe T-lymphocyte deficiencies, including screening parameters and follow-up diagnostics.

The response rate was 83%, and data were collected for 38 countries. Table E2 in the Online Repository available at www.jacionline.org provides an overview of the screening

TABLE I. Heterogeneity in European countries regarding NBS for SCID and severe T lymphocytopenia

Characteristic	Variable	No.
Implementation of NBS for SCID and severe T lymphocytopenia	Nationally	15
	Regionally	2
	Awaiting decisions	8
	Pilot or planning pilot study	5
	No screening and no pilot	6
Performed pilot study for TREC-based NBS or are performing pilot study	Yes	22
	No	16
Pilot study required before implementation of conditions?	Yes	10
	No	28
Markers used in pilot study or after implementation	TREC	5
	TREC/KREC	3
	TREC/SMN1	6
	TREC/KREC/SMN1	12
Algorithm adjusted for preterms in pilot study or after implementation	Yes	19
	No	5
Distinction between nonurgent and urgent referrals	Yes	15
	No	7
National or regional guideline for referral	Yes	17
	No	1
	In development	2
Time frame of referral	Immediate/as soon as possible regardless of urgency	5
	Urgent	
	<24 hours	8
	Not urgent	
	<24 hours	2
	24-72 hours	7
	>72 hours	4
First contact in the case of an abnormal TREC result by	Pediatrician	5
	Pediatric-immunologist	17
	General practitioner	2
	Employee of NBS laboratory/program	5
National or regional guideline for diagnostics	Yes	19
	No	5
	In development	2
Present at first consultation	Pediatrician	1
	Pediatric immunologist	12
	Both pediatrician/pediatrician immunologist	2
	Multidisciplinary team	11
Database for follow-up in place	Yes	16
	No	6
	Not yet	3
Adjustment of public health program	Yes	5
	No	13
	Not yet	4

characteristics of the participating countries from March 2024 to May 2024). As previously published, some countries have no NBS program in place (Albania, most of Kosovo, and Tajikistan), while newborns from other small countries are screened by NBS programs of larger neighboring countries, such as Liechtenstein covered by Switzerland, Andorra by France, San Marino by Italy, and a part of Kosovo by Serbia.[11] The sizes of the NBS programs vary across Europe, screening from 4,500 newborns up to 1,230,000 newborns annually. Most countries have 1 or 2 screening laboratories, depending on the annual number of screened newborns, with up to 86 screening laboratories in Russia. A lot of heterogeneity is observed in the number of disorders European countries are screening for, ranging from 2 or 3 disorders to 44 different conditions based on responses received (Table E2).

Screening parameters related to NBS for SCID and severe T lymphocytopenia are depicted in Table I. TREC-based NBS is nationally implemented in 15 countries and regionally implemented in 2 additional countries (Fig 1). Eight countries are awaiting governmental decisions or funding, while 5 countries are currently performing a pilot study. Six countries reported not having performed any pilot studies or having a TREC-based NBS program in place. In total, 22 countries performed a pilot study in the past or are currently performing a pilot study. Many countries reported that a pilot study is usually performed before implementation of screening for new conditions out of good laboratory practice, but this is not a legal requirement by legislation. On the basis of the countries that are currently screening for SCID and their number of newborns screened on an annual basis, it is estimated that in 2024, more than 2,500,000 newborns will be

