

Clinical Communications

Causes of low neonatal T-cell receptor excision circles: A systematic review

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Clinical Implications

- This systematic review summarizes all the conditions described in the literature that can cause low T-cell receptor excision circles at birth. It aims to aid clinicians in the management of patients and to identify future areas of research if no causative diagnosis is made.

TO THE EDITOR:

For severe combined immunodeficiency (SCID), as well as for various other primary immunodeficiencies (PIDs), hematopoietic stem cell transplant or gene therapy is the only curative option.¹ Neonatal T-cell receptor excision circles (TRECs) screening can allow presymptomatic diagnosis of SCID (defined as <300 autologous T cells/ μ L in peripheral blood and <10% proliferation on PHA stimulation²) and can also help identify patients with disorders associated with T-cell lymphopenia, T-cell dysfunction, or peripheral expansion of T cells (such as Omenn syndrome). Early identification of such patients is pivotal in ensuring their appropriate management and is clearly associated with a significant reduction in mortality and complications.^{3,4}

The current increase in data on neonatal TREC screening has made it difficult for physicians to have an overview of differential diagnosis associated with low TRECs at birth. To provide a summary of causes of low TRECs, we systematically searched keywords including “newborn screening,” “dried blood spot testing,” “guthrie,” “TRECs,” “KRECs,” and different PID names or PID genes, while excluding “human immunodeficiency virus” and “deltaretrovirus infection” in MEDLINE, EMBASE, and Scopus databases, from their respective start dates until November 4, 2016 (see text and Figure E1 in this article’s Online Repository at www.jaci-inpractice.org).

From 1747 records retrieved, we extracted data from 42 original articles (see Table E1 in this article’s Online Repository at www.jaci-inpractice.org) and 58 abstracts or letters to the editor (see Figure E2 in this article’s Online Repository at www.jaci-inpractice.org) (see Table E2 for details on 42 original articles and Table E3 for summary of abstracts and letters to the editor in this article’s Online Repository at www.jaci-inpractice.org). Checking reference lists of included studies complemented electronic searches. The 42 included original articles reported on a total of 6,093,942 individuals. Low TRECs were detected in 1533 individuals (including 1 additional genetic cause of PID from an abstract⁵) (Figure 1, A), measured in newborns (n = 1459), between the neonatal period and the age 36 months (n = 67), at 3 to 18 years (n = 2), or not indicated (n = 5). Low

TRECs were attributed to PIDs in 40% (n = 611) of the patients with 25 different PIDs as defined by the International Union of Immunological Societies.⁶ All these 611 patients had SCID, combined immunodeficiency, or Omenn syndrome, yet in 132 the exact genetic mutation was not indicated. The overall most frequently recorded PID was DiGeorge syndrome (most frequently 22q11.2 deletion syndrome), followed by IL-2 receptor gamma (*IL2RG*) mutations and adenosine deaminase 1 (*ADA1*) deficiency (Figure 1, B and C).

Low TRECs were furthermore reported in 49 (3%) individuals with 12 different well-defined syndromes, the most common of which is Trisomy 21 followed by Trisomy 18, which are not listed in the current International Union of Immunological Societies classification as classic PIDs (Figure 1, D). All remaining patients with low TRECs did not have any identified underlying PID and were not diagnosed as having any well-defined syndrome (Figure 1, E). Even though low TRECs were transient in at least 20% of patients and possibly also transient in 78 preterm births, the other patients in this group (n = 477 [31%]) had no specified underlying genetic disease that could be associated with low TRECs. This group includes patients with secondary or idiopathic T-cell lymphopenia, gastrointestinal disorders, such as gastroschisis, necrotizing enterocolitis, and ileal atresia, or defects in their lymphatic system and other conditions.

The 25 PIDs found throughout the included articles and abstracts only constitute a proportion of the PIDs known to be associated with low T-cell counts.⁶ The genes *PTPRC*, *CD3E*, *CD3Z*, *CORO1A*, and *PRKDC* were not described in any included article but are associated with SCID⁶ and we would therefore expect them to present with low TRECs at birth. Because the incidence of a particular PID is likely to vary from one ethnic group to another and is furthermore dependent on consanguinity, specific requirements of different patient profiles and ethnic groups need consideration.

Several patients with low TRECs and persistent lymphopenia were described without any identified underlying genetic defect or well-defined syndrome. Even though in some of these cases, the reason for low TRECs might have been found in the meantime or was known but not reported, research into unknown genetic causes of PID, triggered by patients presenting with low TRECs, needs to be encouraged.

The role of maternal factors, such as medication being used by the mother, potentially causing low TRECs at birth was not systematically assessed, although recorded in various articles and increasingly in recent abstracts. These developments should be encouraged and the role of maternal illnesses and the use of immunomodulatory or immunosuppressive drugs during pregnancy should be addressed in future studies.

Study design of all included full-text articles was heterogeneous; 10 of the 42 studies were case reports, whereas the remaining 32 studies either reported on mass screening in retrospective cohort studies or on defined patient groups in case series. Also, cutoff values and the quantitative PCR kit and PCR machine used to quantify TRECs differed from one center to the next. TREC levels were quantified mainly on fresh or frozen

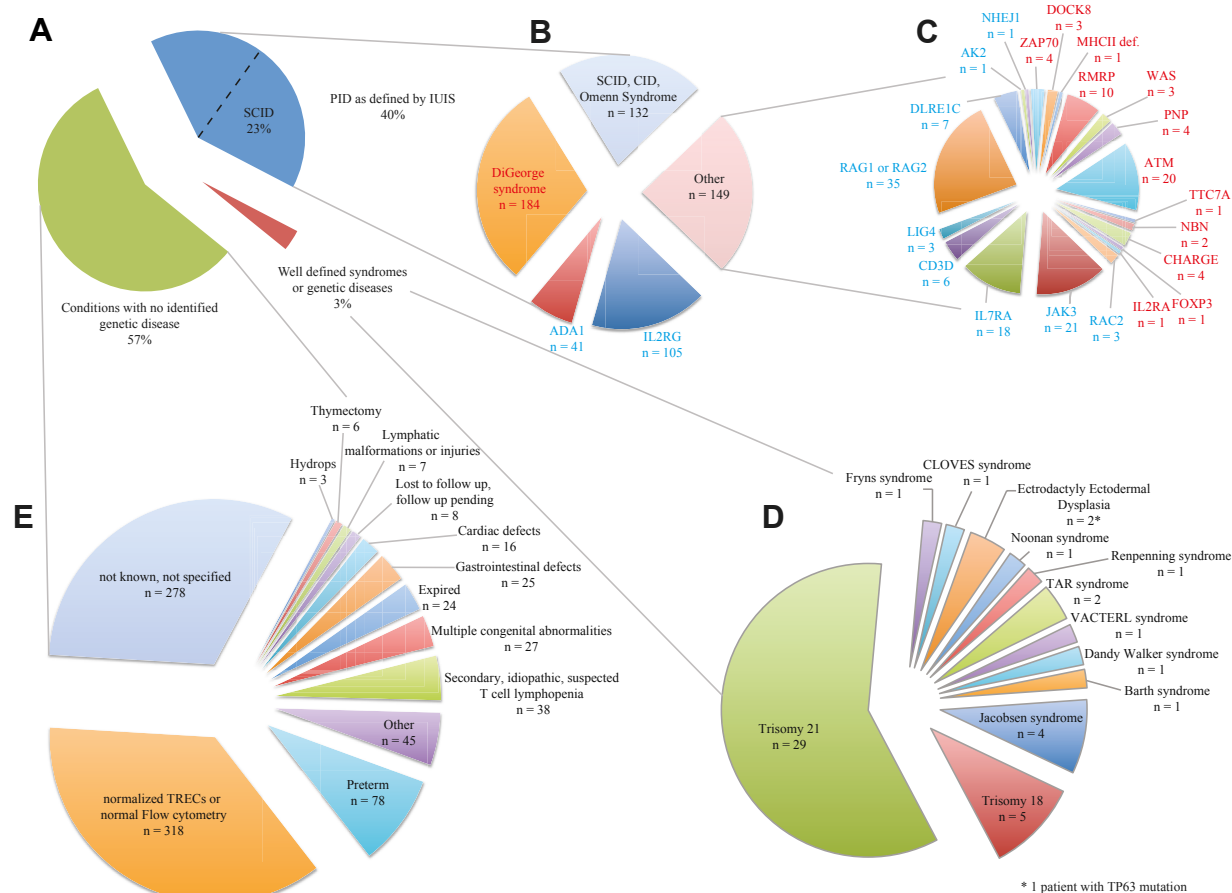


FIGURE 1. Causes for low TRECs at birth as described in the included original articles. **A**, The distribution of all patients with low TRECs ($n = 1533$). **B** and **C**, SCID mutations in blue, CID mutations in red, and 1 additional gene described in an abstract (*NHEJ1*). **C**, Conditions without an identified genetic association. **D**, Mentioned syndromes. *ATM*, Ataxia telangiectasia mutated; *CID*, Combined immunodeficiency; *CHARGE*, coloboma, heart defects, atresia of the nasal cochlea, retardation of growth/development, genital/urinary abnormalities, ear abnormalities; *CLOVES*, congenital, lipomatous, overgrowth, vascular malformations, epidermal nevi and spinal/skeletal anomalies; *PNP*, purine nucleoside phosphorylase; *TAR*, thrombocytopenia with absent radius; *VACTERL*, vertebral, anal, cardiac, trachea-esophageal, renal and limb defects; *WAS*, Wiskott-Aldrich syndrome protein.

dried blood spots and less frequently in whole blood samples. Inconsistent reporting and design of the included studies prevented us from assessing the prevalence of low TRECs and from performing more upstream statistical analyses. We consciously were not more stringent in our inclusion criteria as a compromise, allowing us to include the full range of conditions associated with low TRECs. As a result of this strategy, we also retrieved reports of patients with a secondary decline in TRECs (ie, patients after thymectomy).

Taken together, the current body of published data on neonates with low TRECs implies the need of a workflow to ensure patients with low TRECs at birth are adequately diagnosed and receive medical care without being overtreated. Low TRECs at birth need to be taken seriously, because they have been implicated to be associated with an increased mortality.⁷

A recently published comprehensive systematic review gives recommendations regarding TREC cutoff values to be used as well

and suggestions on schemes to follow regarding retesting and management of premature infants.⁸ We suggest endorsing these recommendations and in Figure 2 also refer to more detailed workflows such as those established by Routes et al.⁹ On the basis of data summarized in this review, we strongly recommend considering at least 25 different PIDs and 12 other well-known syndromes as well as gastrointestinal, cardiac, and lymphatic defects in neonates with confirmed lymphopenia (Figure 2). In parallel to this process, we suggest managing lymphopenic patients as one would patients with SCID¹⁰ until a diagnosis is made, T-cell counts normalize, or further management can be established.

