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Newborn screening for inborn errors of immunity: The status worldwide

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ABSTRACT

Background: Newborn screening (NBS) for the early detection of inborn errors of immunity (IEI) has been implemented in a few countries. The objective of this study was to verify the situation and define obstacles to the implementation of NBS worldwide.

Methods: A questionnaire was developed by the Inborn Errors of Immunity Committee of the World Allergy Organization (WAO) with 17 questions regarding NBS for IEI in the physician's workplace, NBS test type, problems hindering NBS implementation, reimbursement for IEI therapy, presence of a national IEI registry, referral centers, molecular diagnosis, hematopoietic stem cell transplantation centers, gene therapy, and immunoglobulin replacement therapy. The survey was sent by email once a week to doctors and others associated with WAO and the main immunology societies worldwide as a Google Form™ to be completed during September and October 2021.

Results: Two hundred twenty-nine questionnaires were completed, of which 216 (94.3%) were completed by physicians. One hundred seventy-six (76.8%) physicians were both allergists and immunologists. The agreement between allergists/immunologists and non-allergists/non-immunologists for the question "Is there NBS for IEI in the country you work in?" was good (κ = 0,64: 95% CI 0.55–0.69). Ninety-eight (42.8%) participants were from Latin America, 35 (15.3%) from North America, 29 (12.6%) from Europe, 18 (7.9%) from Africa, 44 (19.2%) from Asia, and 5 (2.2%) from Oceania. More than half the participants (n = 124, 54.2%) regularly treated patients with IEI, followed by occasional treatment (n = 77, 33.6%), or never (n = 28, 12.2%). Of the respondents, 14.8% reported that their countries performed NBS for IEI, whereas 42.2% reported their countries did not. T-cell receptor excision circles was the most widely used technique in some countries, with 75 (59.9%) for the diagnosis of NBS for IEI, followed by combined use with kappa deleting-recombination excision circles. Only 13 participants (10.3%) underwent neonatal exon screening in their respective countries. Financial and technical issues were among the major obstacles to the implementation of NBS for IEI.

Conclusions: This pilot study showed that few countries have implemented NBS for IEI, despite the presence of immunology referral centers and the availability of hematopoietic stem cell transplantation and intravenous immunoglobulin replacement therapy. The findings highlight the

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difficulties, mainly financial and technical, hindering wide application of NBS. Sharing experiences, technologies, and resources at the international level can help overcome these difficulties.

Keywords: Newborn screening, Inborn errors of immunity, Hematopoietic stem cell transplantation

INTRODUCTION

Inborn errors of immunity (IEI) are rare monogenic defects in various pathways of the immune system that may be associated with increased susceptibility to infections, autoimmunity, lymphoproliferation, and malignancies. To date, more than 450 known IEI have been identified[1,2] that may affect up to 1% of the population.[3]

Early recognition and treatment of IEI could save affected individuals from the serious and sometimes life-threatening consequences of infections or autoimmunity.[3] This led to the emergence of newborn screening (NBS) for IEI. The main purpose of NBS is the early detection of treatable and severe forms of IEI with profoundly low T and B cell numbers, to decrease morbidity and mortality.[4–6] This is done by quantifying T-cell receptor excision circles (TRECs) and kappa deleting-recombination excision circles (KRECs).[5] These methods are cheaper alternatives for flow cytometry to screen for and diagnose IEI. The methods can be used in small laboratories and rural areas as an initial assessment of the possibility of IEI.[7,8]

TRECs are small circular DNA by-products specific to naïve T cells[9] that are produced during T-cell receptor recombination in these cells. TREC is an accurate measure of thymic function because it arises in the late phase of thymocyte maturation.[10] Their levels decline with age in healthy individuals[9] and are reduced or absent in severe combined immunodeficiency (SCID) and other T-cell lymphopenias.[7] TREC copy numbers are measured by quantitative reverse transcription polymerase chain reaction (qRT-PCR).[9]

