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Review

Newborn Screening for Severe Combined Immunodeficiency

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Abstract

Newborn screening (NBS) for Severe Combined Immunodeficiency (SCID) has been successfully implemented in all 50 United States and Puerto Rico from 2008-2018. This life-saving screening tool has drastically improved overall survival of babies diagnosed with SCID from 74% to 96%. TREC is a stable, circular DNA molecule that is produced during the process of T-cell receptor (TCR) rearrangement and is the target of the quantitative PCR screen on Guthrie cards. Low TRECs are a marker of low naive T cell numbers. This new screening process has facilitated discovery of new genes that cause SCID, new data on patients with SCID, as well as other causes of infant lymphopenia. This new information has prompted the Primary Immune Disease Treatment Consortium to re-classify the diagnosis of SCID in 2022. Providers who are first recipients of a positive screen must understand laboratory methods of the screen, treatment recommendations and options for those with SCID as well as other relevant causes of a positive screen such as 22q11 syndrome, Ataxia Telangiectasia, prematurity. These topics are crucial to cover when reporting results to a family who is receiving unexpected news on their otherwise well appearing newborn. Prompt medical evaluation and prophylaxis have been shown to improve survival and outcomes, and providers play an essential role in relaying this information and care to families. While TREC screen has proven to be a valuable screening tool for conditions with lymphopenia, over 500 immune deficiency diseases exist, and

expansion to include these diseases on the NBS could be possible with Next Generation Sequencing in the future.

Keywords
SCID; severe combined immunodeficiency; newborn screen

1. History of Newborn Screening for SCID

Newborn screening (NBS) for Severe Combined Immunodeficiency Disorders (SCID) has altered the landscape of these disorders and greatly improved morbidity and mortality in affected patients. As a group, SCID are diseases of the immune system caused by defects in the maturation of T cells from their hematopoietic stem cell precursors. This leaves the host susceptible to overwhelming and ultimately fatal infections if not recognized and treated early in infancy.

There are now over twenty described genetic defects that result in SCID [1], and depending on the progenitor involved, other lymphoid cell lines such as B and NK (natural killer) lymphocytes may also be affected. With impairment in T cell maturation, B cell functionality dependent on T cell signaling is also inhibited, resulting in combined cellular and humoral (antibody-production) immune defects [2]. In 2014, the Primary Immune Deficiency Treatment Consortium (PIDTC) proposed definitions for the diagnosis of SCID and other related conditions including leaky SCID and Omenn syndrome, based on criteria for T cell numbers, naïve vs memory T cells, T cell functional activity known as proliferation, and presence of maternally-derived, engrafted T cells that crossed to the patient via the placenta [3]. Given the widespread implementation of the NBS for SCID and availability of updated genetic sequencing tools, infants are now presenting prior to symptomatic or infectious onset. This prompted the PIDTC to revise the 2014 SCID diagnostic criteria in 2022: patients with typical SCID must have less than 0.05×10^9 autologous T cells/L, with either pathogenic mutation(s) in a SCID-associated gene, very low or absent T-cell receptor excision circles (TRECs) or less than 20% of CD4 helper T cells expressing naïve cell markers, and/or the presence of transplacental, maternally engrafted T cells [4] (Table 1).

Table 1 PIDTC defined SCID Diagnostic criteria [5].

SCID subtype	Diagnosis Requires	Criterion 1	Criterion 2	Criterion 3	Criterion 4
Typical SCID	Criteria 1 & 2 OR Criteria 1 & 3 OR Criterion 4	Very low T cells (< 0.05x10^9/L)	Pathogenic gene variant(s)[2]	Undetectable or low T cell receptor excision circles (TRECs) OR <20% of CD4+ T cells have naïve cell surface markers	Presence of transplacental maternal engraftment (TME)