Finally, we stress that normal neonatal TRECs do not exclude the presence of late-onset combined immunodeficiencies and functional T-cell defects. Our recommendations will most likely need to be adapted and expanded over time, as more data on patient ethnicity, family history, and results from ongoing research become available.

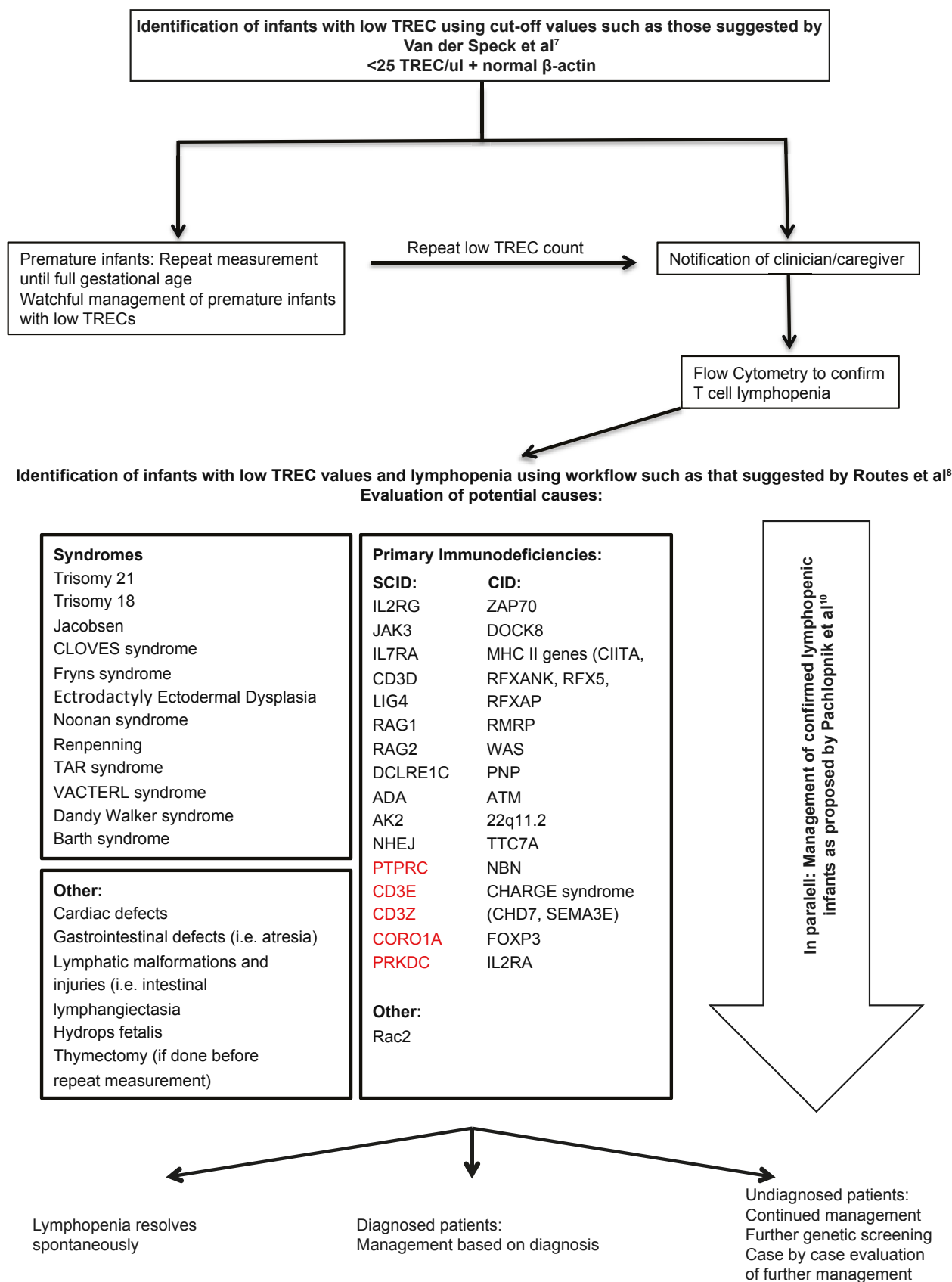


FIGURE 2. TREC cutoff values and workflow suggested to be used in identifying lymphopenic patients.^{8,9} Following the identification of patients, various conditions, described in included articles as being associated with low TRECs, should be considered while managing patients in parallel.¹⁰ Genetic SCID variants not yet described but suspected to be associated with low TRECs depicted in red.

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METHODS

The protocol of this systematic review has been registered with PROSPERO (CRD42016035261) and adhered to the principles of systematic reviews outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (www.prisma-statement.org).

Literature search

Electronic searches were performed (without any language restriction) on (Pre-) MEDLINE (PubMed interface/Ovid interface), Scopus (www.scopus.com), and EMBASE (www.embase.com) databases. A first search was conducted from their respective start dates until November 27, 2015, and a second, identical search was conducted to update results from November 27 onward to November 4, 2016. The keywords included “newborn screening,” “dried blood spot testing,” “guthrie,” “TRECs,” “KRECs,” and different PID names or PID genes, whereas “human immunodeficiency virus” and “deltaretrovirus infection” were excluded as exemplarily shown for the EMBASE search in [Figure E1](#). The full search algorithm is available on request. Checking the reference lists of included review articles identified additional publications.

Eligibility criteria

The following inclusion criteria had to be met by all included articles: (1) Research on human participants in the form of systematic reviews, meta-analyses, randomized controlled trials, case-control studies, case reports, case series, and cohort studies. Abstracts and letters to the editor were also included but were processed separately. (2) Description of at least 1 patient with low TRECs. (3) Text accessible in English, German, Italian, or French in a peer-reviewed journal.

Exclusion criteria included publication of editorials, commentaries, unpublished manuscripts, dissertations, government

reports, books and book chapters, conference proceedings, lectures, speeches, and consensus development statements (including guideline statements).

Screening for inclusion

Two reviewers read the titles and abstracts of all the records retrieved from the electronic database searches. Records that were clearly not related to TREC screening and did not meet the eligibility criteria were excluded. Results were compared; in all unclear cases, a third reviewer decided whether to include or exclude the report. Full-text articles were obtained for all included abstracts, as far as possible. Nine articles (from Iran, Hungary, Spain, and the Czech Republic) that potentially qualified to be read in full text could not be obtained with the access provided by the library of the University of Zurich.

Data extraction and quality assessment

All selected publications were assessed for eligibility and independently extracted using a standardized form. Results were then compared, and any uncertainties or disagreements between the 2 reviewers (A.M. and F.P.) were arbitrated by a third reviewer (J.P.S.); this was necessary in 10 cases. For all reports, the methodological quality was not systematically assessed because of the variability in the studies. The reviewers therefore examined reports for completeness of reporting on patients, test assay, and clinical follow-up. If the same patients were described in various reports, the most recent article was included, but only if no information was lost from earlier reports, in which case both articles would be included. Abstracts and letters to the editor were extracted separately unless already clearly being covered by a full-text article. Given the descriptive nature of this review, a formal statistical analysis was not performed.