KRECs are B cell products produced during rearrangement of the variable, diverse, and joining domains of the B cell immunoglobulin kappa gene.[10] KRECs were first developed for the assessment of patients with antibody deficiency disorders and monitoring B cell recovery following hematopoietic stem cell transplantation (HSCT). In 2011, the utility of the KREC assay in identifying X-linked agammaglobulinemia (XLA)- and XLA-like diseases in neonates was demonstrated.[11]

Pilot TREC-based primary immunodeficiency (PID) screening programs have been widely established globally, including Asia (Singapore, Taiwan, China, Japan, South Korea, and Vietnam), Europe (Austria, Belgium, Czech Republic, Denmark, Germany, Iceland, Ireland, Latvia, Netherlands, Norway, Russia, Slovenia, Sweden, Switzerland, Finland, Italy, Spain, United Kingdom, France, Poland, Slovakia, Turkey, and Ukraine), Latin America (Brazil), Middle East (Israel, Lebanon, and Saudi Arabia), North America (United States and Canada), and Oceania (New Zealand and Australia).[10,12,13] In Western countries, NBS programs have enabled the early diagnosis of SCID, which is cost-effective and beneficial for patient prognosis.[14] The implementing NBS has contributed to the decreased birth prevalence of SCID from 1:100,000 to 1:58,000,[15,16] and a three-times decreased average cost of an early bone marrow transplantation compared to late transplantation.[5,17]

Unfortunately, NBS is not yet available in most countries. Updating the situation and defining the hindrances and obstacles to the implementation of NBS were the main goals of this study.

METHODS

A survey was developed by the Inborn Errors of Immunity Committee of WAO. The survey consisted of 17 questions regarding the use of NBS in general and NBS for IEI specifically in the physicians' workplace, type of test, problems in implementing NBS, reimbursement, national registry for IEI, referral centers, molecular diagnosis, HSCT

centers, gene therapy, and immunoglobulin replacement (Fig. 1).

The survey was sent by email once a week to doctors and others associated with WAO and the main immunodeficiency societies around the world as a Google Form™. The survey was completed during September and October 2021.

The agreement (κ = Cohen's kappa) for this instrument was calculated by comparing the answers of allergists/immunologists and non-allergists/non-immunologists-answers to the following 4 questions:

1. Is there an NBS for IEI in the country in which you work?
2. Is there a national registry for IEI in your country?
3. Are there hematopoietic stem cell transplantation referral centers for IEI in your country?
4. Is immunoglobulin replacement therapy available in this country?

The κ values indicated the level of agreement: $\leq$0, no agreement; 0.01–0.20, none to slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect.[18]

RESULTS

Two hundred twenty-nine questionnaires were collected. Of these, 216 (94.3%) were completed by physicians, with the remaining 13 (5.7%) completed by non-physicians. One hundred and seventy-six (76.8%) physicians were allergists, immunologists, or both allergists/immunologists, 33

1. Are you a physician?
a. Yes
b. No

2. What is your specialty?
a. Allergist
b. Immunologist
c. Both allergist and immunologist
d. Dermatologist
e. Pediatrician
f. General Practitioner
g. Other

3. How frequently do you treat patients with inborn errors of immunity / primary immunodeficiency?
a. Not at all
b. Occasionally
c. Regularly

4. Which country do you work in? Region.
a. Latin America
b. America
c. Europe
d. Africa
e. Asia
f. Oceania

5. Is there general NBS in the country you work in?
a. Universal
b. Partial
c. None

6. Is there NBS for IEI in the country you work in?
a. Yes, nationwide
b. Yes, partial in some cities/provinces/states
c. The country has taken some steps to start an IEI NBS program
d. None

7. Which NBS test is performed for IEI in your country?
a. TREC
b. KREC
c. TREC+KREC
d. Neonatal exome

8. What is/are the problem/s for not implementing IEI NBS? (You can choose more than one answer).
a. Financial
b. Technical
c. Lack of awareness of the importance of early diagnosis of IEI
d. Not a priority amdst many other health problems
e. Other

