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The case for severe combined immunodeficiency (SCID) and T cell lymphopenia newborn screening: saving lives…one at a time

Jessica Quinn[1] · Jordan S. Orange[1] · Vicki Modell[1] · Fred Modell[1]

Abstract

Severe combined immunodeficiency (SCID) is a group of syndromes resulting from genetic defects causing severe deficiency in T cell and B cell function. These conditions are life-threatening and result in susceptibility to serious infections. SCID is often fatal in the first year of life if not detected and properly treated. SCID and related T cell lymphopenias can be detected in newborns by a simple screening test, the T cell receptor excision circle (TREC) assay, using the same dried blood spot samples already collected from newborns to screen for other genetic disorders. The TREC assay facilitates the earliest possible identification of cases of SCID before opportunistic infections, irreversible organ damage, or death, thus allowing for the possibility of curative treatment through hematopoietic stem cell transplant and gene therapy. Infants receiving hematopoietic stem cell transplant in the first few months of life, after being identified through screening, have a high probability of survival (95–100%), along with lower morbidity. The TREC assay has proven to have outstanding specificity and sensitivity to accurately identify almost all infants with SCID (the primary targets) as well as additional infants having other select immunologic abnormalities (secondary targets). The TREC assay is inexpensive and has been effectively integrated into many public health programs. Without timely treatment, SCID is a fatal disease that causes accrual of exorbitant healthcare costs even in just 1 year of life. The cost of care for just one infant with SCID, not diagnosed through newborn screening, could be more than the cost of screening for an entire state or regional population. Continued implementation of TREC screening will undoubtedly enhance early diagnosis, application of treatment, and healthcare cost savings. The Jeffrey Modell Foundation helped initiate newborn screening for SCID in the USA in 2008 and continues its efforts to advocate for SCID screening worldwide. Today, all 50 states and Puerto Rico are screening for SCID and T cell lymphopenia, with 27 million newborns screened to date, and hundreds diagnosed and treated. Additionally, there are at least 20 countries around the world currently conducting screening for SCID at various stages. Newborn screening for SCID and related T cell lymphopenia is cost-effective, and most importantly, it is lifesaving and allows children with SCID the opportunity to live a healthy life.

Keywords Severe combined immunodeficiency (SCID) · T cell lymphopenia · Newborn screening · Primary immunodeficiency (PI) · Jeffrey Modell Foundation (JMF) · Awareness · Education · Diagnosis · Treatment · Immunology

Abbreviations

US	United States
PI	Primary immunodeficiency
SCID	Severe combined immunodeficiency
HHS	US Department of Health and Human Services
DOA	US Department of Agriculture
DOT	US Department of Transportation
EPA	US Environmental Protection Agency
OMB	US Office of Management and Budget
PCR	Polymerase chain reaction
QALY	Quality of adjusted life year
NICU	Neonatal intensive care unit
ADA	Adenosine deaminase

✉ Fred Modell
fmodell@jmfworld.org

[1] Jeffrey Modell Foundation, 780 Third Avenue, 47th Floor, New York City, NY 10017, USA

What is the value of a life?

While it is impossible to truly equate a life with a financial quantity, the United States (US) government defines the value

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of each individual life. Five federal agencies pegged the statistical value of one life at $9.5–$10 million [1].

US Dept. of Health and Human Services (HHS) $9.5 million
US Dept. of Agriculture (DOA) $9.5 million
US Dept. of Transportation (DOT) $9.5 million
US Environmental Protection Agency (EPA) $10 million
US Office of Mgmt. and Budget (OMB) $10 million

A Harvard Medical School study based on findings from "the Global Burden of Disease project" reported that 8 million people die every year from illnesses we know how to treat or cure. Deaths from lack of high-quality healthcare cost the world over $6 trillion annually [2].

What is severe combined immunodeficiency (SCID) and T cell lymphopenia?

Primary immunodeficiencies (PI) are genetic defects of the immune system that result in chronic and often life-threatening infections, if not diagnosed and treated. There are currently over 400 genetically defined single-gene inborn errors of immunity [3]. Severe combined immunodeficiency (SCID) is a group of approximately 20 syndromes resulting from genetic defects causing severe deficiencies in T cell and B cell function, with abnormally low T cell numbers and function and poor to no B cell function, and are among the most serious PI disorders [4]. These conditions are serious and cause life-threatening infections, though affected infants often appear healthy at birth [4]. SCID is often fatal in the first year of life if not detected and properly treated [5–7]. T cell lymphopenia includes other immune conditions and causes of decreased T cell counts, such as DiGeorge syndrome, trisomy 21, ataxia telangiectasia (AT), and CHARGE syndrome, among others. One in 58,000–65,000 infants are affected by SCID in the USA, and one in approximately 15,000 with serious T cell lymphopenia, although these numbers can vary depending on multiple factors, including geographical location [4, 8].