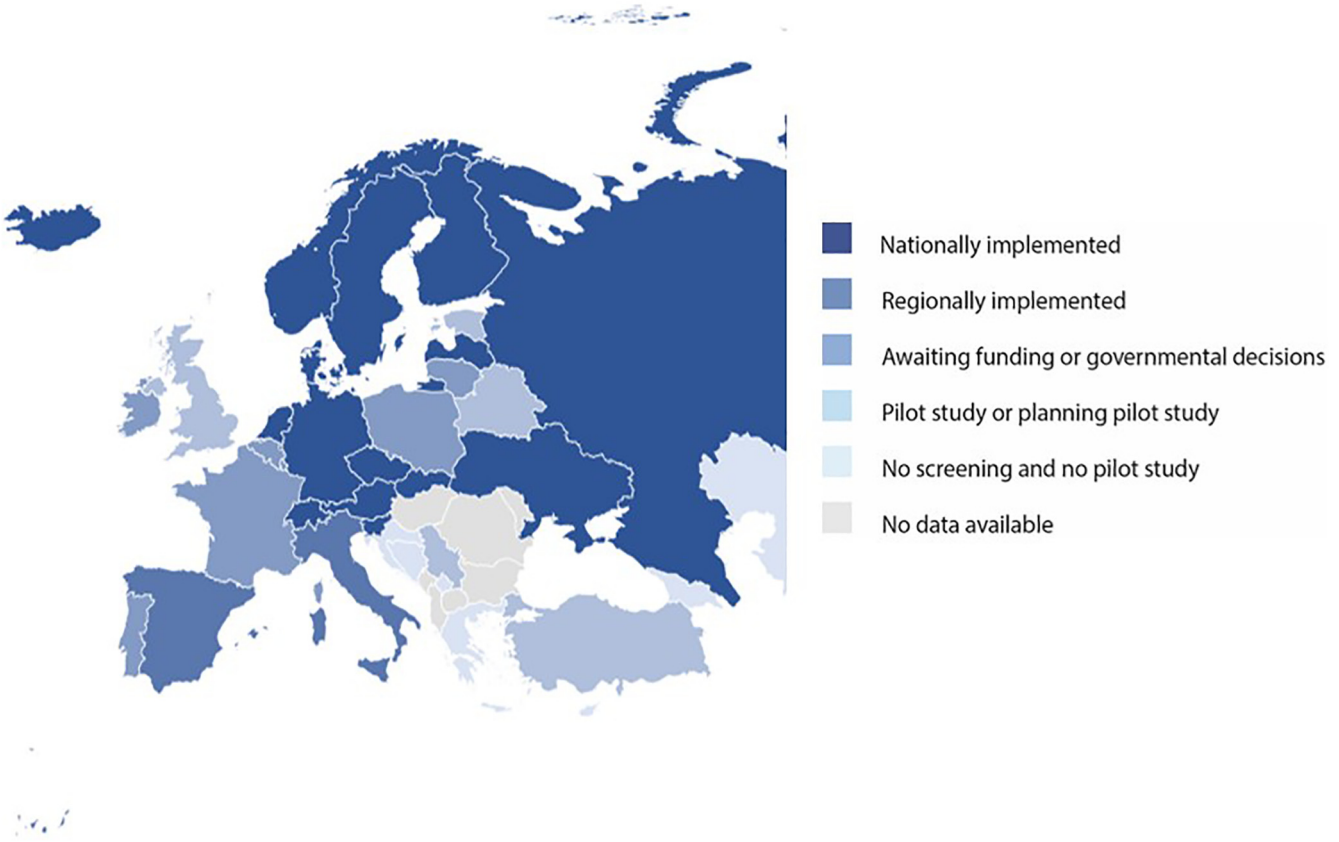

FIG 1. Current situation of TREC-based NBS based on survey results in April 2024.

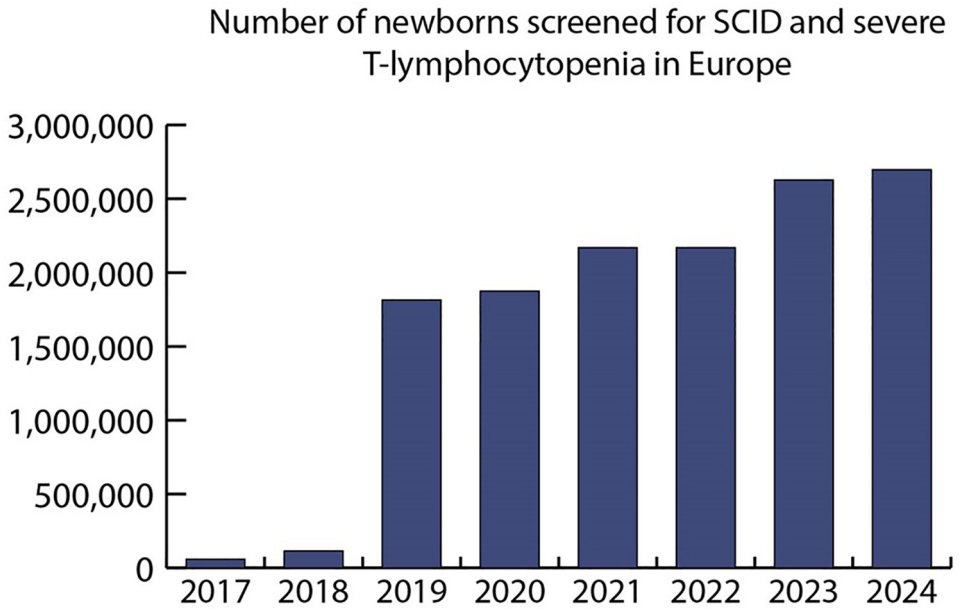

FIG 2. Number of newborns screened for SCID and severe T lymphocytopenia per year in Europe.