☐ History Save Delete Print view Export Email		
Combine using ☒ And ☐ Or ⌵ Collapse		
☐ #6	#1 AND (#2 OR #3) NOT [conference abstract]/lim	337
☐ #5	#1 AND (#2 OR #3) AND [conference abstract]/lim	282
☐ #4	#1 AND (#2 OR #3)	619
☐ #3	il2rg:ab,ti OR jak3:ab,ti OR il7r:ab,ti OR ptpnc:ab,ti OR cd3d:ab,ti OR cd3e:ab,ti OR cd247:ab,ti OR coro1a:ab,ti OR rag1:ab,ti OR rag2:ab,ti OR delre1c:ab,ti OR prkdc:ab,ti OR ak2:ab,ti OR ada:ab,ti OR lig4:ab,ti OR nhej1:ab,ti OR np:ab,ti OR cd3g:ab,ti OR cd8a:ab,ti OR zap70:ab,ti OR 'orai 1':ab,ti OR 'stim 1':ab,ti OR tap1:ab,ti OR tap2:ab,ti OR tapbp:ab,ti OR ciita:ab,ti OR rfx5:ab,ti OR rfxap:ab,ti OR rfxank:ab,ti OR foxn1:ab,ti OR tbx1:ab,ti OR ikzf1:ab,ti OR stat5b:ab,ti OR magt1:ab,ti OR dock8:ab,ti OR rhoa:ab,ti OR cib1:ab,ti OR stk4:ab,ti OR trac:ab,ti OR lck:ab,ti OR malt1:ab,ti OR il21r:ab,ti OR unc119:ab,ti OR card11:ab,ti OR ox40:ab,ti OR ikkb:ab,ti OR pik3cd:ab,ti OR pik3r1:ab,ti OR lrba:ab,ti OR cd27:ab,ti OR ctps1:ab,ti OR nik:ab,ti OR 'ctla 4':ab,ti OR wasp:ab,ti OR atm:ab,ti OR mre11:ab,ti OR nbs1:ab,ti OR blm:ab,ti OR dnmt3b:ab,ti OR pms2:ab,ti OR rnf168:ab,ti OR mrp:ab,ti OR smarcal:ab,ti OR spink5:ab,ti OR stat3:ab,ti OR tyk2:ab,ti OR sp110:ab,ti OR dkc1:ab,ti OR nola2:ab,ti OR nola3:ab,ti OR terc:ab,ti OR tert:ab,ti OR tinf2:ab,ti OR ikaros:ab,ti OR btk:ab,ti OR ighm:ab,ti OR igll1:ab,ti OR cd79a:ab,ti OR cd79b:ab,ti OR blink:ab,ti OR cd19:ab,ti OR cd81:ab,ti OR cd20:ab,ti OR tnfrsf13b:ab,ti OR tnfrsf13c:ab,ti OR cd40lg:ab,ti OR cd40:ab,ti OR aicda:ab,ti OR ung:ab,ti OR lyst:ab,ti OR rab27a:ab,ti OR ap3b1:ab,ti OR pldn:ab,ti OR prf1:ab,ti OR unc13d:ab,ti OR stx11:ab,ti OR stxbp2:ab,ti OR sh2d1a:ab,ti OR xiap:ab,ti OR birc4:ab,ti OR itk:ab,ti OR tnfrsf6:ab,ti OR tnfrsf6:ab,ti OR casp10:ab,ti OR casp8:ab,ti OR nras:ab,ti OR kras:ab,ti OR fadd:ab,ti OR aire:ab,ti OR foxp3:ab,ti OR il2ra:ab,ti OR itch:ab,ti OR elane:ab,ti OR gfi1:ab,ti OR hax1:ab,ti OR g6pc3:ab,ti OR g6pt1:ab,ti OR robld3:ab,ti OR taz:ab,ti OR coh1:ab,ti OR c16orf57:ab,ti OR intg2:ab,ti OR fuct1:ab,ti OR kindlin3:ab,ti OR rac2:ab,ti OR actb:ab,ti OR fpr1:ab,ti OR ctsc:ab,ti OR cebpa:ab,ti OR sbds:ab,ti OR cyba:ab,ti OR ncf1:ab,ti OR ncf2:ab,ti OR ncf4:ab,ti OR nramp1:ab,ti OR il12rb1:ab,ti OR il12b:ab,ti OR ifngr1:ab,ti OR ifngr2:ab,ti OR cybb:ab,ti OR irf8:ab,ti OR gata2:ab,ti OR csf2ra:ab,ti OR nemo:ab,ti OR ikbkg:ab,ti OR ikba:ab,ti OR irak4:ab,ti OR myd88:ab,ti OR cxcr4:ab,ti OR ever1:ab,ti OR ever2:ab,ti OR tlr3:ab,ti OR unc93b1:ab,ti OR traf3:ab,ti OR trif:ab,ti OR tbk1:ab,ti OR il17ra:ab,ti OR il17f:ab,ti OR stat1:ab,ti OR dectn1:ab,ti OR card9:ab,ti OR apol1:ab,ti OR c1qa:ab,ti OR c1qb:ab,ti OR c1qc:ab,ti OR c1r:ab,ti OR c4:ab,ti OR c2:ab,ti OR c3a:ab,ti OR c3b:ab,ti OR c5:ab,ti OR c6:ab,ti OR c7:ab,ti OR c8a:ab,ti OR c8b:ab,ti OR c9:ab,ti OR pfc:ab,ti OR serpin1:ab,ti OR cfd:ab,ti OR cfi:ab,ti OR cfh:ab,ti OR masp1:ab,ti OR colec11:ab,ti OR masp2:ab,ti OR cd46:ab,ti OR cd59:ab,ti OR piga:ab,ti OR mefv:ab,ti OR nlrp3:ab,ti OR il1rn:ab,ti OR lpin2:ab,ti OR il10:ab,ti OR il10r:ab,ti OR adam17:ab,ti OR mvk:ab,ti OR tnfrsf1a:ab,ti OR pstpip1:ab,ti OR nod2:ab,ti OR il36a:ab,ti OR ada2:ab,ti OR tmem173:ab,ti	386,655
☐ #2	'immune deficiency'/exp OR 'chromosome deletion 22q11'/exp OR ' nijmegen breakage syndrome'/exp OR ((primary OR 'severe combined') NEAR/3 ('immune deficiency' OR 'immune deficiencies' OR 'immune deficient' OR immunodeficiency)):ab,ti OR pid:ab,ti OR (familial NEAR/3 reticuloendothelios):ab,ti OR scid:ab,ti OR (bare NEAR/3 lymphocyte):ab,ti OR (('mhc ii' OR mhci OR 'mhc class ii') NEAR/3 deficiency):ab,ti OR omenn:ab,ti OR (22q11 NEAR/3 delet):ab,ti OR digeorge:ab,ti OR ('b-cell' NEAR/3 (lymphopenia OR 'maturation defect')):ab,ti OR agammaglobulinemia:ab,ti OR xla:ab,ti OR 'ataxia telangiectasia':ab,ti OR 'wiskott aldrich':ab,ti OR ' nijmegen breakage':ab,ti OR trec:ab,ti OR trecs:ab,ti OR krec:ab,ti OR krecs:ab,ti OR 't-cell receptor excision circle':ab,ti OR 't-cell receptor excision circles':ab,ti OR 'kappa-deleting recombination excision circle':ab,ti OR 'kappa-deleting recombination excision circles':ab,ti NOT ('human immunodeficiency virus infection'/exp OR 'deltaretrovirus infection'/exp)	147,515
☐ #1	'newborn screening'/exp AND 'dried blood spot testing'/exp OR ((neonatal OR newborn OR 'new born') NEAR/3 screen):ab,ti OR guthrie:ab,ti OR 'dried blood spot':ab,ti OR 'dried blood spots':ab,ti OR 'dry blood spot':ab,ti OR 'dry blood spots':ab,ti	15,077

FIGURE E1. The search strategy used for the EMBASE search.

TABLE E1. Overview of all 42 included original articles

First author	Year	Gene		Study design	Location	Individuals screened	No. of patients described
Accetta ^{E1}	2011	NR		Case series	USA (Wisconsin)	140,533	39
Amariglio ^{E2}	2010	NR		Case series	Israel	53	2
Bayer ^{E3}	2014	IL7RA		Case report	USA (Texas)	1	1
Borte ^{E4}	2014	WAS		Case series	Sweden	>33	3
Borte ^{E5}	2012	RAG1	IL2RG	Retrospective cohort	Sweden	2609	28
		IL2RG	JAK3				
		AK2	IL7RA				
Buchbinder ^{E6}	2013	ADA1		Case report	USA (California)	1	1
Buckley ^{E7}	2012	NR		Retrospective cohort	USA*	961,925	120
Cattaneo ^{E8}	2013	JAK3		Case series	USA (Boston)	3	3
Chan ^{E9}	2005	IL2RG	JAK3	Retrospective cohort	USA (Maryland)	>266	24
Chien ^{E10}	2015	IL2RG	RAG1	Retrospective cohort	Taiwan	106,391	9
		22q11.2					
Comeau ^{E11}	2010	22q11.2		Retrospective cohort	USA (Massachusetts)	68,811	272
Dasouki ^{E12}	2011	DOCK8		Case series	USA (Kansas)	5	3
de Felipe ^{E13}	2012	RAG	ATM	Retrospective cohort	Spain	5165	8
		ADA1					
Fronkova ^{E14}	2015	22q11.2	ADA1	Case series	Greece	207	21
		RAG1	IL2RG				
Giampietro ^{E15}	2013	TP63		Case report	USA (Wisconsin)	1	1
Gul ^{E16}	2015	22q11.2		Case series	Norway	56	46
Jilkina ^{E17}	2014	ADA1	ZAP70	Retrospective cohort	Canada (Manitoba)	1,000	20
		CD3 delta					
Kanegae ^{E18}	2016			Retrospective cohort	Brazil	8,722	56
Kwan ^{E19}	2013	IL2RG	RAG1	Retrospective cohort	California	993,724	54
		JAK3	RMRP1				
		IL7RA	22q11.2				
Kwan ^{E20}	2014	IL2RG	RMRP1	Retrospective cohort	USA†	3,030,083	428
		ADA1	DCLRE1C				
		JAK3	CD3D				
		IL7RA	TTC7A				
		RAG1	RAG2				
		Rac2	22q11.2				
Kwan ^{E21}	2015	DCLRE1C		Retrospective cohort	USA (California)	7,900	5
la Marca ^{E22}	2013	ADA1		Case series	Italy	9	6
la Marca ^{E23}	2014a	PNP		Case series	Italy	10,249	1
Ladinsky ^{E24}	2013	NR		Case report	USA (Florida)	1	1
Lingman Framme ^{E25}	2014	22q11.2	IL2RG	Case series	Sweden	807	15
		RAG1					
Mallott ^{E26}	2013	ATM		Case series	USA (California)	15	9
McGhee ^{E27}	2005	NR		Case series	USA (California)	186	3
Morinishi ^{E28}	2009	IL2RG	LIG4	Retrospective cohort	Japan	489	18
		JAK3	RAG1				
		ADA1					
Myers ^{E29}	2002	ADA1	IL7RA	Retrospective cohort	USA (North Carolina)	117	92
		JAK3	IL2RG				
Nourizadeh ^{E30}	2015	IL2RG		Case report	Iran	78	1
Patel ^{E31}	2015	NBN		Case report	USA (California)	1	1
Roifman ^{E32}	2012	IL2RG	ZAP70	Retrospective cohort	Canada (Ontario)	51	44
		ADA1	FOXP3				
		RAG	IL7RA				
		RMRP	MHCII				
		CD3D	LIG4				
		PNP	JAK3				
		IL2RA					

(continued)

TABLE E1. (Continued)

First author	Year	Gene		Study design	Location	Individuals screened	No. of patients described
Rosenzweig ^{E33}	2013	IL2RG		Case report	USA	1	1
Routes ^{E34}	2009	22q11.2	Rac2	Retrospective cohort	USA (Wisconsin)	71,000	17
Somech ^{E35}	2009	RAG2		Case series	Israel	41	1
Somech ^{E36}	2013	RAG2	22q11.2	Retrospective cohort	Israel	46	7
Verbsky ^{E37,E38}	2012	DCLRE1C		Retrospective cohort	USA (Wisconsin)	207,696	72
		RAC2					
		ADA1					
Vicetti Miguel ^{E39}	2016	JAK3		Case Report	USA (Ohio)	1	1
Vogel ^{E40}	2014	IL7RA	ADA1	Retrospective cohort	USA (New York)	485,912	97
		IL2RG	22q11.2				
Ward ^{E41}	2013	NR		Case report	USA (Michigan)	1	0
Yin ^{E42}	2015	22q11.2		Case report	USA (California)	1	1

NR, Not reported.

*New York, California, Puerto Rico, Louisiana, Navajo Nation, Massachusetts, and Wisconsin.

†California, Colorado, Connecticut, Delaware, Massachusetts, Michigan, Mississippi, Navajo Nation, New York, Texas, and Wisconsin.