What is the TREC assay?

SCID and related T cell lymphopenias can be detected in newborns by a simple screening test, the T cell receptor excision circle (TREC) assay, using the same dried blood spot samples already collected from newborns to screen for other genetic disorders [9, 10]. Infants are just getting ready to experience the world at large and have many naïve T cells under normal circumstances. Infants with genetic defects causing SCID fail to generate adequate numbers of naïve T cells and therefore have low or absent TRECs in their blood. The TREC assay works by identifying a "by product" of T cell development contained in naïve T cells using polymerase chain reaction (PCR) [10]. As such, newborn screening with the TREC assay, which measures levels of these recently formed T cells, is the only way to facilitate the earliest possible identification of affected infants in non-familial cases of SCID and related T cell lymphopenias before opportunistic infections, irreversible organ damage, or death, thus allowing for the possibility of curative treatment through hematopoietic stem cell transplant or gene therapy [4, 10]. Infants receiving hematopoietic stem cell transplantation in the first few months of life, after being identified through screening, have a high probability of survival, (95–100%) along with lower morbidity [5–7, 9, 11–14]. While additional laboratory methods are being developed, the current TREC assay has proven to have outstanding specificity and sensitivity to accurately identify almost all infants with SCID (the primary targets) as well as additional infants with other immune conditions and causes of decreased T cell counts (T cell lymphopenias such as DiGeorge syndrome, trisomy 21, ataxia telangiectasia (AT), and CHARGE syndrome, among others; secondary targets) [5–7, 9, 11, 15].

Importantly, some locations and newborn screening programs are looking at implementing the kappa-deleting element recombination circle (KREC) assay in conjunction with the TREC assay. The KRECs assay can identify certain B cell defects that would otherwise go undetected with just the TREC assay, such as late-onset ADA, Nijmegen breakage syndrome, and X-linked or autosomal recessive agammaglobulinemia, potentially improving the diagnostic value of the screening test [16, 17]. Although the inclusion of this assay is being piloted in various regions around the world, it has not yet been fully and successfully adopted, as there is concern as to whether there is enough evidence that it adds significant value to the screening test by saving lives and decreasing morbidity [17].

Background

The Jeffrey Modell Foundation initiated newborn screening for SCID in the USA in 2008 in collaboration with other passionate stakeholders. In 2010, the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children recommended that SCID be added to the Recommended Uniform Screening Panel, which is a recommended list of disorders to be included as part of state newborn screening programs. Shortly thereafter, implementation of newborn screening for SCID began to be initiated state by state. All 50 states in the USA and Puerto Rico are conducting population screening for SCID, with 27 million newborns screened to date. As of November 2019, it was reported to the Jeffrey Modell Foundation that there are

20 countries around the world currently conducting screening for SCID at various stages. The Jeffrey Modell Foundation continues its efforts to advocate for SCID screening worldwide.

TREC assay—specificity and sensitivity

The TREC assay has been proven to be cost-effective and has extremely high sensitivity and specificity in detecting SCID in the newborn period [4, 11, 18–21]. In fact, the sensitivity has been reported time and time again as nearly reaching 100%, including from the manufacturer [4, 10, 20]. Additionally, the TREC assay has been firmly established as extremely effective in detecting other severe forms of T cell lymphopenia [18].

Variability in TREC levels at birth, especially in preterm infants, often results in much higher false positive rates for SCID newborn screening than for other screened diseases. However, this can be mitigated by adopting modified screening algorithms for pre-term and ill patients, including retesting from separate Guthrie card punches and gradually lowering the threshold for retesting. The adoption of these methods has greatly reduced the number of false positives [10, 20]. In a particular instance, the false positive rate was lowered to roughly 0.02% with changes in DNA extraction and improvements in the efficiency of the RT-qPCR amplification efficiency [20]. There are also instances in which premature infants and neonates from the neonatal intensive care unit did not show the high presumed false positive rate [22].