9. In your opinion, which of these reasons is the biggest problem for not implementing IEI NBS? (Please select one.)
a. Financial
b. Technical
c. Lack of awareness of the importance of early diagnosis of IEI
d. Not a priority amdst many other health problems
e. Other

10. Is there reimbursement for IEI NBS in your country?
a. Public health system
b. Insurance based
c. Both
d. None

11. Is there a national registry for IEI in your country?
a. Yes
b. No

12. Are there referral centers for IEI in your country?
a. Yes
b. No

13. Is molecular diagnosis done for IEI patients?
a. Yes, for all patients
b. Yes, only for some patients
c. Not done at all

14. Are there Hemathopoietic Stem Cell Transplantation referral centers for IEI in your country?
a. Yes
b. No

15. Are there gene-therapy projects available in your country?
a. Yes
b. No

16. Is Immunoglobulin replacement therapy available in your country?
a. Yes
b. No

17. Is there reimbursement for immunoglobulin replacement therapy in your country?
a. Public health system
b. Insurance based
c. Both
d. None

Fig. 1 Questionnaire about NBS and IEI treating

(14.4%) were pediatricians, 1 (0.4%) was a dermatologist, and 19 (8.4%) worked with other specialties.

The agreement between the answers of allergists/immunologists and non-allergists/non-immunologists was substantial for question 1 ($\kappa = 0.64$, 95% CI 0.55–0.69), moderate agreement for question 2 ($\kappa = 0.43$, 95%CI 0.38–0.48), and substantial agreement for questions 3 ($\kappa = 0.66$, 95% CI 0.58–0.70) and 4 ($\kappa = 0.69$, 95% CI 0.61–0.75).

Ninety-eight (42.8%) participants were from Latin America, 35 (15.3%) from North America, 29(12.6%) from Europe, 18 (7.9%) from Africa, 44 (19.2%) from Asia, and 5 (2.2%) from Oceania. Most participants treated patients with IEI regularly 124 (54.2%), followed by occasionally (n = 77, 33.6%), and never (n = 28, 12.2%).

Of the participating countries, 110 (53.4%) have an IEI registry. Respondents from Africa and Oceania reported only one country with an IEI registry. There are several referral centers in almost all continents; however, molecular diagnosis is offered in only 35 (17%) countries. As a reflection of improved management, HSCT centers are present in 154 (74.8%) of the countries included in the survey, and IVIG therapy is offered in 203 (98.5%) of the countries. Table 1 presents the general characteristics of IEI management worldwide.

Of the participants, 103 (45%) reported the use of NBS in their respective countries. NBS specifically for IEI is only available in 34 (14.8%) countries, with 57 (42.2%) respondents reporting the adoption of NBS for IEI in some cities or parts of their countries. Ninety-seven (42.2%) respondents confirmed the absence of NBS for IEI in their countries, mainly in Asia and Africa (Table 2 and Fig. 2).

TRECS was the most widely used technique for the diagnosis of NBS in IEI 75(59.5%), followed by both TRECS and KRECS, and 34(27%) in some countries. Only 13 participants (10.3%) underwent neonatal exon screening in their respective countries. (Table 2).

Financial issues, technical problems, lack of awareness of the importance of early diagnosis of IEI, and IEI not being prioritized among other health problems were all reasons for delays in the implementation of NBS programs for IEI. The most common reason (n = 64, 27.9%) was high cost, followed by a lack of awareness of the importance of early diagnosis of IEI (n = 61, 26.6%).

Table 3 identifies the participants' countries having national registries, referral centers for IEI, HSCT referral centers, gene therapy, and IVIG reimbursement.