Leaky/ Atypical SCID	Criteria 1&2&4 OR Criteria 1&3&4	<u>Two or more of</u>: • Low T cell number for age (0.05-1.0x10^9/L) • Oligoclonal T cells • Abnormal TRECs OR <20% of CD4+ T cells are naïve	Pathogenic gene variant(s)	Reduced proliferation	<u>Does not have</u>: • Other SCID subtype • CID with known genotype • Thymic disorder • Other disorder with low T cell numbers
Omenn Syndrome	All 4 criteria	Any number of T cells AND >80% of CD4+ T cells have CD45RO+ memory phenotype	Pathogenic gene variant(s)	Generalized rash AND Absence of TME (at time of rash)	<u>Two or more of</u>: • Eosinophilia (>0.8x10^9/L) • Elevated IgE • Abnormal TRECs • Lymphadenopathy • Hepatomegaly and/or splenomegaly • Oligoclonal T cells

Pathogenic gene mutations are identified in the large majority of patients with typical SCID, with 7 genes (*IL2RG, RAG1, ADA, IL7R, DCLRE1C, JAK3,* and *RAG2)* comprising 89% of the cases [5]. Leaky or atypical SCID patients have partial T cell defects due to hypomorphic or "leaky" variants in SCID genes, with *RAG1, ADA,* and *RMRP* genes accounting for more than half of the reported cases. NBS is less sensitive for these hypomorphic variants and if not detect by NBS they are more likely to be diagnosed after age 1 year [5]. Omenn syndrome is a form of leaky SCID that is associated with a generalized, erythematous rash and patients may also develop enlarged lymph nodes with hepatosplenomegaly [3]. Omenn syndrome is rare, found in 5% of cases of SCID, and the updated 2022 revised criteria do not require a minimum number of T cells, though at least 80% of CD4 helper T cells must have the memory cell marker CD45RO+ [5].

Prior to the advent and widespread implementation of NBS for SCID in the United States, affected infants would typically present with recurrent and severe infections. A recent large, multicenter study from India (where widespread NBS is not in effect) reported opportunistic infections as the hallmark presenting symptom in patients with SCID, including 82% with pneumonia and 8.3% with disseminated CMV; reported invasive fungal infections included *Pneumocystis jiroveci (PC)*, aspergillosis, esophageal candidiasis, and pulmonary cryptococcosis [6]. Early detection and intervention for infants with SCID has clear benefits from the standpoint of overall survival, with affected infants undergoing hematopoietic stem cell transplant (HSCT) in the first three months of life having greater than 95% survival compared with 74% of those undergoing HSCT beyond this window [7].

Given the potentially fatal consequence of missing a diagnosis of SCID, particularly given the absence of clues in a typically well-appearing newborn, screening of newborns had been proposed for many years to detect cases before the onset of potentially fatal infections In 2005, it was found that TREC counts for SCID screening could be obtained from dried blood spots on Guthrie cards,

already in use for screening other severe diagnoses in newborn infants [8, 9] making widespread screening feasible.

TREC is a stable, circular DNA molecule that is produced during the process of T-cell receptor (TCR) rearrangements and diversification in the thymus, and TRECs are markers of naïve thymic emigrant T cells [9, 10]. A quantitative PCR assay can provide the TREC copy number, and an absent or very low TREC count suggests an inability to produce T cells; peripheral blood of patients with SCID would be expected to have little to no detectable TRECs [9]. Wisconsin was the first state to pilot NBS for SCID in 2008, followed by Massachusetts a year later, and a third pilot in Arizona in 2009. These pilots led to the recommendation of the addition of SCID to the Recommended Universal Screening Panel in January 2010 [11]. In 2011, a report submitted by the United States Secretary's Advisory Committee on Heritable Disorders in Newborns and Children updated data from newborn SCID screening pilots in California, Louisiana, Massachusetts, New York, Puerto Rico, Wisconsin, and the Navajo Nation, which included approximately a quarter of U.S. births. Of the 961,925 screened infants, 60 infants (~1 in 16,032) were identified to have low TREC counts, and 14 of these infants were diagnosed with SCID (~1 in 68,000); additionally, there were no reported "missed" cases of SCID later identified in the pilot states [12]. California reported its data on newborn SCID screening from over 3 million infants born in the first 6.5 years of the program, with abnormal TREC counts observed in 1 in 15,300 births. Fifty cases of SCID were diagnosed (1 in 65,000 births). Additionally, 4 patients were identified with complete DiGeorge syndrome and underwent thymus transplants. No known cases of typical SCID were missed, though two patients with leaky SCID initially had normal TREC screens but presented with clinical symptoms later in infancy [13]. By the end of 2018, newborn screening for SCID was adopted in all 50 states and Puerto Rico, along with at least 20 other countries around the world [14, 15] (Figure 1).