In addition to maintaining high sensitivity for detecting SCID cases, TREC specificity has been excellent with automated methods that have reduced the number of DNA amplification failures to as good or better than the false positive rates of many tests currently in use for newborn screening for other conditions [11].

It is important to note, however, that having a limited number of false positive results is necessary to avoid missing affected infants. Thus, the assay needs to be very sensitive, but not completely specific, which is the case for the performance of the TREC assay. Public health laboratories have exceptional outreach systems in place to contact families for additional testing when screening results are abnormal, as has been developed to facilitate the many longstanding newborn screens applied for other diseases [11]. As with other newborn screening assays, follow-up testing for abnormal TREC assays is used to confirm false positives so that families can be reassured if their infant is unaffected [11].

Algorithm for TREC cut-off value

Screening algorithms and specific techniques for measuring TRECs vary between locations that have successfully implemented newborn screening for SCID. Typically, these algorithms begin with the quantification of TREC content, with an abnormal value resulting in a re-test, and conclude with the possibility of referral for diagnostic evaluation [10]. However, specific details vary between locations, including TREC cut-off values and the management of inconclusive results [10].

An algorithm using 25 TREC/μL as a cutoff was established to screen 71,000 infants for SCID between January 1 and December 31, 2008, in Wisconsin [19]. Infants with TREC levels below the cutoff value were retested using the same dried blood spot with co-amplification of β-actin as a control. A second result again indicating TREC levels below the cut-off, but successful β-actin amplification warranted further evaluation by flow-cytometry. Inconclusive results also required retesting until a conclusive result was obtained. In this study the rate of repeat testing was 0.168%. The TREC assay was demonstrated as being highly sensitive and specific for the detection of severe T cell lymphopenia using this algorithm [19].

An additional example is the California SCID newborn screening algorithm [4]. Samples with more than 18 TREC/μL on initial testing are considered normal. Samples with 18 TREC/μL or fewer have repeat TREC and β-actin testing; of these, samples fewer than 4 TREC are urgent positive, with lymphocyte subset determination by flow cytometry ordered immediately. Samples with 4–18 TREC/μL are categorized as positive in non-NICU infants if β-actin values are above 35 copies, and lymphocyte subset determination by flow cytometry is ordered. Samples with insufficient control actin DNA amplification are designated as DNA amplification failure. These infants require a repeat heel-stick sample for TREC testing, or if it is already a second sample, lymphocyte subset determination [4, 23]. This algorithm has proven to be highly effective for the early detection of SCID and other T cell lymphopenias [4].

Economic impact

The decision to implement newborn screening for SCID and related T cell lymphopenia depends upon the cost and effectiveness of the screening test, the incidence of SCID and related T cell lymphopenia within a population, the cost ratio of the intervention, and the benefit of earliest possible treatment [24–26]. If an assumption is made that the number of births within a region is 100,000 per year, and the incidence of SCID is approximately 1:58,000 newborns, two cases per year can be predicted [4, 9, 24].

The cost to screen 100,000 newborns, at $4.25 per patient, totals $425,000, although this amount can vary depending on several factors, including geographical location [24, 25]. The cost to transplant one newborn is approximately $120,000 on

the conservative end of the spectrum but can be significantly higher, as there are many factors at play (in a recent publication mean charges ranged from $365,785 for early transplantation to $1.43 million for late transplantation) [27–29]. The cost of post-transplant care over the next 5 years may be as much as $200,000 for one newborn [24]. Therefore, the potential cost to screen 100,000 newborns and treatment of one patient would be approximately $745,000. The potential cost to screen 100,000 newborns and treat two patients totals approximately $1,065,000. However, this cost remains significantly lower than not screening, and instead, treating the inevitable infections, supporting hospitalizations, and managing complications that each of these patients will endure.

If newborns are not screened at birth, they will sustain overwhelming infections, require extensive or intensive hospitalizations, with cumulative costs estimated to be at least $2 million in the first year of life [30, 31]. Given the incidence and population, the total costs of care for the predicted two affected newborns will amount to $4 million in healthcare costs [19, 30]. This amounts to a significant potential total cost savings of approximately $3 million.

In a previous analysis, Chan et al. [25] found that the incremental cost-effective ratio was $27,907 per quality of adjusted life year (QALY), given 70 years of life saved [25]. This ratio is highly favorable and compares closely with some of the metabolic diseases for which newborns are currently screened. Additionally, this analysis stated that assuming society is willing to pay $50,000 per QALY, preference for screening occurred if incidence of SCID was at least 1:250,000 [25]. Since of course the incidence of SCID is more frequent than this the financial analysis speaks favorably to TREC screening.