DISCUSSION

SCID is one of the most severe forms of primary immunodeficiency. SCID is characterized by the absence or dysfunction of T lymphocytes associated with a defective antibody response, which may result from intrinsic defects in B lymphocytes or inadequate T-cell activity. Patients with SCID present with bacterial, viral, or fungal infections in the first few months of life.[19] If left untreated, patients with SCID will eventually die by the second year of life. Therefore, early diagnosis and effective clinical management are crucial.[19]

Supportive treatments include broad-spectrum antibiotics, antifungal drugs, and IVIG. HSCT and gene therapy are the only currently available curative treatments. Younger age and absence of viral infection before transplantation are associated with an overall better prognosis.[20] Railey et al reported an overall survival rate of 94% for those transplanted in the first 3.5 months of life in a cohort of 161 transplant patients in the United States.[21]

Newborn screening programs were performed to identify infants with different and significant conditions for which there is a pre-symptomatic phase and for which effective treatment is available[22] to decrease morbidity, mortality, and poorer outcomes in cases of delayed diagnosis.[23] In our study, most participating countries had well-established NBS for different diseases.

Regarding IEI, the NBS test using the TREC assay has been performed in some US states since 2008.[24,25] In the same year, the first successful transplant was performed on an SCID diagnosed

Region	North America n = 35 (15.3)	Latin America 90 (39.3)	Asia 46 (20.1)	Africa 18 (7.9)	Europe 27 (11.8)	Oceania 5 (2.2)	Total 229 (100)
Is there a national registry for IEI in your country?							
Yes	18 (56.3)	58 (65.2)	’20 (46.5)	1 (6.3)	12 (54.5)	1 (25)	110 (53.4)
No	14 (43.7)	31 (34.8)	23 (53.5)	15 (93.7)	10 (45.5)	3 (75)	96 (46.6)
Are there referral centers for IEI in your country?							
Yes	32 (100)	75 (84.3)	26 (60.5)	10 (62.5)	18 (81.8)	3 (75)	176 (85.4)
No		14 (15.7)	17 (39.5)	6 (37.5)	4 (18.2)	1 (25)	30 (14.6)
Is molecular diagnosis done for IEI patients?							
Yes, for all patients	13 (40.6)	6 (6.7)	10 (23.3)		5 (22.7)	1 (25)	35 (17)
Yes, only for some patients	18 (56.3)	73 (82)	31 (72.1)	11 (68.8)	15 (68.2)	3 (75)	151 (73.3)
Not done at all	1 (3.1)	10 (11.3)	2 (4.6)	5 (31.2)	2 (9.1)	0 (0)	20 (9.7)
Are there Hematopoietic Stem Cell Transplantation centers for IEI in your country?							
Yes	32 (100)	69 (77.5)	26 (60.4)	7 (43.8)	16 (72.3)	4 (100)	154 (74.8)
No		20 (22.5)	17 (39.6)	9 (56.3)	6 (27.3)		52 (25.2)
Are there gene-therapy projects available in your country?							
Yes	25 (78.1)	21 (23.6)	6 (14)	16 (100)	3 (13.6)	4 (100)	55 (26.7)
No	7 (21.9)	68 (76.4)	37 (86)	0 (0)	19 (86.4)		151 (73.3)
Is Immunoglobulin replacement therapy available in your country?							
Yes	32 (100)	88 (98.9)	43 (100)	15 (93.8)	22 (100)	3 (75)	203 (98.5)
No		1 (1.1)	0 (0)	1 (6.2)		1(25)	3 (1.5)

(continued)

Region	North America n = 35 (15.3)	Latin America 90 (39.3)	Asia 46 (20.1)	Africa 18 (7.9)	Europe 27 (11.8)	Oceania 5 (2.2)	Total 229 (100)
Is there reimbursement for immunoglobulin replacement therapy in your country?							
Public health system	10 (31.3)	18 (20.2)	24 (55.8)	4 (25)	17 (77.3)	4 (100)	77 (37.4)
Insurance based	9 (28.1)	4 (4.5)	3 (7)	5 (31.3)		0 (0)	21 (10.2)
Both	13 (40.7)	60 (67.4)	7 (16.3)	3 (18.7)	4 (18.2)	0 (0)	87 (42.2)
None	0 (0)	7 (7.9)	9 (20.9)	4 (25)	1 (4.5)	0 (0)	21 (10.2)