TABLE E2. Details on all 42 included original articles

First author	Year	No. of patients	Symptoms	Diagnosis/cause	Sex	Age	Gene	Mutation	TREC values	TREC cutoff
Accetta ^{E1}	2011	33	Complications secondary to severe prematurity, congenital abnormalities, pregnancy-related complications, severe hydrops fetalis, severe encephalomalacia	Severe prematurity (<33 wk EGA)	24 M, 9 F	Newborn	NR	NR	Inconclusive or 2-19 TRECs/μL	<25 TRECs/μL
		1	33-37 wk EGA, hydrops, respiratory and renal failure, CNS hemorrhage	Heterotaxy without chromosomal abnormalities	M	Newborn	NR	NR	19 TRECs/μL	<25 TRECs/μL
		1	33-37 wk EGA	Severe hydrops fetalis	M	Newborn	NR	NR	Inconclusive	<25 TRECs/μL
		1	33-37 wk EGA	Sepsis due to necrotizing enterocolitis	M	Newborn	NR	NR	Inconclusive	<25 TRECs/μL
		1	>37 wk EGA	Trisomy 18	M	Newborn	NR	NR	Inconclusive	<25 TRECs/μL
		1	>37 wk EGA, sickle cell disease, cardiogenic shock	Hypoplastic left heart	M	Newborn	NR	NR	17 TRECs/μL	<25 TRECs/μL
		1	>37 wk EGA, pulmonary hypertension, chylothorax	Pulmonary hypoplasia	M	Newborn	NR	NR	7 TRECs/μL	<25 TRECs/μL
Amariglio ^{E2}	2010	2	Respiratory symptoms, reduced-sized tonsils and cervical lymph nodes, pneumonia, bronchiectasis, oral thrush, recurrent skin infections	Suspected T-cell immunodeficiency	2 F	NR	NR	NR	Undetectable, 50/0.5 μg DNA	<400 TRECs/0.5 μg DNA
Bayer ^{E3}	2014	1	Cutaneous infection, lower respiratory tract infection, chronic cough, hand foot mouth disease, oral mucositis, acute otitis media, neutropenia, isolated CD4 lymphocytopenia, poor lymphocyte proliferation, hypergammaglobulinemia, poor specific antibody production to VZV infection and immunizations	SCID	F	Newborn	IL7RA	Compound heterozygous mutation: c.361dupA, Exon 3 del	0 TRECs/μL	NR
Borte ^{E4}	2014	1	Classical severe Wiskott-Aldrich syndrome, otitis	WAS	NR	Newborn	WAS	c.777+1G>A	6.2 TRECs/μL	<8 TRECs/μL
		2	Classical severe Wiskott-Aldrich syndrome and pulmonary infections	WAS	NR	Newborn	WAS	c.931delG	5.6, 6.7 TRECs/μL	<8 TRECs/μL
Borte ^{E5}	2012	5	NR	SCID	NR	Newborn	RAG1	NR	NR	<15 TRECs/μL
		4	NR	SCID	NR	Newborn	IL2RG	NR	NR	<15 TRECs/μL
		1	NR	SCID	NR	Newborn	AK2	NR	NR	<15 TRECs/μL
		2	NR	SCID	NR	Newborn	JAK3	NR	NR	<15 TRECs/μL
		3	NR	SCID	NR	Newborn	IL7RA	NR	NR	<15 TRECs/μL
		3	NR	SCID	NR	Newborn	NR	NR	NR	<15 TRECs/μL
		4	NR	Ataxia telangiectasia	NR	Newborn	ATM	NR	NR	<15 TRECs/μL

(continued)

TABLE E2. (Continued)

First author	Year	No. of patients	Symptoms	Diagnosis/cause	Sex	Age	Gene	Mutation	TREC values	TREC cutoff
Buchbinder ^{E6}	2013	6	NR	NR	NR	Newborn	NR	NR	NR	<15 TRECs/μL
		1	Neutropenia, thrombocytopenia, feeding intolerance, cyanosis, abdominal distension	SCID	F	1 mo	ADA1	c320T>C, c790delT	0 TRECs/μL	25 TRECs/μL
Buckley ^{E7}	2012	28	NR	SCID	NR	Newborn	NR	NR	NR	NR
		12	NR	SCID variant	NR	Newborn	NR	NR	NR	NR
		80	NR	Non-SCID (including DiGeorge syndrome, Trisomy 21, and other)	NR	Newborn	NR	NR	NR	NR
Cattaneo ^{E8}	2013	2	Eczema, lymphopenia, high IgE	SCID	1 F, 1 M	Newborn	JAK3	c.578G>A (p.Cys193Tyr); c.1786+3G>T	Undetectable	>252 copies/μL whole blood
		1	Multiple infections (disseminated mycobacterium, <i>Pneumocystis jiroveci</i> , disseminated varicella zoster postvaccination)	SCID	M	23 mo	JAK3	c.1767C>T; c.678_679delCT	Undetectable	>801 copies/million PBMC
Chan ^{E9}	2005	2	Healthy	SCID	M	2 d, 1 mo	IL2RG	NR	NR, 0 TRECs/μL	30 TRECs/μL
		10	Lower respiratory tract infections, failure to thrive, rash eczema, thrush, diarrhea, dehydration, sepsis, cyanosis,	SCID	9 M, 1 F	2 wk-12 mo	IL2RG	NR	0-<30 TRECs/μL	30 TRECs/μL
		1	Healthy	SCID	M	1 wk	JAK3	NR	0 TRECs/μL	30 TRECs/μL
		1	Failure to thrive, diarrhea, lower respiratory tract infection	SCID	M	8 mo	JAK3	NR	0 TRECs/μL	30 TRECs/μL
		10	Failure to thrive, diarrhea, lower and upper respiratory tract infections, rash, elevated IgE	SCID	7 M, 3 F	4-13 mo	NR	NR	0-<30 TRECs/μL	30 TRECs/μL
		1	NR	SCID	NR	Newborn	IL2RG	NR	NR	<40 TRECs/μL
Chien ^{E10}	2015	1	NR	SCID	NR	Newborn	NR	NR	NR	<40 TRECs/μL
		2	NR	SCID	NR	Newborn	NR	NR	NR	<40 TRECs/μL
		1	NR	NR	NR	Newborn	NR	NR	NR	<40 TRECs/μL
		4	NR	DiGeorge syndrome	NR	Newborn	22q11.2	NR	NR	<40 TRECs/μL
		195	NR	Resolved on repeat NBS and/or no further diagnostic testing required	NR	Newborn	NR	NR	NR	NR
		23	NR	Expired	NR	Newborn	NR	NR	NR	NR
		4	NR	Thymectomy	NR	Newborn	NR	NR	NR	NR
		5	NR	Not newborn	NR	Newborn	NR	NR	NR	NR
Comeau ^{E11}	2010	5	NR	Pending flow cytometry or repeat NBS	NR	Newborn	NR	NR	NR	NR
		6	NR	Normal flow cytometry results or functional tests	NR	Newborn	NR	NR	NR	NR
		14	NR	NBS normalized	NR	Newborn	NR	NR	NR	NR
		1	NR	Lost to follow-up	NR	Newborn	NR	NR	NR	NR
		4	NR	DiGeorge syndrome	NR	Newborn	22q11.2	NR	NR	NR

		1	NR	Jacobsen	NR	Newborn	NR	NR	NR	NR
		1	NR	Multiple congenital abnormalities with unspecific T-cell lymphopenia	NR	Newborn	NR	NR	NR	NR
		2	NR	Thymectomy	NR	Newborn	NR	NR	NR	NR
		9	NR	Idiopathic lymphopenia	NR	Newborn	NR	NR	NR	NR
		1	NR	Pending	NR	Newborn	NR	NR	NR	NR
		1	NR	Expired	NR	Newborn	NR	NR	NR	NR
Dasouki ^{E12}	2011	3	Severe eczema, superinfections, pruritus, cutaneous ulcers, leukocytosis, eosinophilia, skin infections	Autosomal-recessive hyper-IgE syndrome	2 F, 1 M	13 mo, 4 y, 6 y	DOCK8	2bp deletion in exon 14 at codon 510	0-54 TRECs/3 μ L	<100 TRECs/3 μ L
de Felipe ^{E13}	2015	1	Hydrops fetalis, Ebstein anomaly	Trisomy, monosomy	F	Newborn	NR	46XX, der(7)t(7;15)(p22;q22)mat	1 TRECs/ μ L	<6 TRECs/ μ L
		2	NR	Extreme preterm	M	Newborn	NR	NR	0, 1 TRECs/ μ L	<6 TRECs/ μ L
		1	NR	SCID	M	9.6 mo	NR	NR	0 TRECs/ μ L	<6 TRECs/ μ L
		1	NR	SCID	M	Newborn	RAG	NR	0.5 TRECs/ μ L	<6 TRECs/ μ L
		1	NR	SCID	F	Newborn	ADA1	NR	4 TRECs/ μ L	<6 TRECs/ μ L
		1	NR	Omenn syndrome	M	Newborn	NR	NR	1.9 TRECs/ μ L	<6 TRECs/ μ L
		1	NR	Ataxia telangiectasia	M	20 mo	ATM	NR	0 TRECs/ μ L	<6 TRECs/ μ L
Fronkova ^{E14}	2015	5	Repeated respiratory infections, allergies, and/or autoimmunity	DiGeorge syndrome	NR	Newborn-18 y	22q11.2	NR	0-1400 copies/ μ g DNA	<1400 copies/ μ g DNA
		1	Complete athymia, CHARGE syndrome	DiGeorge syndrome	NR	Newborn	22q11.2	NR	0 copies/ μ g DNA	<1400 copies/ μ g DNA
		2	NR	SCID	NR	Newborn	RAG1	NR	0 copies/ μ g DNA	<1400 copies/ μ g DNA
		1	NR	SCID	NR	Newborn	ADA1	NR	0 copies/ μ g DNA	<1400 copies/ μ g DNA
		6	NR	SCID	NR	Newborn	IL2RG	NR	0 copies/ μ g DNA	<1400 copies/ μ g DNA
		6	NR	SCID	NR	Newborn	NR	NR	0 copies/ μ g DNA	<1400 copies/ μ g DNA
Giampietro ^{E15}	2013	1	T-cell lymphopenia, ectrodactyly, bilateral hydronephrosis, cleft palate, right nasolacrimal sac abscess, periorbital cellulitis, chronic otitis media	EEC/EECUT plus syndrome (ectrodactyly, ectodermal dysplasia, clefting, urinary tract abnormalities, and thymic abnormalities), maternal preeclampsia	M	Newborn	TP63	c.970_972delATT	Abnormal	NR
Gul ^{E16}	2015	2	Thymus aplasia, opportunistic infections, interrupted aortic arch, and aorta stenosis	DiGeorge syndrome	NR	Newborn	22q11.2	NR	0 TRECs/ μ L	< 70, <130, <180, <973 TRECs/ μ L

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TABLE E2. (Continued)