In 2017, three US federal agencies estimated the value of one life saved to be $9.7 million [32]. This estimate is an average provided by the Environmental Protection Agency ($10 million), Food and Drug Administration ($9.5 million), and the Transportation Department ($9.6 million) [32]. Given this economic information, a newborn baby with SCID or T cell lymphopenia that is screened and treated in the first 3.5 months of life, generates a contribution to society that is at least 20 times greater than the cost of screening and curative treatment.

The TREC assay is inexpensive, highly sensitive, and has been effectively integrated into public health programs [33–35]. SCID is a fatal disease that causes accrual of exorbitant healthcare costs in just 1 year of life [32, 36]. The cost of care for just one infant with SCID, not diagnosed through newborn screening, could be more than the cost of screening for an entire regional population [36]. Implementation of screening through the TREC assay will provide the earliest possible identification and allow for intervention of early transplantation before infants suffer from severe infections, organ damage, and ultimately death [12]. Newborn screening for SCID and related T cell lymphopenia is cost effective, and most importantly, it is lifesaving and allows children with SCID the opportunity to live a healthy life.

Global status of SCID screening

The global status of newborn screening for SCID is shown in Table 1 below. All 50 states in the USA and Puerto Rico are conducting population screening for SCID. It was reported to the Jeffrey Modell Foundation that as of November 2019, 20 countries around the world are conducting SCID screening at various stages, although this number is constantly changing. In addition to the USA, nine countries around the world are conducting population screening for SCID. There are ten countries currently conducting screening pilot programs and/or screening in select areas, though there are additional countries not yet screening that have conducted pilots in the past. Population screening for SCID is planned for implementation during 2020 in the Netherlands and in Manitoba, Canada.

Table 1 Global status of SCID screening[34, 35]

Currently conducting population screening	Currently conducting screening pilot programs and/or screening in select areas
1. Germany	11. Brazil (Brasilia)
2. Iceland	12. Canada (Alberta, The Maritimes, Northwest Territories, Ontario)
3. Israel	13. Finland (2/5 Hospital Districts)
4. Lebanon	14. Italy (Tuscany)
5. New Zealand	15. Japan
6. Norway	16. Netherlands
7. Sweden	17. Poland
8. Switzerland	18. Saudi Arabia
9. Taiwan	19. Spain (Catalonia)
10. United States	20. Turkey

Conclusion

Infants born with SCID, as well as related conditions with T cell lymphopenia, suffer from serious, life-threatening infections, and will likely not survive their first year of life without specific therapy to protect them from infections and restore their immune function [5, 11, 36].

SCID and related T cell lymphopenias can be detected by a simple screening test, the TREC assay, using the same dried blood spot samples already collected from newborns to screen for other genetic disorders [11, 36]. The TREC assay provides earliest possible postnatal identification at a population level allowing for intervention before opportunistic infections, irreversible organ damage, or death. Infants receiving hematopoietic stem cell transplantation in the first few months of life, after being identified through screening, have a high probability of survival, and will have the chance to grow up and live a healthy life [5–7, 9, 11, 37, 38]. While additional laboratory methods are being developed, such as the KREC assay, the current TREC assay has proven to have outstanding specificity and sensitivity to accurately identify almost all infants affected with SCID (the primary targets), as well as, additional infants with other T cell lymphopenia (secondary targets) [11, 36].

SCID is a fatal disease that causes accrual of exorbitant healthcare costs in just 1 year of life [30, 31]. The cost of care for just one infant with SCID, not diagnosed through newborn screening, could be more than the cost of screening for an entire regional population [31]. The TREC assay is inexpensive, highly sensitive, and has been effectively integrated into numerous public health programs (e.g., Wisconsin, California, New York, Sweden) [15, 33, 39]. The cost of the screen is $4–5 per infant, including equipment usage, labor, and reagents [25]. There is a 95–100% success rate of survivorship for babies transplanted in the first 3 months of life [6, 7, 9, 13, 14]. However, the survival rate sharply declines with time [13, 14, 40]. SCID is fatal in infancy if not treated, and as more serious infections develop, it is more difficult to successfully transplant [5–7, 9, 12–14, 37, 38].