Table 1. (Continued) IEI management around the world. n = 229 (%)

by NBS (Jeffrey Model Foundation, http://www.info4pi.org). Since then, NBS has been gradually implemented in different states and countries. According to our results, NBS has been implemented in several countries. A quarter of the included countries have partially implemented NBS, whereas less than one-fifth have begun this process. The remaining countries in the present survey have begun to apply NBS for IEI. The main reason for the delayed implementation of NBS for IEI is financial considerations. This highlights the need for the development of new, low-cost technologies for testing newborns for a broad range of conditions, a crucial solution to this problem.[26]

In most countries that use NBS for IEI, screening is performed using the TREC/KREC assay. However, such screening techniques cannot detect many serious IEI and immune dysregulation disorders. Sequencing could provide a potential method for screening a wider array of health conditions. This has raised the issue of using genomics-based NBS.[27–29] However, this approach is not feasible from a logistic or economic perspective in the context of NBS.[30] Genetic screening might be economically unfeasible; therefore, we suggest a two-tiered approach for expanding the number of IEIs that could be diagnosed via NBS.

The survey data revealed that the second most common reason for a lack of NBS was an absence of awareness of the importance of NBS for IEI. Hence, another solution may be worldwide research to identify the successful implementation of NBS in decreasing mortality rates. This could serve to draw the attention of health authorities to the efficiency of NBS. Increased awareness of disease management is reflected in the number of referral centers available worldwide; however, the presence of national registries is a challenge. According to our results, national registries for IEI were present in 110 (53.4%) countries, mainly in North America and Europe. There are very few registries in the Middle East and North Africa, despite the anticipated increased prevalence of IEI in this region because of the high rate of consanguinity with a predominance of autosomal recessive disorders.[31] Still, the burden of disease is underestimated in countries from middle- and low-income regions for many reasons, including the lack of registries.[32]

Region	North America n = 35 (15.3)	Latin America 90 (39.3)	Asia 46 (20.1)	Africa 18 (7.9)	Europe 27 (11.8)	Oceania 5 (2.2)	Total 229 (100)
Is there general NBS in the country you work in?							
Universal	28 (80)	32 (32.7)	24 (52.2)	4 (22.2)	12 (44.4)	3 (60)	103 (45)
Partial	6 (17.1)	40 (40.8)	14 (30.4)	1 (5.6)	7 (25.9)	1 (20)	69 (30.1)
None	2 (2.9)	26 (26.5)	8 (17.4)	13 (72.2)	8 (29.6)	1 (20)	57 (24.9)
Is there NBS for IEI in the country you work in?							
Yes, nationwide	18 (51.4)	3 (3.1)	8 (17.4)	1 (5.6)	4 (14.8)	2 (40)	34 (14.8)
Yes, partial in some cities/provinces/ states	14 (40)	33 (33.7)	4 (8.7)	2 (11.1)	2 (7.4)	1 (20)	57 (24.9)
The country has taken some steps to start an IEI NBS program	2 (5.7)	26 (26.5)	3 (6.5)	0 (0)	9 (33.3)	2 (40)	41 (17.9)
None	1 (2.9)	36 (36.7)	31 (67.4)	15 (83.3)	12 (44.5)	0 (0)	97 (42.4)
Which NBS test is performed for IEI in your country?							
TREC	31 (91.1)	27 (45)	10 (71.4)	0 (0)	5 (41.7)	2 (66.7)	75 (59.5)
KREC	2 (5.9)	3 (5)	3 (21.4)	0 (0)	4 (33.3)	0 (0)	4 (3.2)
TREC + KREC	1 (3)	24 (40)	1 (7.2)	3 (16.7)	2 (16.7)	1 (33.3)	34 (27)
Neonatal exome	0 (0)	6 (10)	0 (0)	0 (0)	1 (8.3)	0 (0)	13 (10.3)
What is/are the problem/s for not implementing IEI NBS? (You can choose more than one answer).							
Financial	1 (2.9)	23 (25.6)	22 (47.8)	11 (61.1)	9 (33.3)	2 (40)	64 (27.9)
Technical		12 (13.3)	8 (17.4)	5 (27.8)	4 (14.8)	1 (20)	30 (13.1)
Lack of awareness of the importance of early diagnosis of IEI		21 (23.3)	21 (45.7)	12 (66.7)	5 (18.5)	2 (20)	61 (26.6)
Not a priority amidst many other health problems		19 (21.1)	24 (52.2)	9 (50)	4 (14.8)	0 (0)	58 (25.3)
Other		6 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)	7 (3.1)