First author	Year	No. of patients	Symptoms	Diagnosis/cause	Sex	Age	Gene	Mutation	TREC values	TREC cutoff
		44	Cardiovascular abnormalities, Cleft palate, hypocalcemia, polyhydramnion, upper and lower respiratory tract infections, middle ear infections, gastrointestinal infections, urinary tract infections	DiGeorge syndrome	NR	Newborn	22q11.2	NR	8-973 TRECs/ μ L	< 70, <130, <180, <973 TRECs/ μ L
Jilkina ^{E17}	2014	3	NR	SCID	2 M, 1 F	Newborn	ADA1	NR	0 TRECs/ μ L	<252 TRECs/ μ L
		1	NR	SCID	F	Newborn	CD3D	NR	0 TRECs/ μ L	<252 TRECs/ μ L
		1	NR	Cartilage-hair hypoplasia	NR	Newborn	NR	NR	0 TRECs/ μ L	<252 TRECs/ μ L
		2	NR	SCID	2 F	Newborn	ZAP70	NR	71-216 TRECs/ μ L	<252 TRECs/ μ L
		1	NR	CID	M	Newborn	NR	NR	163-235 TRECs/ μ L	<252 TRECs/ μ L
		5	NR	Preterm	NR	Newborn	NR	NR	NR	<252 TRECs/ μ L
		6	NR	NR	NR	Newborn	NR	NR	NR	<252 TRECs/ μ L
		1	NR	SCID	F	Newborn	NR	NR	0 TRECs/ μ L	<252 TRECs/ μ L
Kanegae ^{E18}	2016	45	NR	Normalized on repeat screening	NR	Newborn	NR	NR	First screening <30 TRECs/ μ L, repeat screening >30 TRECs/ μ L	<30 TRECs/ μ L
		3	NR	Normal flow cytometry	NR	Newborn	NR	NR	21 TRECs/ μ L, 16 TRECs/ μ L, <30 TRECs/ μ L	<30 TRECs/ μ L
		1	NR	NR	NR	Newborn	NR	NR	<30 TRECs/ μ L	<30 TRECs/ μ L
		2	NR	DiGeorge syndrome	NR	Newborn	22q11.2	NR	5, 24 TRECs/ μ L	<30 TRECs/ μ L
		1	NR	SCID	NR	Newborn	RAG1	NR	0 TRECs/ μ L	<30 TRECs/ μ L
		4	NR	SCID	NR	Newborn	NR	NR	0-2 TRECs/ μ L	<30 TRECs/ μ L
Kwan ^{E19}	2013	4	Asymptomatic	SCID	M	Newborn	IL2RG	R226C, M270fs, W177X, L132R	0 TRECs/ μ L	<25-40 TRECs/ μ L
		1	Rash and cellulitis	SCID	F	Newborn	JAK3	L527_G528del	4 TRECs/ μ L	<25-40 TRECs/ μ L
		3	Asymptomatic	SCID	F	Newborn	IL7RA	F71S, H180P, I94fs, G215V	0 TRECs/ μ L	<25-40 TRECs/ μ L
		2	Asymptomatic	SCID	2 M	Newborn	RAG1	M661del, R404Q R764P	0 TRECs/ μ L	<25-40 TRECs/ μ L
		1	Asymptomatic	Omenn syndrome	F	Newborn	RAG1	W522C, N968K		<25-40 TRECs/ μ L
		1	Asymptomatic	Leaky SCID	F	Newborn	RAG1	R474C, I956T		<25-40 TRECs/ μ L
		1	Intrauterine growth retardation, short limbs	Leaky SCID	F	Newborn	RMRP	r.211c>g, 262g>u	0 TRECs/ μ L	<25-40 TRECs/ μ L
		1	Respiratory distress, hepatomegaly, feeding difficulties	SCID	M	Newborn	NR	NR	0 TRECs/ μ L	<25-40 TRECs/ μ L
		6	Lower respiratory tract infection, dysmorphic features, bicuspid aortic valve, T-cell lymphopenia	Variant SCID or CID	NR	Newborn	NR	NR	0-21 TRECs/ μ L	<25-40 TRECs/ μ L
		2	Healthy at birth	Ataxia telangiectasia	NR	Newborn	NR	NR	8-21 TRECs/ μ L	<25-40 TRECs/ μ L

		9	Heart disease, dysmorphic features, tetralogy of Fallot, T-cell lymphopenia, respiratory distress, pulmonary and intracranial hemorrhage	DiGeorge syndrome	NR	Newborn	22q11.2	NR	0-26 TRECs/μL	<25-40 TRECs/μL
		4	Oral thrush, myeloproliferative disorder, hydrops, cardiac abnormalities	Trisomy 21	NR	Newborn	NR	NR	8-25 TRECs/μL	<25-40 TRECs/μL
		1	Multiple cardiac abnormalities	Charge syndrome	NR	Newborn	NR	NR	12 TRECs/μL	<25-40 TRECs/μL
		2	Heart defects, hypothyroidism, anemia, lower respiratory tract infections, renal failure, retroperitoneal failure, necrotizing enterocolitis	Congenital heart defects	NR	Newborn	NR	NR	0-21 TRECs/μL	<25-40 TRECs/μL
		1	Meconium peritonitis, anemia	Ileal atresia	NR	Newborn	NR	NR	0 TRECs/μL	<25-40 TRECs/μL
		2	Bowel obstruction	Gastroschisis	NR	Newborn	NR	NR	23-25 TRECs/μL	<25-40 TRECs/μL
		2	Anemia, thrombocytopenia, bilateral pleural effusions, ascites, cardiac myopathy	Hydrops	NR	Newborn	NR	NR	8-25 TRECs/μL	<25-40 TRECs/μL
		2	Multiple abnormalities, hypothyroidism, renal failure, intrauterine growth retardation, brain hemorrhage, pulmonary edema	Multiple congenital abnormalities	NR	Newborn	NR	NR	5-22 TRECs/μL	<25-40 TRECs/μL
		1	Respiratory complications, neutropenia	Chylothorax	NR	Newborn	NR	NR	0 TRECs/μL	<25-40 TRECs/μL
Kwan ^{E20}	2014	8	NR	Preterm	NR	Newborn	NR	NR		<25-40 TRECs/μL
		10	NR	9 SCID, 1 leaky SCID	NR	Newborn	IL2RG	NR	NR	NR
		5	NR	SCID	NR	Newborn	ADA1	NR	NR	NR
		3	NR	SCID	NR	Newborn	JAK3	NR	NR	NR
		6	NR	SCID	NR	Newborn	IL7RA	NR	NR	NR
		8	NR	4 SCID, 4 leaky SCID	NR	Newborn	RAG1	NR	NR	NR
		1	NR	SCID	NR	Newborn	RAG2	NR	NR	NR
		2	NR	Leaky SCID	NR	Newborn	RMRP	NR	NR	NR
		2	NR	1 SCID, 1 leaky SCID	NR	Newborn	DCLRE1C	NR	NR	NR
		1	NR	SCID	NR	Newborn	CD3D	NR	NR	NR
		1	NR	SCID	NR	Newborn	TTC7A	NR	NR	NR
		2	NR	SCID	NR	Newborn	NR	NR	NR	NR
		12	NR	Variant SCID	NR	Newborn	NR	NR	NR	NR
		1	NR	Rac2 defect	NR	Newborn	RAC2	NR	NR	NR
		78	NR	DiGeorge syndrome	NR	Newborn	22q11.2	NR	NR	NR
		21	NR	Trisomy 21	NR	Newborn	NR	NR	NR	NR
		4	NR	Ataxia telangiectasia	NR	Newborn	NR	NR	NR	NR
		4	NR	Trisomy 18	NR	Newborn	NR	NR	NR	NR
		3	NR	CHARGE	NR	Newborn	NR	NR	NR	NR
		2	NR	Jacobsen	NR	Newborn	NR	NR	NR	NR
		1	NR	CLOVES	NR	Newborn	NR	NR	NR	NR

(continued)

TABLE E2. (Continued)

First author	Year	No. of patients	Symptoms	Diagnosis/cause	Sex	Age	Gene	Mutation	TREC values	TREC cutoff
		1	NR	ECC	NR	Newborn	NR	NR	NR	NR
		1	NR	Fryns	NR	newborn	NR	NR	NR	NR
		1	NR	Nijmegen breakage	NR	Newborn	NR	NR	NR	NR
		1	NR	Noonan	NR	Newborn	NR	NR	NR	NR
		1	NR	Renpenning	NR	Newborn	NR	NR	NR	NR
		1	NR	TAR	NR	Newborn	NR	NR	NR	NR
		6	NR	Cytogenetic abnormalities	NR	Newborn	NR	NR	NR	NR
		6	NR	Cardiac abnormalities	NR	Newborn	NR	NR	NR	NR
		23	NR	Multiple congenital abnormalities	NR	Newborn	NR	NR	NR	NR
		15	NR	Loss into third space	NR	Newborn	NR	NR	NR	NR
		15	NR	Gastrointestinal anomalies	NR	Newborn	NR	NR	NR	NR
		4	NR	Neonatal leukemia	NR	Newborn	NR	NR	NR	NR
		29	NR	Preterm birth alone	NR	Newborn	NR	NR	NR	NR
		157	NR	Not specified	NR	Newborn	NR	NR	NR	NR
Kwan ^{E21}	2015	1	Neonatal tetany, hypoparathyroidism	T-cell lymphopenia	F	Newborn	NR	NR	11 TRECs/μL	<25 TRECs/μL
		4	Oral ulcer, healthy	SCID	3 F, 1 M	Newborn, 2 mo	DCLRE1C	c.597C>A	0 TRECs/μL	
la Marca ^{E22}	2013	1	Upper and lower airway diseases: otitis, pneumonia, toxic alveolitis	Delayed-onset ADA1 deficiency	NR	7 y	ADA1	c.780+1G>A; c.396dupA	0 TRECs/μL	<25 TRECs/μL
		1	Upper and lower airway diseases: otitis, pneumonia, toxic alveolitis	Delayed-onset ADA1 deficiency	NR	4 y	ADA1	Exon 6: V177M; Exon 10: E319fsX321	0 TRECs/μL	<25 TRECs/μL
		1	Upper and lower airway diseases: otitis, pneumonia, toxic alveolitis	Delayed-onset ADA1 deficiency	NR	3 y	ADA1	Exon 5: V129M; Exon 10: S291L	0 TRECs/μL	<25 TRECs/μL
		1	NR	Early onset ADA1 deficiency	NR	Newborn	ADA1	Exon 3: F61fsX87; Exon 11: E337X	0 TRECs/μL	<25 TRECs/μL
		1	NR	Early onset ADA1 deficiency	NR	Newborn	ADA1	Exon 5: p.R156C; Exon 10: c.956_960delAAGAG	0 TRECs/μL	<25 TRECs/μL
		1	NR	Early onset ADA1 deficiency	NR	Newborn	ADA1	Exon 10: T294K homozygous	0 TRECs/μL	<25 TRECs/μL
la Marca ^{E23}	2014a	1	Veno-occlusive disease, severe pneumonitis, skin, gut, renal graft vs host disease after HSCT, nonprogressive global developmental delay	PNP-combined immunodeficiency	NR	Newborn	PNP	D128G homozygous	0 TRECs/μL	<10 TRECs/μL
Ladinsky ^{E24}	2013	1	D-transposition of great arteries, chylothorax, chylous ascites, hypogammaglobulinemia, T, B, and NK lymphopenia	Thoracic duct injury	F	31 d	NR	NR	2 normal, third: 0 TRECs/μL	<25 TRECs/μL
								NR		
Lingman Framme ^{E25}	2014	9	Significant viral infections	DiGeorge syndrome	NR	Newborn	22q11.2	NR	<8 TRECs/μL	<8 TRECs/μL