screened for SCID and severe T lymphocytopenia in Europe (Fig 2). Most countries used "NBS for SCID" to define the target disease, although some countries used different terminology, such as "NBS for congenital severe immune deficiencies," "NBS for severe inborn errors of immunity," "NBS for SCID and severe T-cell deficiencies," and "NBS for T-cell lymphopenia."

Countries either use TREC cutoff values that are based on their own pilot studies, or they use cutoff values advised by the

manufacturer of the assay. In some countries, like Germany, TREC cutoff levels and PCR platforms are not harmonized across the country but are individually defined by the screening laboratory. Nine countries used different cutoff values for retesting of samples and referral of newborns. Only Norway used genetic analysis as a second-tier test within the NBS program. Eighteen countries have adjusted their screening algorithm for premature neonates in pilot studies or during implementation, and some countries/regions such as Belarus, the Czech Republic, and Tuscany take other factors into account, such as maternal medication receipt during pregnancy. The referral process is documented in a regional or national guideline by 17 countries.

Abnormal TREC values are most commonly communicated by a pediatric immunologist, and less often by a general practitioner or health worker from the NBS program. Local pediatricians can also be involved, depending on the availability of a pediatric immunologist. Newborns with abnormal TREC values have their first visit at the pediatric immunologist usually within 48 hours. Urgent referrals are seen the same or next day (within 24 hours). In some programs, some families receive medical advice on hygiene and cessation of breast-feeding as the low TREC results are communicated, before the first appointment with the pediatric immunologist. The majority of countries have national or regional guidelines for follow-up diagnostics including specific markers used for flow cytometry and genes included in gene panels. More than two thirds of the countries reported that they registered referred patients in a national database, but long-term follow-up and outcomes were rarely included. Finally, most countries did not need to adjust their public health program because of implementation of NBS for SCID, but 5 countries reported alterations in their BCG or rotavirus vaccine programs. Even though not all European countries have a TREC-based NBS programs in place, other important collaborative programs in East and Central Europe have created more awareness, leading to earlier diagnosis of these important health conditions.[26-28]

SCREENING BEYOND TREC

The majority of countries used combined methods, combining TREC with additional markers such as kappa-deleting recombination excision circles (KRECs) or *SNM1* for spinal muscular atrophy detection. Both in-house methods and commercially available assays such as Enlite (PerkinElmer), SPOT-it (ImmunoIVD), Eonis (PerkinElmer/Revitty), or Labsystems are used. It should be noted that inclusion of more targets into a multiplex assay requires additional validation and verification. KRECs are used as markers of B-lymphocyte differentiation,[29] which are easily combined in a multiplex assay with TRECs. Adding KRECs in the context of NBS for SCID and severe T lymphocytopenia has the potential to increase sensitivity for adenosine deaminase deficiency (ADA)-SCID.[30] Late-onset ADA, however, can still be missed with the TREC/KREC assay, but some countries such as Ireland, Slovenia, and Norway and regions such as Catalonia and Tuscany measure adenosine metabolites by tandem mass spectrometry to detect ADA-SCID, including late-onset SCID.[22,31] Adding KRECs in NBS allows for the identification of agammaglobulinemia[32,33] and some other forms of IEI.[34,35] Although it is technically feasible to implement TREC/KREC screening, there is still controversy whether agammaglobulinemia is a condition that fulfills the Wilson and Jungner criteria for NBS and whether it is cost-effective.[36] An international retrospective clinical study (coordinated from the Netherlands) is investigating whether early diagnosis of X-linked agammaglobulinemia is associated with improved outcomes. Some European countries have already added KRECs to the screening program, demonstrating that SCID, agammaglobulinemia, and other IEI can be identified (Tables E1 and E2). In the United States, KREC has not been recommended by state programs or the Recommended Uniform Screening Panel.