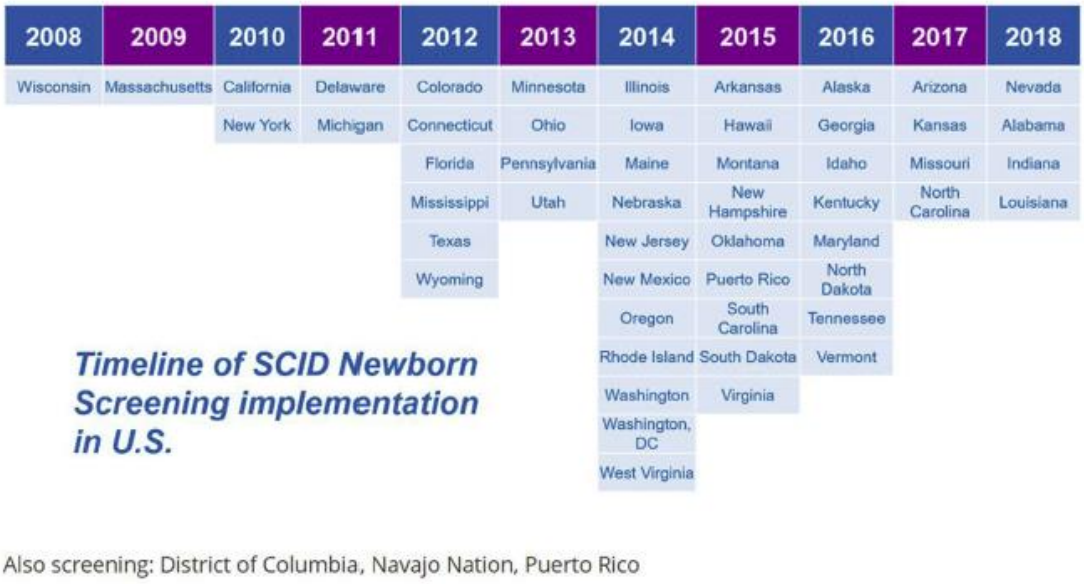

Figure 1 Timeline of SCID newborn screening implementation in the United States. [16]

The benefit of SCID NBS is demonstrated in a report showing that prior to the SCID screen era, over half of patients with SCID were diagnosed after infection, but by 2016, that number dropped to only 10% of cases with 90 percent of cases diagnosed through screening [17] The true marker of