Newborn screening for SCID and related T cell lymphopenia is cost-effective, and most importantly, it is lifesaving and allows children with SCID the opportunity to live a healthy life. Uniform screening globally represents a humanitarian, medical, and economic value proposition that must be advanced.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest except for the following:

Jordan Orange, MD, PhD, Takeda Consultant, Enzyvant Consultant, received speaking honoraria from Takeda, ADMA Scientific Advisory Board, author and editor in immunology for Up To Date receiving royalties.

References

1. Merrill D. No one values your life more than the Federal Government. Bloomberg October 19, 2017. https://www.bloomberg.com/graphics/2017-value-of-life/. Accessed 2 March 2018.
2. Miller J. The high cost of preventable deaths. June 4, 2018. https://hms.harvard.edu/news/high-cost-preventable-deaths
3. Mullen A. Immune deficiency disorders: types. Denver: National Jewish Health; 2019. https://www.nationaljewish.org/conditions/immune-deficiency-disorders/types
4. Amatuni GS, Currier RJ, Church JA, Bishop T, Grimbacher E, Nguyen AA, et al. Newborn Screening for Severe Combined Immunodeficiency and T-cell Lymphopenia in California, 2010–2017. Pediatrics. 2019;143(2). https://doi.org/10.1542/peds.2018-2300.
5. Buckley RH, Schiff SE, Schif RI, et al. Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med. 1999;340(7):508–16.
6. Buckley RH. Transplantation of hematopoietic stem cells in human severe combined immunodeficiency: longterm outcomes. Immunol Res. 2011;49:25–43.
7. Myers LA, Patel DD, Puck JM, Buckley RH. Hematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival. Blood. 2002;99:872–8.
8. Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. JAMA. 2014 August 20;312(7):729–38. https://doi.org/10.1001/jama.2014.9132.
9. Patel NC, et al. Outcomes of severe combined immunodeficiency patients treated with hematopoietic stem cell transplantation with and without pre-conditioning. J Allergy Clin Immunol. 2009;124(5):1062–9.e1–4.
10. van der Spek J, Groenwold RH, van der Burg M, van Montfrans JM. TREC based newborn screening for severe combined immunodeficiency disease: a systematic review. J Clin Immunol. 2015;35(4):416–30. https://doi.org/10.1007/s10875-015-0152-6.
11. Puck JM. Laboratory technology for population-based screening for severe combined immunodeficiency in neonates: the winner is T-cell receptor excision circles. J Allergy Clin Immunol. 2012;129(3):607–16. https://doi.org/10.1016/j.jaci.2012.01.032.
12. Buckley RH. The multiple causes of human SCID. J Clin Investig. 2004;114:1409–11.
13. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000–2009. N Engl J Med. 2014;371:434–46. https://doi.org/10.1056/NEJMoa1401177.
14. Haddad, et al. SCID genotype and 6-month posttransplant CD4 count predict survival and immune recovery. Blood. 2018;132(17):1737–49. https://doi.org/10.1182/blood-2018-03-840702.
15. Baker M. Universal newborn screening for severe combined immunodeficiency (SCID). [PowerPoint]. APHL CDC Newborn Screening Molecular Workshop: Atlanta; 2012.
16. Korsunskiy I, Blyuss O, Gordukova M, Davydova N, Gordleeva S, Molchanov R, et al. TREC and KREC levels as a predictors of