CONFIRMATORY DIAGNOSTICS

All infants with abnormal TREC results—that is, below the cutoff value—are referred to a specialized pediatric immunology clinic for clinical evaluation and confirmatory diagnostics. Fifteen of 22 countries make a distinction between urgent and nonurgent referrals, using a different cutoff value for urgent referrals. Infants with an urgent abnormal value are referred directly, whereas in case of an abnormal value, a new sample test is performed for which a new sample is requested (based on responses received). The strategies for referral of preterm newborns with (urgent) abnormal values also differ. In some countries, these preterm newborns are normally referred using a lower TREC cutoff value, while in other countries, a new sample test is performed when preterm newborns reach a certain gestational age, sometimes even with NBS specimens collected every 2 weeks until a corrected term gestational age is reached.

In all referral centers, laboratory investigations are performed as confirmatory diagnostics for SCID and severe T lymphocytopenia, which includes as least the markers CD3/CD4/CD45RA to determine the total amount of T lymphocytes and the number or frequency of naive T lymphocytes. Interpretation of this basic flow cytometric screening is not always sufficient when T lymphocytes are present, either due to a hypomorphic gene defect or due to the presence of maternal T lymphocyte engraftment. In those cases, more detailed phenotyping of T lymphocytes, including analysis of newly generated T lymphocytes (recent thymic emigrants), is informative.[37] DNA typing for short tandem repeat markers of T lymphocytes is the preferred method to determine whether the T lymphocytes are autologous or of maternal origin.

Genetic testing is performed in all centers to obtain a molecular diagnosis based on a gene panel, such as predesigned amplicon based panel or an *in silico* gene panel based on whole-exome sequencing or whole-genome sequencing with a variable number of target genes, often complemented with copy-number variation testing (ie, to find 22q11.2 deletions [DiGeorge syndrome]). Only in Norway is genetic testing performed as a second-tier test on dried blood spots, before children are referred.[38] Next-generation sequencing integrated in the TREC-based NBS program has been demonstrated to reduce the number of retests and referrals, and it increases the positive predictive value.[38] Currently there are several studies exploring the option for next-generation sequencing as first-tier testing in screening programs,[39] which opens possibilities for screening for conditions for which currently no biomarker-based screening is available, including other severe IEI such as hemophagocytic lymphohistiocytosis. However, it also raises several challenges, which need to be carefully considered before implementation can be considered:

1. Clinical aspects (which diseases to screen for in light of Wilson and Jungner criteria).[36]

2. Technical feasibility and fast turnaround time.
3. Capability to perform rapid interpretation of sequence data and selection of which variants to report or not.
4. Ethical, legal, and societal implications.
5. Costs and health economic aspects.
6. Easy access to recognized and licensed treatment.

A genetic diagnosis is not always reached. In absence of a clear genetic diagnosis but isolated, persistently low T lymphocytes, a distinction needs to be made between a T lymphocyte intrinsic or T lymphocyte extrinsic defect in order to choose the correct therapy, HSCT, or thymus transplantation. A 3-D organoid T-lymphocyte differentiation assay using peripheral blood $CD34^+$ cells from patients would permit making this distinction.[40,41] However, this research-only assay is currently available in only a very few research laboratories in Europe and North America, and studies on its clinical validation are not yet available.

PREVENTIVE MEASURES

Unfortunately, an early diagnosis via NBS does not guarantee 100% survival in SCID.[4,7,42-44] Different HSCT cohorts have reported 5% to 14% mortality in infants despite early diagnosis via NBS, with infections remaining the most common cause of death.[4,7,42,43] Infection prevention is therefore of paramount importance. In North America, the Primary Immune Deficiency Treatment Consortium (aka PIDTC) has published a detailed analysis of infections in SCID patients identified via NBS or a positive family history and has also issued recommendations for prophylactic measures.[44] In Europe, in-depth data on infection profiles are available from Germany[9] and Switzerland,[7] but recommendations on prophylactic measures have only been published for Switzerland.[45] Because of the rarity of the disease and the high stakes for individual patients, all recommendations for prophylactic measures are based on expert opinion and not on results of randomized controlled trials.