		3	NR	SCID	NR	Newborn	IL2RG	NR	<8 TRECs/μL	<8 TRECs/μL
		3	NR	SCID	NR	Newborn	RAG1	NR	<8 TRECs/μL	<8 TRECs/μL
Mallott ^{E26}	2013	1	Lymphopenia, mild truncal ataxia	Ataxia telangiectasia	NR	Newborn	ATM	c.1787delAA (K468fs); c.6238delA (F1952fs)	4 TRECs/μL	<25 TRECs/μL
		1	None	Ataxia telangiectasia	NR	Newborn	ATM	c.1260C>T (P292L); c.7064C>T (R2227C)	21 TRECs/μL	<25 TRECs/μL
		7	Ataxia, abnormal gait	Ataxia telangiectasia	3 M, 4 F	Newborn	ATM	NR	3-25 TRECs/μL	<25 TRECs/μL
McGhee ^{E27}	2005	3	NR	SCID	NR	At presentation	NR	NR	0 TRECs/μL	NR
Morinishi ^{E28}	2009	7	NR	SCID	M	Newborn and 0-10 mo	IL2RG	NR	<10 TRECs/μg DNA	NR
		4	NR	SCID, maternal T- cell engraftment	M	Newborn	IL2RG	NR	<10 TRECs/μg DNA	NR
		2	NR	SCID	1 M, 1 F	Newborn and 0-1 y	JAK3	NR	<10 TRECs/μg DNA	NR
		1	NR	SCID	M	Newborn and 2 mo	ADA1	NR	<10 TRECs/μg DNA	NR
		1	NR	SCID	M	Newborn and 1 mo	ADA1	NR	Newborn: 6.2 × 10 ² TRECs/μg DNA; 1 mo: <10 TRECs/μg DNA	NR
		2	NR	SCID	1 M, 1 F	Newborn and 2-4 y	LIG4	NR	<10 TRECs/μg DNA	NR
		1	NR	SCID	F	2 y	RAG1	NR	80 TRECs/μg DNA	NR
Myers ^{E29}	2002	16	NR	SCID	NR	Newborn	ADA1	NR	Undetectable	NR
		5	NR	SCID	NR	Newborn	JAK3	NR	Undetectable	NR
		2	NR	SCID	NR	Newborn	IL7RA	NR	Undetectable	NR
		44	NR	SCID	NR	Newborn	IL2RG	NR	Undetectable	NR
		21	NR	SCID	NR	Newborn	NR	NR	Undetectable	NR
		3	NR	Recombinase activating genes	NR	Newborn	NR	NR	Undetectable	NR
Nourizadeh ^{E30}	2015	1	NR	Cartilage-hair hypoplasia	NR	Newborn	NR	NR	Undetectable	NR
		1	None	SCID	M	6 d	IL2RG	c.675C>A	0 TRECs/μL	NR
Patel ^{E31}	2015	1	Meconium aspiration, hydrocephalus, UTI, hydronephrosis, developmental delay, failure to thrive	Nijmegen breakage syndrome	M	Newborn	NBN	c.842T>G (p.L281X); c.1030C>T (p.Q344X)	12TRECs/μL	<25 TRECs/μL
Roifman ^{E32}	2012	4	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	IL2RG	NR	Undetectable	<400 TRECs/μg DNA
		3	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	ADA1	NR	Undetectable, very low	<400 TRECs/μg DNA
		5	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	RAG1/2	NR	0-30 TRECs/μg DNA	<400 TRECs/μg DNA
		5	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	RMRP	NR	0-30 TRECs/μg DNA	<400 TRECs/μg DNA

(continued)

TABLE E2. (Continued)

First author	Year	No. of patients	Symptoms	Diagnosis/cause	Sex	Age	Gene	Mutation	TREC values	TREC cutoff
		4	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	CD3D	NR	0-30 TRECs/μg DNA	<400 TRECs/μg DNA
		2	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	ZAP70	NR	21, 86 TRECs/μg DNA	<400 TRECs/μg DNA
		1	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	FOXP3	NR	<400 TRECs/μg DNA	<400 TRECs/μg DNA
		2	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	IL7RA	NR	<400 TRECs/μg DNA	<400 TRECs/μg DNA
		1	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	MHCII	NR	<400 TRECs/μg DNA	<400 TRECs/μg DNA
		3	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	PNP	NR	<400 TRECs/μg DNA	<400 TRECs/μg DNA
		1	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	IL2RA	NR	Undetectable, very low	<400 TRECs/μg DNA
		1	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	LIG4	NR	Undetectable, very low	<400 TRECs/μg DNA
		2	NR	T-cell dysfunction	NR	At diagnosis, by 3 y	JAK3	NR	Undetectable, very low	<400 TRECs/μg DNA
		3	NR	SCID	NR	At diagnosis, by 3 y	NR	NR	<400 TRECs/μg DNA	<400 TRECs/μg DNA
		5	NR	CID	NR	At diagnosis, by 3 y	NR	NR	<400 TRECs/μg DNA	<400 TRECs/μg DNA
		2	NR	Omenn	NR	At diagnosis, by 3 y	NR	NR	<400 TRECs/μg DNA	<400 TRECs/μg DNA
Rosenzweig ^{E33}	2013	1	Poor weight gain, oral thrush	SCID	M	Newborn	IL2RG	c.C717T, p.Q235X	<40 TRECs/μL	<40 TRECs/μL
Routes ^{E34}	2009	2	T-cell lymphopenia	DiGeorge syndrome	NR	Newborn	22q11.2	NR	3-19 TRECs/μL	<25 TRECs/μL
		1	NR	Chylothorax	NR	Newborn	NR	NR	6-17 TRECs/μL	<25 TRECs/μL
		1	NR	Chyloperitoneum	NR	Newborn	NR	NR	5-6 TRECs/μL	<25 TRECs/μL
		1	NR	Gastroschisis	NR	Newborn	NR	NR	6-15 TRECs/μL	<25 TRECs/μL
		2	Cleft palate, T-cell lymphopenia	Idiopathic T-cell lymphopenia	1 M, 1 NR	Newborn	NR	NR	0-23 TRECs/μL	<25 TRECs/μL
		1	Omphalitis, paratracheal abscess, lymphopenia	SCID	M	Newborn	RAC2	p.D57N	0-4 TRECs/μL	<25 TRECs/μL
		9	No further testing due to death, no further testing, normal repeat NBS, normal flow cytometry	Other	NR	Newborn	NR	NR	Abnormal	<25 TRECs/μL
Somech ^{E35}	2009	1	Failure to thrive, fever, cough, diarrhea, respiratory distress, erythroderma, alopecia, lymphadenopathy, hepatosplenomegaly	Omenn SCID	M	Newborn	RAG2	c.G1305T	Undetectable	<400 TRECs/μg DNA
Somech ^{E36}	2013	4	Rash, infection, pneumonia	2 SCID, 2 Omenn	NR	Newborn and at diagnosis	RAG2	NR	Undetectable	<30 TRECs/3-mm punch
		1	Stomatitis, infection	SCID	NR	Newborn and at diagnosis	DCLRE1C	NR	Undetectable	<30 TRECs/3-mm punch

		1	Dysmorphism, cardiac defect, infection	DiGeorge syndrome	NR	Newborn and at diagnosis	22q11.2	NR	Newborn: 18TREC/3-mm punch; At diagnosis undetectable	<30 TREC/3-mm punch
		1	Failure to thrive, infection	SCID	NR	Newborn and at diagnosis	NR	NR	Undetectable	<30 TREC/3-mm punch
Verbsky ^{E37,E38}	2011	1	Multiple abscesses	SCID	NR	Newborn	RAC2	NR	0-4 TREC/μL	<25 TREC/μL, <40 TREC/μL
		1	NR	SCID	NR	Newborn	ADA1	NR	0 TREC/μL	<25 TREC/μL, <40 TREC/μL
		3	NR	SCID	NR	Newborn	NR	NR	0-4 TREC/μL	<25 TREC/μL, <40 TREC/μL
		4	NR	DiGeorge syndrome	NR	Newborn	22q11.2	NR	3-45 TREC/μL	<25 TREC/μL, <40 TREC/μL
		5	NR	Reversible TCL	NR	Newborn	NR	NR	<25 TREC/μL	<25 TREC/μL, <40 TREC/μL
		3	NR	Lymphatic malformation	NR	Newborn	NR	NR	<25 TREC/μL	<25 TREC/μL, <40 TREC/μL
		2	NR	NEC, gastroschisis	NR	Newborn	NR	NR	<25 TREC/μL	<25 TREC/μL, <40 TREC/μL
		3	Multiorgan failure	Metabolic	NR	Newborn	NR	NR	14-46 TREC/μL	<25 TREC/μL, <40 TREC/μL
		1	NR	Jacobsen	NR	Newborn	NR	NR	19-21 TREC/μL	<25 TREC/μL, <40 TREC/μL
		1	NR	Degenerative neuromuscular disease	NR	Newborn	NR	NR	31-57 TREC/μL	<25 TREC/μL, <40 TREC/μL
		1	NR	Barth syndrome	NR	Newborn	NR	NR	11-32 TREC/μL	<25 TREC/μL, <40 TREC/μL
		1	NR	VACTERL	NR	Newborn	NR	NR	0 TREC/μL	<25 TREC/μL, <40 TREC/μL
		1	NR	TAR syndrome	NR	Newborn	NR	NR	28-37 TREC/μL	<25 TREC/μL, <40 TREC/μL
		1	NR	Cardiac defect	NR	Newborn	NR	NR	17-37 TREC/μL	<25 TREC/μL, <40 TREC/μL
		2	Duodenal atresia	Trisomy 21	NR	Newborn	NR	NR	11-22 TREC/μL	<25 TREC/μL, <40 TREC/μL
		1	NR	Hypoplastic left heart	NR	Newborn	NR	NR	9-13 TREC/μL	<25 TREC/μL, <40 TREC/μL
		1	Hearing defect	Multiple congenital abnormalities	NR	Newborn	NR	NR	17-44 TREC/μL	<25 TREC/μL, <40 TREC/μL
		1	NR	Ectrodactyly ectodermic dysplasia syndrome	NR	Newborn	NR	NR	28-38 TREC/μL	<25 TREC/μL, <40 TREC/μL
		38	NR	Normal T-cell counts	NR	Newborn	NR	NR	<25 TREC/μL	<25 TREC/μL, <40 TREC/μL
		1	NR	Family refused further testing	NR	Newborn	NR	NR	<25 TREC/μL	<25 TREC/μL, <40 TREC/μL
Vicetti Miguel ^{E39}	2016	1	Fever, CMV infection	SCID	F	Newborn	JAK3	NR	Undetectable	NR