an effective screen would be lives saved, and indeed, after SCID screening in over 3 million infants in California, the overall survival was reported to be 96% with overall survival for SCID compared to around 74% prior to SCID screening [13]. Screening for SCID has also taught us lessons about SCID as well as other diseases presenting with profound lymphopenia. The incidence of SCID prior to screening was reported as 1 in 100,000 births through various retrospective reports from around the world [2]. Early data from 11 screening centers across the United States found the incidence to be closer to 1 in 58,000 births, Further reports found even higher incidence of SCID; in its first two years of SCID screening, Arizona identified 1 in 22,819 live births as having SCID, more than double the national rate. This was thought to be due to their particular patient population made up of a larger percentage of those of Native American and Hispanic/Latino ancestry, with an incidence of 1:2000 live births in the Navajo Indian Reservation [18, 19]. Multiple countries have implemented universal or regional efforts for newborn SCID screening, with variations in the incidence of SCID in their populations. Taiwan implemented universal newborn SCID screening in 2012, and with 106,391 patients screened over 19 months, the incidence of T-cell lymphopenia was 1:11,281, with SCID and 22q11.2 deletion patients among other conditions identified in this population [20]. Israel began a national program for SCID screening on newborn screening in 2015 and the reported five-year data show an incidence of 1 in 29,000 births [21]. A 2017 collaboration in the Poland-German border region was the first SCID screening program in Central and Eastern Europe: 44,287 newborns were screened with TRECs and kappa-deleting recombination excision circles (KRECs). This effort identified one case of SCID, one case of combined immunodeficiency, one case of autosomal recessive agammaglobulinemia, and one case of Nijmegen breakage syndrome; three other positive results were related to other causes of lymphocytopenia that normalized over time, and a fourth case was classified as false positive. France completed a multicenter newborn SCID screening feasibility and cost-effectiveness program from 2015-2017 that screened 190,517 newborns, with 62 infants found to be lymphopenic, ultimately identifying 3 cases of SCID and 3 cases of leaky SCID [22]. The incidence of SCID was found to be 1 in 63,500 births, and while universal SCID screening in France has not yet been adopted, newborn TREC screening is provided in the Pays de Loire region through a program called NeoSKID [23]. As more countries add SCID NBS to their newborn screen, we will learn more about the true incidence of SCID worldwide.

2. What Diagnoses Can be Positive on a SCID Newborn Screen

There are over 20 different genetic defects implicated in SCID with a small percentage of patients having no identifiable genetic cause despite testing. Prior to screening, with data largely from Duke, over half of all cases of SCID were thought to be due to mutations in the gene that encodes the IL2 Receptor gamma chain (IL2RG) with ADA SCID the second cause at 14% of reported cases. RAG1 and RAG2 each accounted for only 1% of identified SCID cases, with unknown genetic diagnosis in only 3%. California, however, after over 3 million screened infants reported that IL2RG only accounted for 28% of SCID cases, with ADA SCID still second at 18% of cases, and RAG1 in 16% and RAG2 in 6%. Furthermore, those with SCID where a genetic cause was not identified made up 13% of SCID cases in California and 23% of SCID cases from 12 different centers [13, 24].

The SCID newborn screen appears to have a high sensitivity for classical SCID, but also detects other causes of T-cell immune deficiencies. In fact, SCID accounts for a small fraction of positive screens and the vast majority of infants identified with lymphopenia at birth have other causes.

Preterm birth alone is a cause of lymphopenia identified by SCID screening. In California, of the total samples screened, 85% of the abnormal screens were from infants in the neonatal intensive care unit (NICU) [13]. Lower birth weight also correlated with likelihood for a positive SCID screen. Despite this, only 11% of second samples sent a few weeks later remained abnormal. In some states, there are protocols in place repeating screening for pre-term infants before the abnormal screens are reported [24]. Genetic syndromes account for more than one-third of the non-SCID conditions identified by SCID NBS, Of the syndromes, 22q11 deletion syndrome accounts for over half of all the congenital syndromes identified, with other syndromes including trisomy 21, Kabuki syndrome, ataxia telangiectasia (AT) and many others. The sensitivity of NBS for non-SCID immune deficiencies is not known, but it is important to note that this is not a test that will identify all cases of AT or trisomy 21 or even 22q11 deletion, but identifies only those cases with more profound lymphopenia [25-27]. Other non-SCID causes of T cell lymphopenia include losses through cardiac or gastrointestinal disease, or vascular or lymphatic malformations. In addition, there are several reports of transient lymphopenia due to maternal use of immunosuppressive medications [24, 26, 28]. (Table 2) Maternal immunosuppressive medications as the cause of a positive SCID screen has been reported elsewhere as well with a single center in Illinois reporting on maternal use of fingolimod, hydroxychloroquine, and 2 cases of azathioprine causing lymphopenia identified on screening. Thus far these reports of iatrogenic lymphopenia all had resolution and normal lymphocyte counts over time [29].