(continued)

Region	North America n = 35 (15.3)	Latin America 90 (39.3)	Asia 46 (20.1)	Africa 18 (7.9)	Europe 27 (11.8)	Oceania 5 (2.2)	Total 229 (100)
In your opinion, which of these reasons is the biggest problem for not implementing IEI NBS? (Please select one.)							
Financial		13 (37.1)	7 (24.2)	4 (26.7)	6 (54.5)		30 (32,3)
Technical		10 (28.6)	9 (31.1)	8 (53.3)	5 (45.5)	1 (50)	33 (35,5)
Lack of awareness of the importance of early diagnosis of IEI	1 (2.9)	11 (31.4)	11 (37.9)	3 (20)	0 (0)		26 (28)
Not a priority amidst many other health problems		1 (2.9)	1 (3.4)	0 (0)	0 (0)	1 (50)	3 (3,2)
Other		0 (0)	1 (3.4)	0 (0)	0 (0)		1 (0,1)
Is there reimbursement for IEI NBS in your country?							
Public health system	15 (46.9)	22 (24.7)	12 (27.9)	3 (18.8)	11 (50)	2 (50)	65 (31,6)
Insurance based	3 (9.4)	11 (12.4)	2 (4.7)		2 (9.1)		18 (8.7)
Both	12 (37.5)	13 (14.6)	1 (2.3)	1 (6.2)	2 (9.1)		29 (14.1)
None	2 (6.2)	43 (48.3)	28 (65.1)	12 (75)	7 (31.8)	2 (50)	94 (45.6)

Table 2. (Continued) NBS availability around the world, problems of implementation, and reimbursement. n = 229 (%)