Infection prevention needs to start even before collecting dried blood spots, as administering live vaccines such as BCG vaccine and rotavirus vaccine to children with SCID is known to often lead to detrimental outcomes.[7,46-49] For this reason, in regions planning to start screening for severe T-lymphocyte deficiencies but also vaccinating with BCG and/or rotavirus, the exact timing of these 2 public health interventions needs to be considered.[50,51] Timing of life-attenuated vaccines such as BCG and rotavirus vaccines differ greatly between individual countries. The BCG World Atlas (bcgatlas.org) provides the most recent overview of BCG vaccination policy including timing and recent changes worldwide. Usually BCG vaccines are provided shortly after birth, but some countries, such as the United Kingdom and Sweden, changed their policy after the introduction of (pilot studies for) TREC-based NBS and now await TREC results before immunization. Rotavirus vaccines are usually provided from 6 weeks of age onward, such as in the Netherlands, Germany, Sweden, and Spain. TREC screening results will be available by then, and parents have usually visited a pediatrician or pediatric immunologist, thus causing no obstacles when implementing TREC-based screening in NBS programs. It is recommended to have a system in place in which screening results will be available for practices ahead of the immunization appointment. Immunizers should make reasonable efforts to be certain of the SCID screening results before administering life-attenuated vaccines. Currently, a large-scale study assessing the advantages of such as screening as well as potential disadvantages of delaying BCG until NBS results are available is being conducted in England.[52] In addition to BCG and rotavirus, all other live vaccines need to be strictly avoided in infants with severe T-lymphocyte deficiencies.

Because cases of very early postnatal infections, acquired even before confirmatory diagnostics, have been described,[7,43] in some countries, the families of infants with a high suspicion of a severe T-lymphocyte deficiency ("urgent positive") are recommended to avoid sick contacts and pause breast-feeding to reduce the risk of cytomegalovirus transmission even before confirmatory diagnostics take place.[45] For preterm children, believed to obtain particular benefits from breast milk, pasteurization might be a reasonable compromise.

Pharmacologic prophylaxis is universally recommended in children with a confirmed severe T-lymphocyte deficiency. Despite local variations in starting time points, there is general consensus on initiation of early *Pneumocystis jirovecii* active prophylaxis. All infants with a confirmed diagnosis are usually also receiving IgG replacement therapy. Recommendations on fungal prophylaxis for *Candida* strains are very heterogenous, as are recommendations on prophylactic antiviral treatment. Because fatal cases of respiratory syncytial virus in SCID are known,[43] prophylactic regimens for infants with a severe T-lymphocyte deficiency often include recommendations on seasonal administration of anti–respiratory syncytial virus antibodies. Some countries also recommend cocooning strategies, such as checking that close contacts have up-to-date regular vaccinations (including varicella zoster virus) and get immunized against influenza.

The above-outlined approach for managing infants with SCID before transplantation, although complex and not universally harmonized, is relatively widely accepted. However, managing infants with less severe T lymphocytopenia remains much more varied. Although certain subpopulations of these children are likely to benefit from antimicrobial prophylaxis and postponing or avoiding live vaccines, there are no uniform guidelines for this highly diverse population.[53,54]

TREATMENT AND ACCESS TO TREATMENT

In patients with severe congenital T lymphocytopenia, timely correction of the defective immune system is crucial to prevent death from infections and/or immune dysregulation in the first year of life. Curative treatment usually consists of HSCT, or gene therapy for specific diseases. A significant minority of patients with severe congenital T lymphocytopenia have athymia requiring thymus transplantation. The outcome of all aforementioned treatment procedures is significantly better in patients in whom early diagnosis and prophylactic measures prevent critical infections and end-organ damage.[8,42]

Ensuring timely access to the correct definitive treatment (HSCT, thymus transplantation, or gene therapy) is of paramount importance. While access is not a major problem in larger countries, this can be a significant hurdle for the introduction of screening programs in smaller countries with smaller patient numbers and therefore less experience. National and international medical societies such as the European Society for Blood and Marrow Transplantation are working to harmonize treatment protocols to improve outcomes and to facilitate the establishment of new transplant programs. ERN-RITA brings together leading