(continued)

TABLE E2. (Continued)

First author	Year	No. of patients	Symptoms	Diagnosis/cause	Sex	Age	Gene	Mutation	TREC values	TREC cutoff
Vogel ^{E40}	2014	1	NR	SCID	F	Newborn	IL7RA	c.353G>A, c.83-2A>T	Undetectable	<200 TRECs/μL
		4	NR	SCID	M	Newborn	IL2RG	NR	Undetectable-65 TRECs/μL	<200 TRECs/μL
		2	NR	SCID	1 F, 1 M	Newborn	ADA1	NR	Undetectable	<200 TRECs/μL
		1	NR	SCID, 3p.13-p.14.d deletion	M	Newborn	3p.13-p.14.d deletion	NR	Undetectable	<200 TRECs/μL
		2	NR	SCID	1 M, 1 F	Newborn	NR	NR	Undetectable-55 TRECs/μL	<200 TRECs/μL
		14	NR	DiGeorge syndrome	7 F, 7 M	Newborn	22q11.2	NR	Undetectable-904 TRECs/μL	<200 TRECs/μL
		3	1 patient diabetic embryopathy	DiGeorge syndrome	2 F, 1 M	Newborn	NR	NR	Undetectable-188 TRECs/μL	<200 TRECs/μL
		1	NR	DiGeorge syndrome	F	Newborn	46XYdel(10)(p13)	NR	96 TRECs/μL	<200 TRECs/μL
		11	NR	Resolved idiopathic T-cell lymphopenia	4 F, 7 M	Newborn	NR	NR	Undetectable-156 TRECs/μL	<200 TRECs/μL
		2	NR	Trisomy 21	2 M	Newborn	NR	NR	1.642-31 TRECs/μL	<200 TRECs/μL
		3	NR	Gastroschisis	3 M	Newborn	NR	NR	0-96 TRECs/μL	<200 TRECs/μL
		5	NR	Congenital heart defects	2 F, 3 M	Newborn	NR	NR	58-769 TRECs/μL	<200 TRECs/μL
		1	NR	Dandy Walker	M	Newborn	NR	NR	181 TRECs/μL	<200 TRECs/μL
		7	NR	Secondary T-cell lymphopenia	3 F, 4 M	Newborn	NR	NR	0-1670 TRECs/μL	<200 TRECs/μL
		9	NR	Syndrome with T- cell impairment	NR	Newborn	NR	NR	NR	<200 TRECs/μL
Ward ^{E41}	2013	NR	Prenatal betamethasone, hydrops fetalis, sepsis, edema	Premature birth	F	1 d, 14 d	NR	NR	3, >30 TRECs/μL	<30 TRECs/μL
Yin ^{E42}	2015	1	Fever, cough, lower respiratory tract infection, solitary right kidney, cardiac defect, hypocalcemia, lytic bone lesions, large necrotic lymph nodes in mediastinum, <i>Mycobacterium kansasii</i> and <i>Pneumocystis jirovecii</i> infection	DiGeorge syndrome	M	Newborn	22q11.2	NR	Low	NR

CHARGE, Coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities and ear abnormalities; *ECC*, ectodermal dysplasia, ectrodactyly, and clefting; *CLOVES*, congenital, lipomatous overgrowth, vascular malformations, epidermal naevi, skeletal anomalies; *CMV*, cytomegalovirus; *CNS*, central nervous system; *EEC*, ectrodactyly-ectodermal dysplasia-cleft syndrome; *EECUT*, ectodermal dysplasia, ectrodactyly, cleft palate, and urinary tract abnormalities; *EGA*, early gestational age; *F*, female; *HSCT*, hematopoietic stem cell transplant; *M*, male; *NBS*, newborn screening; *NEC*, necrotizing enterocolitis; *NK*, natural killer; *NR*, not reported; *PNP*, purine nucleoside phosphorylase; *TAR*, thrombocytopenia-absent radius; *VACTERL*, vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula and/or esophageal atresia, renal, and radial anomalies and limb defects; *UTI*, urinary tract infection; *VZV*, varicella-zoster virus.

TABLE E3. Details on abstracts and letters to the editor

First author	Year	Country	Individuals screened	No. of patients described	Diagnosis	Gene	Mutation	TREC values	Cutoff
Abghari ^{E43}	2015	USA (Michigan)	>189						
				2	SCID	NR	NR	Low	NR
				1	CID	NR	NR	Low	NR
				9	22q11.2 DS	22q11.2	NR	Low	NR
				2	Lymphopenia secondary to thymectomy	NR	NR	Low	NR
				5	Refused follow-up care	NR	NR	Low	NR
				5	Died with complications of other diseases	NR	NR	Low	NR
				2	Pending cases	NR	NR	Low	NR
				65	Lymphopenia without a diagnosis	NR	NR	Low	NR
				98	Not followed	NR	NR	Low	NR
Albin ^{E44}	2014	USA (New York)	14	6	Idiopathic T-cell lymphopenia	NR	NR	Average 76 copies/μL	<150 copies/μL
Aleem ^{E45}	2014	USA (Iowa)	43,930	14					
				1	22q11.2 Deletion syndrome	22q11.2	NR	Low	NR
				1	Jacobsen syndrome	NR	NR	Low	NR
				1	18p deletion syndrome	NR	NR	Low	NR
				10	No significant T-cell lymphopenia	NR	NR	Low	NR
				1	Significant T-cell lymphopenia	NR	NR	Low	NR
Andreac ^{E46}	2013	USA (New York)	1	1	Cartilage-hair hypoplasia	NR	NR	0-270 TRECs	NR
Andreac ^{E47}	2014	USA (New York)	6	4	22q11.2 Deletion syndrome	22q11.2	NR	0-889 TRECs	<125 TRECs
Bayer ^{E48}	2014	USA (Texas)	1	1	SCID	NR	NR	Absent	NR
									NR
Bhatti ^{E49}	2014	USA (Michigan)	1	1	SCID	NHEJ1	NR	Very low	NR
Bornstein ^{E50}	2014	USA (New York)	1	1	Lymphopenia and agammaglobulinemia	NR	NR	0-164 TRECs/μL	<200 TRECs/μL
Borte ^{E51}	2012	Sweden	1052						
				NR	SCID	NR	NR	Abnormal	NR
				NR	Ataxia telangiectasia	NR	NR	Abnormal	NR
				NR	Nijmegen breakage syndrome	NR	NR	Abnormal	NR
									NR
Buyantseva ^{E52}	2013	USA (Pennsylvania)	1	1	Myelodysplastic syndrome (MDS)	Mosaic monosomy of chromosome 7	Mosaic monosomy of chromosome 7	Undetectable	NR
Canessa ^{E53}	2013	Italy	1	1	SCID	RAG1	c.1156del2T	0 TRECs/μL	<25 TRECs/μL
Chan ^{E54}	2013	USA (California)	2	2					

(continued)

TABLE E3. (Continued)

First author	Year	Country	Individuals screened	No. of patients described	Diagnosis	Gene	Mutation	TREC values	Cutoff
				1	Leaky SCID	IL2RG	R222C	0 TRECs/μL	NR
				1	Leaky SCID	RAG2	E407X	15 TRECs/μL	NR
								NR	NR
Čiznár ^{E55}	2014	Slovakia*	10	4	SCID	ADA1	NR	Undetectable	NR
				2	SCID	IL2RG	NR	Undetectable	NR
				1	22q11.2 DS	NR	NR	Undetectable	NR
				3	SCID	NR	NR	Undetectable	NR
Crestani ^{E56}	2015	USA (Massachusetts)	2	2	SCID	JAK3	Leu201Pro	Undetectable and not measured	NR
Dvorak ^{E57}	2013	USA (California, Wisconsin, Massachusetts, Texas, Utah, North Carolina)	50	37	SCID	NR	NR	0-11 TRECs/μL	NR
				13	Leaky SCID, Omenn syndrome, reticular dysgenesis	NR	NR	0 TRECs/μL	NR
Dy ^{E58}	2013	USA (New York)	1	1	X-linked SCID	IL2R	c.982C>T	65 TRECs/μL	<150 TRECs/μL
Galowitz ^{E59}	2015	USA (Delaware)	33,000	24					
				2	SCID	NR	NR	NR	NR
				3	22q11.2 Deletion syndrome	22q11.2	NR	NR	NR
				10	Unspecified T-cell lymphopenia		NR	NR	NR
				9	Normal T-cell counts		NR	NR	NR
Grazioli ^{E60}	2014	Canada	1	1	SCID	ZAP70	IVS12-11G>A(g.24417G>A)	0-148 copies/3 μL	<82
Greemberg ^{E61}	2016	USA (Ohio)	1	1	Normalized repeat screening	NR	NR	Low, normalized	NR
Hale ^{E62}	2010	USA (Massachusetts)	100,597	1	SCID	JAK3	c.578G>A, c.1786+3G>T,	0	NR
Henderson ^{E63}	2013	USA (Massachusetts)	1	1					
				1	Early onset autoimmunity and T- cell lymphopenia	RAG1	c.2522G>A, c.2920T>C,	0	NR
Huhtinen ^{E64}	2011	Finland*	38	8	SCID-like	NR	NR	Low	NR
Kamae ^{E65}	2013	Japan	106	69					
				14	Hypogammaglobulinemia		NR	Undetectable	<100 TRECs/μg DNA
				18	SCID	IL2RG	NR	Undetectable	<100 TRECs/μg DNA