lymphocyte subpopulations measured by flow Cytometry. Front Physiol. 2019;9:1877. https://doi.org/10.3389/fphys.2018.01877.
17. van der Burg M, Mahlaoui N, Gaspar HB, Pai S-Y. Universal newborn screening for severe combined immunodeficiency (SCID). Front Pediatr. 2019;7:373. https://doi.org/10.3389/fped.2019.00373.
18. Thakar MS, Hintermeyer MK, Gries MG, Routes JM, Verbsky JW. A practical approach to newborn screening for severe combined immunodeficiency using the T cell receptor excision circle assay. Front Immunol. 2017;8:1470. https://doi.org/10.3389/fimmu.2017.01470.
19. Bausch-Jurken MT, Verbsky JW, Routes JM. Newborn screening for severe combined immunodeficiency-a history of the TREC assay. Int J Neonatal Screen. 2017;3:14. https://doi.org/10.3390/ijns3020014.
20. Rechavi E, Lev A, Saraf-Levy T, Etzioni A, Almashanu S, Somech R. Newborn screening for severe combined immunodeficiency in Israel. Int J Neonatal Screen. 2017;3:13. https://doi.org/10.3390/ijns3020013.
21. Kelly BT, Tam JS, Verbsky JW, Routes JM. Screening for severe combined immunodeficiency in neonates. Clin Epidemiol. 2013;5:363–9. Published 2013 Sep 16. https://doi.org/10.2147/CLEP.S48890.
22. Adams SP, Rashid S, Premachandra T, Harvey K, Ifederu A, Wilson MC, et al. Screening of neonatal UK dried blood spots using a duplex TREC screening assay. J Clin Immunol. 2014;34:323–30. https://doi.org/10.1007/s10875-014-0007-6.
23. Dorsey M, Puck J. Screening for severe combined immunodeficiency in the US: current status and approach to management. Int J Neonatal Screen. 2017;3:15.
24. Modell V, Knaus M, Modell F. An analysis and decision tool to measure cost benefit of newborn screening for severe combined immunodeficiency (SCID) and related T-cell lymphopenia. Immunol Res. 2014;60:145–52. https://doi.org/10.1007/s12026-014-8485-4.
25. Chan K, Davis J, Pai SY, Bonilla FA, Puck JM, Apkon M. A Markov model to analyze cost-effectiveness of screening for severe combined immunodeficiency (SCID). Mol Genet Metab. 2011;104(3):383–9.
26. Lipstein EA, Vorono S, Browning MF, Green NS, Kemper AR, Knapp AA, et al. Systematic evidence review of newborn screening and treatment of severe combined immunodeficiency. Pediatrics. 2010;125(5):e1226–35. https://doi.org/10.1542/peds.2009-1567.
27. Hospital Cost and Utilization Project (HCUP), Nationwide Inpatient Database under the auspices of the Agency for Healthcare Research and Quality (AHRQ). ICD-9 CM Principal Diagnosis Code for HSCT.
28. Centers for Medicare and Medicaid Services, Hospital Accounting Records, April 28, 2010.
29. Kubiak C, Jyonouchi S, Kuo C, Garcia-Lloret M, Dorsey MJ, Sleasman J, et al. Fiscal implications of newborn screening in the diagnosis of severe combined immunodeficiency. J Allergy Clin Immunol Pract. 2014;2(6):697–702. https://doi.org/10.1016/j.jaip.2014.05.013.
30. Caggana M, Brower A, Baker M, Comeau AM, Lorey F. National SCID Pilot Study http://preview.tinyurl.com/lsanbqh.
31. Kuehn BM. State, federal efforts under way to identify children with "bubble boy syndrome". JAMA. 2010;304(16):1771–3.
32. Appelbaum B. As US Agencies put more value on a life, businesses fret [newspaper]. New York Times, February 16, 2011. http://tinyurl.com/mlynth7. Accessed 16 Aug 2013.
33. CBCNews Canada. 'Bubble boy' welcomes new Ontario screening test. Published online Aug 20, 2013. http://www.cbc.ca/news/canada/story/2013/08/20/newborn-screening-bubble-boyscid.html. Accessed 21 Aug 2013.
34. Immunodeficiency Canada. Newborn Screening For SCID. https://immunodeficiency.ca/newborn-screening-for-scid/. Accessed Sept 19, 2019.
35. Direct communication with Public Health Officials and Jeffrey Modell Centers Network Directors.
36. Routes JM, Grossman WJ, Verbsky J, Laessig RH, Hoffman GL, Brokopp CD, et al. Statewide newborn screening for severe T-cell lymphopenia. JAMA. 2009;302(22):2465–70.
37. Antoine C, Muller S, Cant A, et al. Long-term survival and transplantation of hemopoietic stem cells for immunodeficiencies; report of the European experience 1986–1999. Lancet. 2003;361(9357):553–60.
38. Hassan A, Booth C, Brightwell A, Allwood Z, Veys P, Rao K, et al. Outcome of hematopoietic stem cell transplantation for adenosine deaminase-deficient severe combined immunodeficiency. Blood. 2012;120(17):3615–24.
39. Kwan A, Church JA, Cowan MJ, Agarwal R, Kapoor N, Kohn DB, et al. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia in California: results of the first 2 years. J Allergy Clin Immunol. 2013;132(1):140–50. https://doi.org/10.1016/j.jaci.2013.04.024.
40. The University of Texas Health Science Center at San Antonio (UTHSCSA). National newborn screening status report. November 21, 2011. http://genes-r-us.uthscsa.edu.