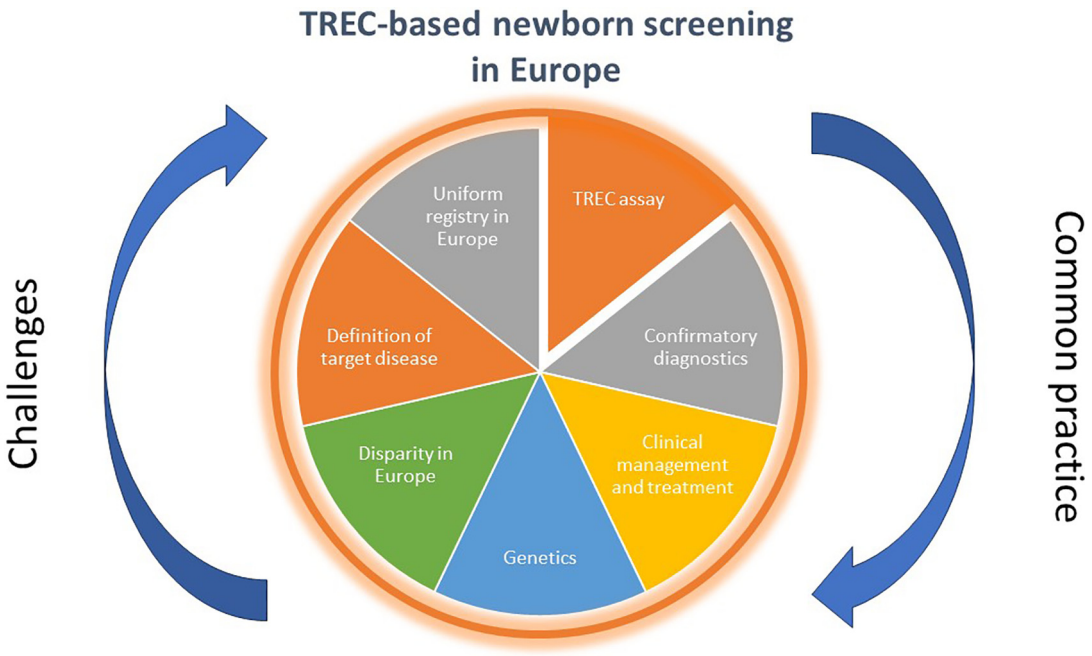

FIG 3. Common practices and challenges across European TREC-based NBS programs.

European centers with expertise in diagnosis and treatment of rare immunologic disorders with the aim of improving the care for all such patients within Europe. With increasing numbers of TREC-based NBS programs, continuous assurance of treatment access will remain a political health challenge of the utmost importance.

LONG-TERM FOLLOW-UP OF PATIENTS OTHER THAN SCID AND COMPLETE ATHYMIA

Because several other entities leading to T-lymphocyte deficiency may be detected by TREC-based NBS, it is extremely important to define how to approach to these patients and their families, especially in the case of non-SCID T lymphocytopenia as defined by Blom et al.[55] The diagnosis, treatment, and follow-up of reversible conditions with T-lymphocyte impairment such as those secondary to T lymphocyte loss due to chylothorax, intestinal lymphangiectasia, T-lymphocyte impairment due to maternal immunosuppressive treatments, or syndromes with T-lymphocyte impairment (eg, incomplete 22q11.2 del syndrome,[56] CHARGE syndrome, Down syndrome,[57] or ataxia telangiectasia[58]) are well defined and usually lead by nonimmunologists. However, our current understanding of idiopathic T lymphocytopenia (ITL) pathogenesis and natural history remains limited, and follow-up protocols are not well defined.[59-61] Careful long-term evaluation of the patients, ideally within dedicated registries, would be important to review treatment (and nontreatment) decisions. In these registries, uniform case definitions would be of utmost importance.[55]

There are also babies with a positive result in TREC-based NBS, who are initially classified as ITL and at last follow-up partly remain undiagnosed,[62] highlighting the importance to standardize the approach to these patients. Continued follow-up is recommended for this group of children, but how frequently and for how long remain unclear. There is inadequate information on how to manage these patients optimally, especially concerning the safety of live-virus vaccines.

Deciding which patients should be prescribed antimicrobial prophylaxis or replacement immunoglobulin differs between institutions, but most infants with ITL do not require it. Finally, the creation of a uniform European registry would allow a better clinical and immunologic description of those babies with ITL and better-harmonized follow-up.