				2	SCID	JAK3	NR	Undetectable	<100 TRECs/μg DNA
				2	SCID	RAG1	NR	Undetectable	<100 TRECs/μg DNA
				1	SCID	RAG2	NR	Undetectable	<100 TRECs/μg DNA
				1	SCID	DCLRE1C	NR	Undetectable	<100 TRECs/μg DNA
				2	SCID	LIG4	NR	Undetectable	<100 TRECs/μg DNA
				2	SCID	ADA1	NR	Undetectable	<100 TRECs/μg DNA
				23	Ataxia telangiectasia	ATM	NR	Undetectable	<100 TRECs/μg DNA
				4	Nijmegen breakage syndrome	NBN	NR	Undetectable	<100 TRECs/μg DNA
Kamili ^{E66}	2014	USA (Texas)	60	56	NR	NR	NR	Abnormal	NR
				4	Chronic chylous loss syndrome	NR	NR	Abnormal	NR
									NR
Khan ^{E67}	2013	USA (Delaware)	1	1	SCID	RAG1	NR	0 TRECs	NR
Kloepfer ^{E68}	2011	USA (Wisconsin)	1	1	SCID	NR	NR	Undetectable-normal	NR
Knutsen ^{E69}	2011	USA (Missouri)	1	1	22q11.2 DS	NR	NR	5-96.0 copies/μL	<25 copies/μL
Kubiak ^{E70}	2015	USA (Florida)	1	1	SCID	NR	NR	Low	NR
									NR
Lee ^{E71}	2016	USA (Pennsylvania)	6	6	SCID	NR	NR	Low	NR
Lev ^{E72}	2012	Israel	7	7	SCID	NR	NR	Undetectable or significantly low	NR
Lippi ^{E73}	2012	Italy	1	1	SCID	RAG1	Novel homozygous small deletion in exon 2	0	NR
Mustillo ^{E74}	2016	Canada (Ontario)	1	1	Ataxia telangiectasia	ATM	NR	16 TRECs/μL	<200 TRECs/μL
Palacios ^{E75}	2016	USA (Virginia)	27,000	6	Preterm	NR	NR	Low	NR
				8	Normalized repeat testing	NR	NR	Low	NR
				1	Partial 22q11.2 deletion syndrome	NR	NR	Low	NR
				4	NR	NR	NR	Low	NR
Patel ^{E76}	2014	USA (California)	1,500,000	88					
				70	T-cell lymphopenia	NR	NR	Low	NR
				18	22q11.2 deletion syndrome	22q11.2	NR	Low	NR
Patel ^{E77}	2015	USA (Texas)	1	1	SCID	IL2RG	c.173C>G (p.P58R)	Undetectable	NR

(continued)

TABLE E3. (Continued)

First author	Year	Country	Individuals screened	No. of patients described	Diagnosis	Gene	Mutation	TREC values	Cutoff
Petroni ^{E78}	2016	USA (Washington)	1	1	TRECs normalized, prenatal exposure to FOLFIRINOX	NR	NR	14, 8, 28 TRECs/μL	<20 TRECs/μL
Poowuttikul ^{E79}	2011	USA (Michigan)	285	2	SCID	NR	NR	Low/absent	NR
				2	NR	NR	NR	Low/absent	NR
						NR	NR		NR
Reichenbach ^{E80}	2014	Switzerland*	53	6	SCID	NR	NR	0-9	NR
Rosenberg ^{E81}	2013	USA (Pennsylvania)	1	1	None, healthy	NR	NR	<25 TRECs/μL, later normal	<25 TRECs/μL
Rubin ^{E82}	2013	USA (Connecticut)	1	1	SCID	NR	NR	Undetectable	NR
Scherzer ^{E83}	2015	USA (Ohio)	14,000	19			NR		NR
				3	SCID	NR	NR	Absent	
				1	NR	NR	NR	Absent	
				2	Preterm	NR	NR	NR	
				13	Expired before follow-up	NR	NR	NR	
Schuetz ^{E84}	2012	Germany*	NR	4	SCID	RAG	NR	Not detectable	NR
				1	SCID	RAG	NR	Low	NR
Seroogy ^{E85}	2013	USA (Wisconsin)	2	2	SCID	NR	NR	Undetectable	NR
Shah ^{E86}	2012	USA (Louisiana)	1	1	Jacobsen syndrome	NR	NR	Near absent	NR
Shankar ^{E87}	2015	USA (Pennsylvania)	1	1	Ataxia telangiectasia	ATM	c.3802del, c.4358_4359,	6 TRECs	NR
Smith ^{E88}	2015	USA (New York)	1	1	Maternal use of 6-mercaptopurine	NR	NR	Average 49 TRECs	<200 TRECs
Spoter ^{E89}	2014	USA	NR	119					
				1	SCID	IL7RA	NR	Low	<150 copies/μL or 2× <200 TRECs/μL
				1	SCID	ADA1	NR	Low	<150 copies/μL or 2× <200 TRECs/μL
				5	22q11.2 deletion syndrome	22q11.2	NR	Low	<150 copies/μL or 2× <200 TRECs/μL
				3	Unspecified immune defects	NR	NR	Low	<150 copies/μL or 2× <200 TRECs/μL
				20	Idiopathic lymphopenia	NR	NR	Low	<150 copies/μL or 2× <200 TRECs/μL

				89	Normal T-cell numbers in flow cytometry	NR	NR	Low	<150 copies/μL or 2× <200 TRECs/μL
Tam ^{E90}	2012	USA (Wisconsin)	1	1	22q11.2 deletion syndrome	NR	NR	0	NR
Taylor-Black ^{E91}	2012	USA (New York)	9	9	T-cell lymphopenia	NR	NR	0-156	NR
Thomas ^{E92}	2011	USA (Wisconsin)	1	1	SCID	NR	NR	Low	NR
Tierce ^{E93}	2012	USA (Michigan)	NR	149	NR	NR	NR	<30 TRECs	<30 TRECs
				25	Deceased	NR	NR	<30 TRECs	<30 TRECs
Tierce ^{E94}	2012	USA (Michigan)	1	1	Chylothorax	NR	NR	2 normal NBS, third 0 TRECs	NR
Tierce ^{E95}	2012	USA (Michigan)	27,252	57	Various	NR	NR	NR	NR
Verstegen ^{E96}	2014	Netherlands*	1,316	10	Trisomy 21	NR	NR	<15 TRECs/μL	<15 TRECs/μL
Wasserman ^{E97}	2014	USA (Texas)	1	1	Juvenile myelomonocytic leukemia	NR	NR	Abnormal	NR
									NR
Yates ^{E98}	2016	USA (Mississippi)	114,137	18	NR	NR	NR	NR	NR
				4	SCID	NR	NR	NR	NR
Yin-Hsiu ^{E99}	2011	Taiwan	30,836	10					
				1	22q11.2 deletion syndrome	22q11.2	NR	<40 TRECs/μL	<40 TRECs/μL
				1	Congenital CMV	NR	NR	<40 TRECs/μL	<40 TRECs/μL
				1	Chylothorax	NR	NR	<40 TRECs/μL	<40 TRECs/μL
				2	Congenital heart disease	NR	NR	<40 TRECs/μL	<40 TRECs/μL
				5	Low leucocyte count	NR	NR	<40 TRECs/μL	<40 TRECs/μL
Youssif ^{E100}	2014	Egypt*	100	29			NR	Low	NR
				5	Bacterial septicemia	NR	NR	Low	NR
				2	Prematurity	NR	NR	Low	NR
				1	Omphalocele and facial dysmorphism	NR	NR	Low	NR
				1	Congenital adrenal hyperplasia	NR	NR	Low	NR
				1	Microvillus inclusion disease	NR	NR	Low	NR
				1	Idiopathic T-cell lymphopenia	NR	NR	Low	NR
				16	SCID	NR	NR	Low	NR
				1	SCID variant (Omenn)	NR	NR	Low	NR
				1	SCID variant (MHC II deficiency)	MHC II	NR	Low	NR

FOLFIRINOX, Folinic acid, fluorouracil, irinotecan, oxaliplatin; NR, Not reported.

*Additional countries identified not included in original articles.

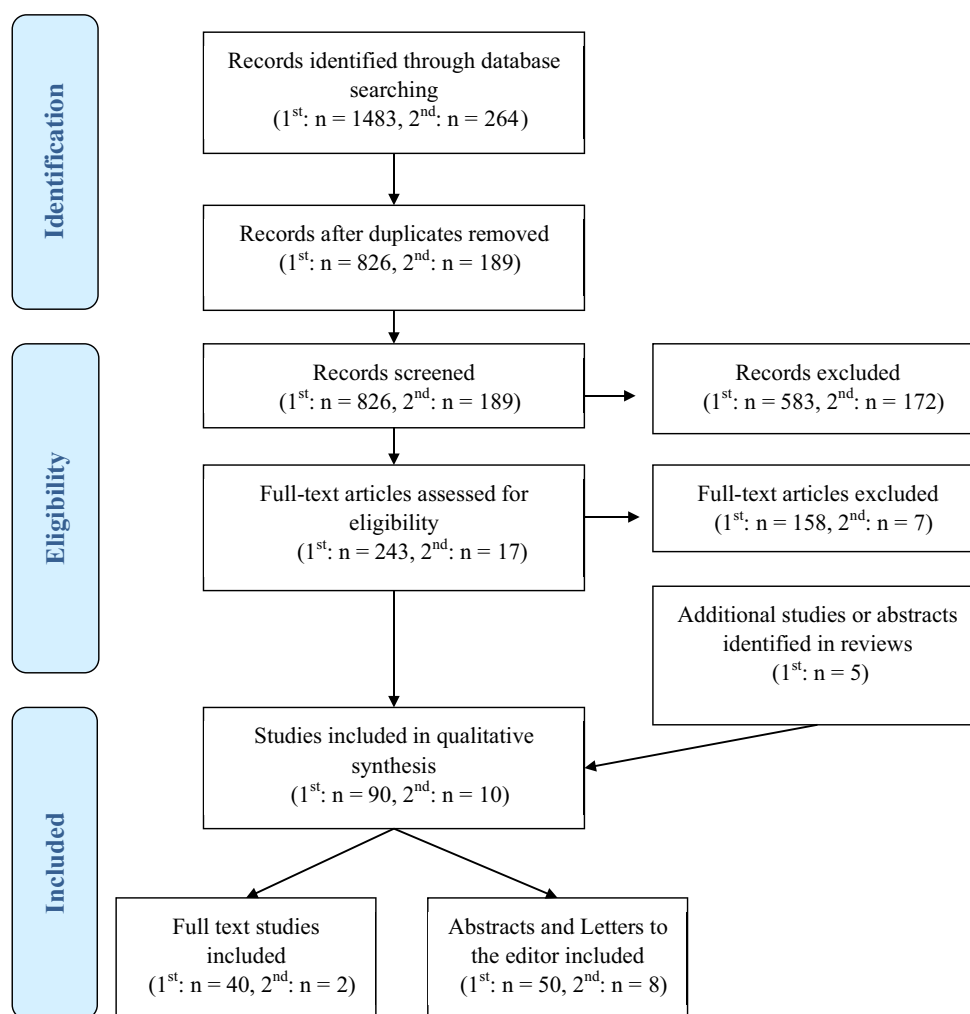


FIGURE E2. Depiction of workflow used to identify original articles, abstracts, and letters to the editor included. Divided into first and second searches: first search until November 27, 2015, second search November 27, 2015, until November 4, 2016.

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