Table 2 Secondary conditions associated with non-SCID T cell lymphopenia that may be identified by NBS for SCID [28].

Syndromes with T cell impairment
CHARGE syndrome (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities)
Partial DiGeorge syndrome (congenital heart defects, hypoparathyroidism, and hypofunction of thymus)
VACTERL (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistulas, renal and limb abnormalities)
Trisomy 21 (Down syndrome)
Ataxia-telangiectasia
Trisomy 18 (congenital heart defects and multiple anomalies)
Jacobsen syndrome (developmental delay, dysmorphic facies, abnormal bleeding, attention-deficit/hyperactivity disorder, and frequent ear and sinus infections)
CLOVES (congenital lipomatous [fatty] overgrowth, vascular malformations, and epidermal nevi and scoliosis)
Nijmegen breakage (microcephaly, hypogammaglobulinemia, decrease T cells, increased cancer risk, and abnormal DNA breakage repair)
Fryns (associated with congenital diaphragmatic hernia and dysmorphic features)
Ectrodactyly ectodermic dysplasia syndrome
EXTL3 deficiency (skeletal dysplasia, developmental delay)

Rac2 defect (neutrophil killing defects)
Noonan (dysmorphic facies, short neck, short stature, and congenital heart defects)
Renpenning (*PQBP1* loss of function leading to short stature, intellectual disability and dysmorphisms)
Barth syndrome (*TAZ* loss of function leading to cardiomyopathy at birth and neutropenia; mostly affects males)
TAR syndrome (*RBM8A* deficiency leading to thrombocytopenia and absent radius)
WHIM syndrome (*CXCR4* gain of function leading to warts, hypogammaglobulinemia, infections, myelokathexis)
Diabetic embryopathy
Other cytogenetic abnormalities (including metabolic diseases)
T cell loss or destruction
Congenital cardiac anomalies
Gastrointestinal anomalies (gastroschisis, omphalocele and intestinal lymphangiectasia)
Third spacing (anasarca, hydrops, and vascular leakage)
Neonatal leukemia
Other conditions
Maternal immunosuppressive medication (azathioprine and 6-mercaptopurine and adalimumab)
Extreme preterm birth (T cells normalize over time)
Idiopathic T lymphopenia

3. Management of a Positive SCID Newborn Screen

Given that the TREC screen was added to the state screening panel as recently as 2018 (Figure 1), and fewer than 80 babies are born in the U.S. annually with SCID [30], pediatricians may not have encountered a positive screening result and are not typically comfortable how to approach a positive screen. There is no universally accepted process for evaluating a positive newborn screening result. Identifying and reporting a positive screen follows different workflows depending on the techniques of the state health laboratory, typically there is an internal check for quality prior to reporting [12, 31, 32]. Figure 2. A positive SCID screen warrants prompt and careful evaluation as children with severe combined immunodeficiency are at risk for life threatening infections. However, because screening results are not definitive, families should be counseled that an abnormal result does not necessarily mean that the infant has severe combined immunodeficiency [33-35]. In discussing the positive result with parents, it is important to remember that the majority of positive screens are non-SCID lymphopenia [32]. The positive and negative predictive values of the TREC screen vary from state to state as do false positive results [24]. TREC results are usually delivered around 2 weeks of age, which coincides with onset of post-partum depression. Typically, the newborn is otherwise healthy and thriving and the news is unexpected. It is important to deliver the results in an appropriate setting that would be used to deliver serious news. Recognizing family's

shock and emotions with hearing this unexpected result and considering other psychosocial support that you may be able to offer is extremely important [33].