PATIENT-REPORTED EXPERIENCE AND PUBLIC INVOLVEMENT IN POLICYMAKING

Health care policymakers are increasingly recognizing the need to strengthen public involvement and to actively consult and engage the public when setting priorities and designing services to improve patient care. Public and patient involvement will result in more democratic decision-making, promoting accountability and demonstrating transparency and openness.[63,64] In addition, public involvement will help to build trust and public confidence—key factors in NBS programs. Societal acceptance is a major criterion when introducing new disorders in NBS, and even though the effectiveness of TREC quantification for SCID detection had been demonstrated, the availability of a high-quality test method does not automatically guarantee acceptance from the perspective of stakeholders. Parents are key stakeholders in NBS programs, and their support is paramount. Previous studies that have investigated the societal and psychosocial aspects of NBS for SCID showed that parents of healthy newborns have a very positive attitude toward NBS for SCID. The majority of parents stated that they wanted SCID to be detected as early as possible for their child.[65] Parents of healthy newborns even showed support for early diagnosis of findings secondary to TREC-based NBS such as ataxia telangiectasia, favoring the advantages of its early detection in the asymptomatic phase over the disadvantages.[65]

Interview studies revealed that parents experienced anxiety and stress when receiving an abnormal screening result for TREC-based NBS. Even parents with a confirmed healthy newborn after

follow-up (false-positive result) perceived their newborn as more "vulnerable" later in life.[65] Uncertainties were chronic and multifaceted, and parents expressed a variety of negative emotional reactions: uncertainty; anxiety, worry, or fear; doubt, guilt, or grief; and even anger, frustration, or depression.[66] These findings highlight the importance of providing adequate information and the need for health care providers to provide resources to manage and cope with these types of uncertainties. Managing uncertainty can be achieved by providing hope, optimism, and psychological support to create coping efficacy and overall adaption. For adequate information provision, receiving information in person from either health care providers or other parents was the preferred option for parents. Reading printed information, interacting on social media, and reading websites were the next preferred formats by parents with newborns diagnosed via NBS.[67] These findings were confirmed by parents of newborns with suspected athymia identified via NBS for SCID, expressing a need for basic, unambiguous information from trusted sources, preferably in written format. In addition, these families reported peer interaction to be another important source of information, reassurance, and comfort.[68] Finally, interviews with parents of newborns diagnosed with SCID or a SCID-like condition through NBS showed that parents used a variety of behavioral, cognitive, and affective coping strategies.[69] Coping strategies included reaching out to other SCID parents or seeking second medical opinions, positive thinking, self-reflection, and relying on family and community. These findings can provide aid for parents whose child is newly diagnosed with SCID and for health care professionals such as social workers, genetic counselors, and psychologists.

Even though public participation in health policymaking is growing, translating outcomes of public engagement to policy remains challenging. Questions arise about the form and level of involvement and the relationship with opinions of other stakeholders. Other actors involved in NBS decisions are laboratory scientists; health care workers; ethical, legal, and economic experts; governmental and nongovernmental agencies; and health care providers.[70] Policymakers need to balance these different perspectives and needs in NBS discussions while including considerations about high-quality evidence, benefits or harms for the routine screening program, costs, the population's values, and contextual considerations.

CONCLUSION

European countries have a heterogeneous approach when it comes to NBS programs, and implementation of new conditions such as SCID and severe T lymphocytopenia can vary widely as a result of differences in national health care structures and available resources. Our review shows the diversity in screening approaches in published data and survey results, but additionally highlights the similarities in TREC-based NBS program across Europe (Fig 3). There is a wide consensus on the adjustment of TREC-based screening algorithms for preterm infants and urgent referrals, as well as on confirmatory diagnostics including flow cytometry. Although the role of genetic testing in confirmatory diagnostics is undisputed, genetics as a second-tier or even first-tier assessment remains a subject for debate. European countries have clear treatment guidelines and common practices when treating SCID patients with HSCT, although the assurance of treatment access will be of utmost importance with the increasing numbers of TREC-based NBS programs. Curative treatment options for SCID and severe T lymphocytopenia have been available for many years; however, follow-up and treatment of ITL is far from harmonized across NBS programs. Careful long-term evaluation of these patients, ideally within registries with uniform case definitions in Europe, would be important to review treatment (and nontreatment) decisions. The tremendous efforts of health care professionals, policymakers, patient organizations, and others have led to the national and regional implementation of TREC-based NBS in 17 European countries and the screening of more than 2,500,000 newborns for SCID and severe T lymphocytopenia in Europe in 2024. Although not all European countries have a TREC-based NBS program in place, other important collaborative programs in East and Central Europe have created more awareness, leading to earlier diagnosis of these important health conditions. Complete harmonization of TREC-based NBS programs across Europe might be difficult to achieve, but our review shows the differences and agreements between European countries helping countries with upcoming implementation or optimization of their NBS programs. Collaboration and close partnerships across countries will help in moving forward with universal European TREC-based screening for all newborns, resulting in ever more infants with SCID being detected throughout Europe each year.

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