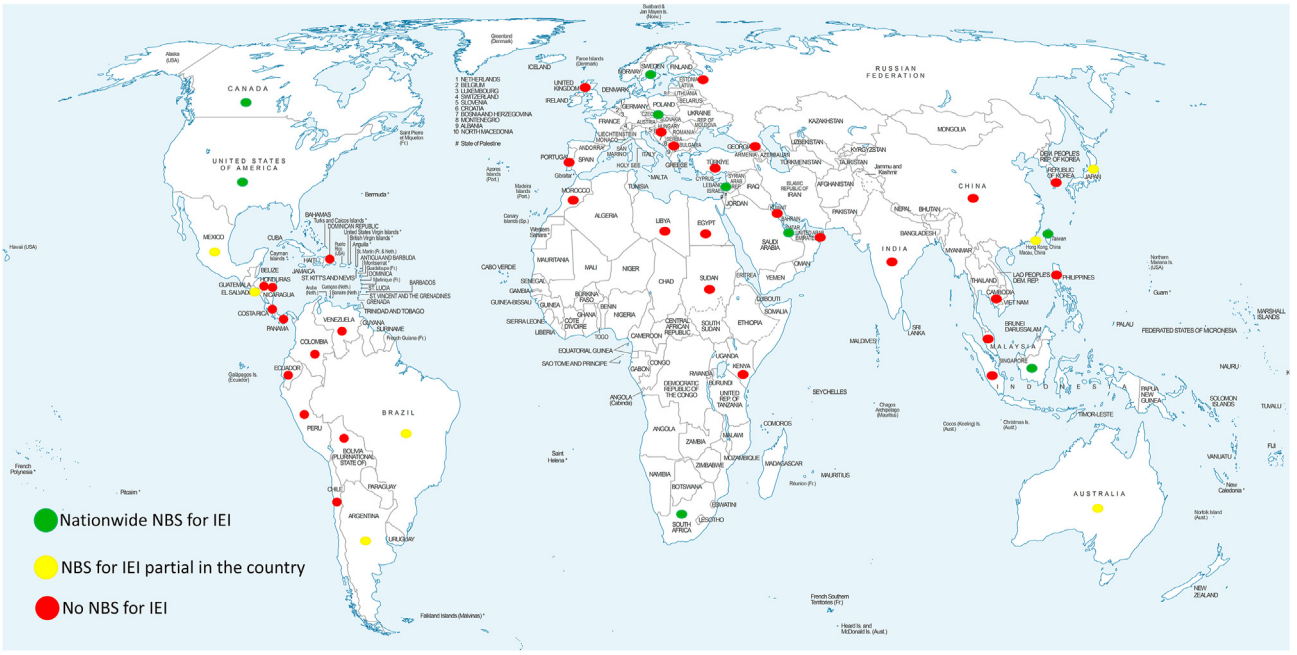

Fig. 2 Worldwide Newborn Screening status.

Seventeen percent of the respondents reported the use of molecular diagnosis for all patients with IEI. By contrast, the majority of respondents declared the use of molecular diagnosis for only some patients. The delayed diagnosis[31] that is partly attributed to the unavailability of molecular diagnosis can result in a more severe disease phenotype in low and middle income countries in comparison to other regions.[32]

Transplants in patients with IEI are highly complex and should be performed in centers with continuous and significant experience in these procedures and that participate in collaborative studies.[33] Referral centers and treatment by HSCT are present in almost all of the surveyed regions, making early intervention feasible when NBS is used. Another important issue that limits the worldwide implementation of NBS is the need for a well-established setting to confirm or rule out IEI diagnosis in positive cases before referral to HSCT centers. In this regard, the selection of referral centers must be accurate with proven experience in the field. The European Reference Network-Rare Immunodeficiency, Autoinflammatory, and Autoimmune Disease Network continues to perform relevant research.

The limited number of participants, lack of representation in all countries, and the use of a non-validated questionnaire are limitations of this study.

In conclusion, this pilot study focused on the status of NBS for IEI worldwide. The survey data indicate that few countries perform NBS, with NBS in the early stages of implementation in a few other countries. The findings highlight the difficulties, mainly financial and technical, hindering the application of NBS for IEI in resource-challenged countries. This is despite the widespread presence of immunology referral centers and the availability of HSCT and IVIG replacement therapy. NBS helps doctors establish an early diagnosis of IEI and provide timely curative treatment, which saves the lives of these patients. Therefore, there is an urgent need to expand NBS for IEI by overcoming the difficulties in its implementation. This can only be achieved by sharing experiences, technologies, and resources at an international level.