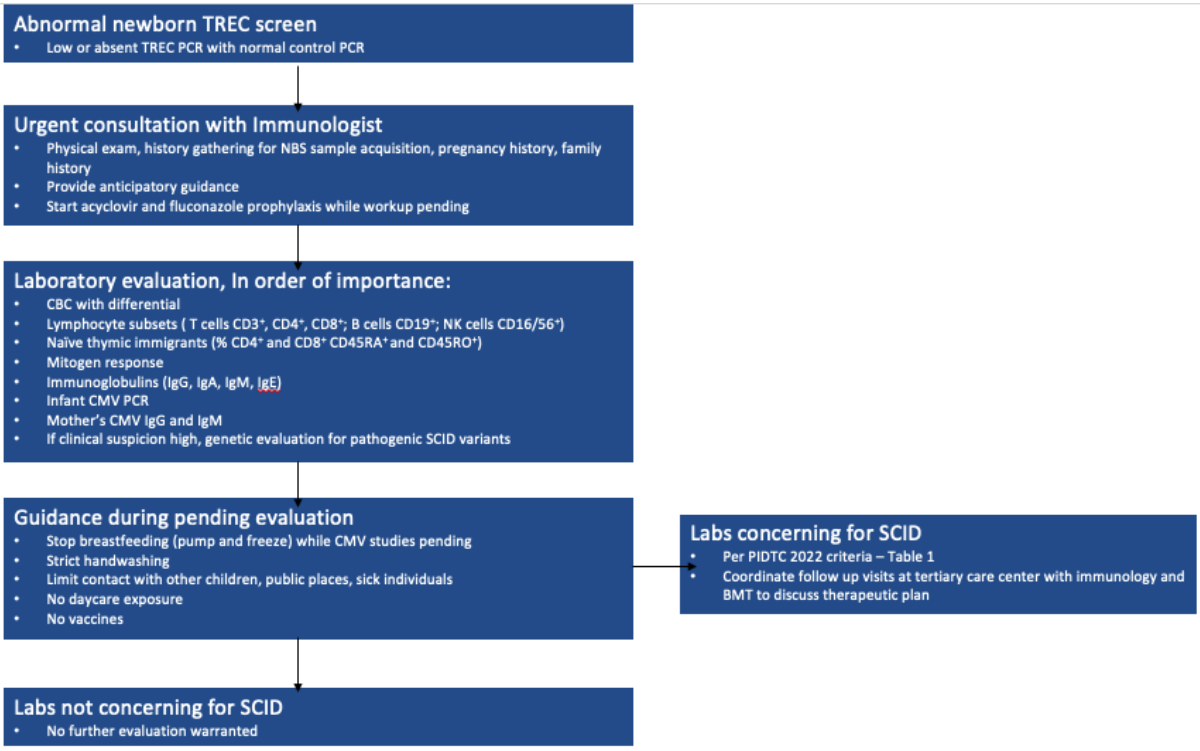

Figure 2 Workflow for positive Severe Combined Immunodeficiency (SCID) newborn screen. Based on author's institutional protocol. TREC = T-cell Receptor Excision Circle, PCR = Polymerase Chain Reaction NBS = Newborn Screen, CMV = Cytomegalovirus.