	Countries
Is there a national registry for IEI in your country?	
Yes	Argentina, Bolivia, Brazil, Colombia, Chile, Costa Rica, El Salvador, Mexico, Venezuela, United States of America, Morocco, Czech Republic, Estonia, Georgia, Portugal, Serbia, Sweden, Turkey, United Kingdom, Uzbekistan, Hong Kong, India, Indonesia, Japan, Korea, Kuwait, Lebanon, Malaysia, Peoples Republic of China, Philippines, Qatar, Singapore, Taiwan.
Are there referral centers for IEI in your country?	
Yes	Argentina, Bolivia, Brazil, Colombia, Chile, Costa Rica, Ecuador, El Salvador, Honduras, Mexico, Peru, Venezuela, Canada, United States of America, Australia, Morocco, Sudan, Egypt, Kenya, Czech Republic, Georgia, Portugal, Croatia, Sweden, Turkey, United Kingdom, Uzbekistan, Hong Kong, India, Indonesia, Israel, Japan, Korea, Kuwait, Lebanon, Malaysia, Philippines, Qatar, Singapore, Taiwan.
Are there Hemathopoietic Stem Cell Transplantation referral centers for IEI in your country?	
Yes	Argentina, Bolivia, Brazil, Colombia, Chile, Costa Rica, Dominican Republic, Ecuador, El Salvador, Honduras, Mexico, Peru, Venezuela, Canada, United States of America, Australia, Morocco, Egypt, South Africa, Czech Republic, Georgia, Portugal, Croatia, Sweden, Turkey, United Kingdom, Uzbekistan, Hong Kong, India, Indonesia, Israel, Kuwait, Lebanon, Malaysia, Philippines, Qatar, Taiwan, United Arab Emirates.
Are there gene-therapy projects available in your country?	
Yes	Brazil, Colombia, Chile, Costa Rica, Dominican Republic, El Salvador, Mexico, Venezuela, Canada, United States of America, Czech Republic, Portugal, Hong Kong, Malaysia, Philippines, Qatar.
Is there reimbursement for immunoglobulin replacement therapy in your country?	
Public health system	Panama, Canada, Australia, Lybia, Morocco, Sudan, Czech Republic, Georgia, Portugal, Croatia, Sweden, United Kingdom, Uzbekistan, Kosovo, Serbia, Hong Kong, India, Israel, Kuwait, Lebanon, Philippines, Taiwan, Singapore.
Insurance based	Colombia, Dominican Republic, Nicaragua, Kenya, Egypt, Sudan, Japan, Philippines.
Both	Argentina, Bolivia, Brazil, Colombia, Chile, Costa Rica, Ecuador, El Salvador, Honduras, Mexico, Peru, Venezuela, United States of America, Egypt, Kenya, Estonia, Turkey, India, Korea, Indonesia, Malaysia, Peoples Republic of China, Qatar.

Table 3. Registry, referral centers, HSCT, gene-therapy and IVIG reimbursement availability around the world

Abbreviations

DNA, desoxyribonucleic acid; HSCT, hematopoietic stem cell transplantation; IVIG, intravenous immunoglobulin; IEI, inborn errors of immunity; KRECs, kappa deleting-recombination excision circles; NBS, newborn screening; PID, primary immunodeficiency; qRT-PCR, quantitative reverse transcription polymerase chain reaction; SCID, severe combined immunodeficiency; TRECs, T-cell receptor excision circles.

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Availability of data and materials

The material is available with authors.

Author's contribution

Herberto José Chong-Neto: Conceptualization; investigation; writing –original draft; methodology; validation; visualization; writing –review and editing; formal analysis; data curation; supervision. Nesrine Radwan: Conceptualization, writing original draft, reviewing results, editing. Antônio Condino-Neto: Conceptualization, reviewing manuscript. Nelson Augusto Rosário Filho: Conceptualization; investigation; writing –original draft; methodology; validation; visualization; writing –review and editing; formal analysis; data curation; supervision. José Antonio Ortega-Martell: Conceptualization, writing original draft, reviewing manuscript and editing. Zeinab A El-Sayed: Conceptualization, constructing investigational tool, writing original draft, revising methodology and results, reviewing manuscript and editing, supervision.

Ethics approval and consent to participate
The project was approved by the World Allergy Organization Board of Directors as an initiative of Inborn Errors of Immunity Committee.

Consent for publication
All authors agreed for this work to be published in the World Allergy Organization Journal.

Declaration of competing interest
Nothing to declare.

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