As soon as is feasible, a thorough physical exam should be performed to evaluate for potential syndromic/dysmorphic features which could indicate chromosomal abnormalities such as 22q11.2 deletion syndrome, trisomy 21 or others [30]. Close attention to any rashes which can be an indication of maternal T cell engraftment and Omenn syndrome is also important. We also look for hepatosplenomegaly and lymphadenopathy. Also important is a thorough history to look for iatrogenic or secondary causes of lymphopenia. Maternal medications during pregnancy, history of gestational diabetes, prematurity, timing/method of blood application to the Guthrie card are all important factors that can impact a TREC screen [9, 35, 36]. Our institutional protocol for all newborns who screen positive for SCID is to immediately counsel mothers to stop breastfeeding and pump and freeze breast milk while awaiting results back of confirmatory testing in order to prevent CMV transmission through the breast milk. Once SCID has been ruled out, we allow mothers to return to breast feeding. We ask families to avoid public places, daycare and limit contact with other young children while test results are pending. If families are not able to adhere to these guidelines, we offer inpatient admission to provide isolation precautions for the infant. We see the patient weekly as an outpatient to review results, counsel on infection prevention, and discuss therapeutic options.

Prophylaxis while definitive treatment is being decided is crucial given the impact an infection prior to transplant has on survival curves. Two-year overall survival for patients treated with transplant was 95% in those who were infection free versus 81% who received transplant with active

infection [36]. Therefore, we recommend immediate prophylaxis with fluconazole and acyclovir while workup for SCID is pending. Antifungal prophylaxis, typically fluconazole, is recommended by 79% of PIDTC centers. Antiviral prophylaxis is practiced among 45% of PIDTC centers. We also start immunoglobulin replacement, which is recommended by 98% of PIDTC centers. During the appropriate season, we also recommend every 4-week palivizumab injections. PC pneumonia prophylaxis is initiated universally at PIDTC centers; in our center we begin at 1 month of age to minimize side effects [37].

Historically, the only curative treatment for SCID was early prophylaxis to prevent infections, followed by hematopoietic stem cell transplant (HSCT). HSCT has excellent 5-year event free survival curves of >90% with matched sibling, matched unrelated donor, and haplo-identical transplant if the patient is infection-free prior to transplant [38]. Additionally, gene therapy or enzyme replacement therapy are also treatment options for certain genetic etiologies of SCID [39, 40]. Patients who have successful engraftment can live a long and potentially normal life span with the oldest reported post-transplant patient in his 50s [41].

4. Conclusion and Future Directions

In conclusion, we recommend that pediatricians familiarize themselves with the protocols of their state or national health departments to understand their SCID newborn screening workflow. A positive newborn SCID screen should promptly be evaluated, and families counseled on infection prevention strategies and appropriate follow up testing performed. Timely evaluation, infection prevention and appropriate treatment results in excellent survival rates [10]. Trustworthy resources for physicians and families are readily available (Table 3).

Table 3 Resources for physicians and families.

Immune Deficiency Foundation:	https://primaryimmune.org
Jeffrey Modell Foundation:	https://info4pi.org
SCID:	https://scid.net
SCID Angels:	https://www.scidangelsforlife.com

Besides severe combined immunodeficiency, there are nearly 500 other inborn errors of immunity as classified by the International Union of the Immunological Societies [42]. Many of these are diagnosed after the patient presents with severe infection, autoinflammation, or autoimmunity significantly affecting morbidity and mortality. Like SCID, some of these diseases have definitive if not curative treatments with better outcomes if diagnosed early. Considering the heterogeneity of these genetic disorders of immunity, only those with severe T cell lymphopenia will be identified via current TREC newborn screening, and disorders affecting B cells or innate immunity will be missed. For the hundreds of disorders with known genetic basis, rapid next generation sequencing (NGS) would be a way to identify these infants early. Proof of concept of rapid NGS to identify genetic conditions at birth has been demonstrated in several studies involving both critically ill as well as healthy infants. Moving from PCR on dried blood spots as just a surrogate for one feature of immune deficiency, in the future, NGS will offer rapid and accurate diagnosis of the exact immune disorder, potentially saving time, money and lives [43, 44].

Author Contributions

Dr. Coffey wrote section one, Dr. Chong wrote section two. Dr. Deal wrote section three. Dr. Deal designed the figures and tables. All authors contributed to editing and approving the final article.

Competing Interests

The authors have declared that no competing interests exist.

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