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The diagnosis of severe combined immunodeficiency (SCID): The Primary Immune Deficiency Treatment Consortium (PIDTC) 2022 Definitions

Christopher C. Dvorak, MD[a], **Elie Haddad, MD, PhD**[b], **Jennifer Heimall, MD**[c], **Elizabeth Dunn, MA**[a], **Rebecca H. Buckley, MD**[d], **Donald B. Kohn, MD**[e,f], **Morton J. Cowan, MD**[a], **Sung-Yun Pai, MD**[g], **Linda M. Griffith, MD, PhD**[h], **Geoffrey D. E. Cuvelier, MD**[i], **Hesham Eissa, MD**[j], **Ami J. Shah, MD**[k], **Richard J. O'Reilly, MD**[l], **Michael A. Pulsipher, MD**[m], **Nicola A. M. Wright, MD**[n], **Roshini S. Abraham, PhD**[o], **Lisa Forbes Satter, MD**[p], **Luigi D. Notarangelo, MD**[h,*], **Jennifer M. Puck, MD**[a,*]

[a]Division of Pediatric Allergy, Immunology, and Bone Marrow Transplantation, University of California San Francisco, San Francisco;

[b]Department of Pediatrics, University of Montreal, CHU Sainte-Justine, Montreal, Quebec;

[c]Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, and Division of Allergy and Immunology, Children's Hospital of Philadelphia, Philadelphia;

[d]Division of Pediatric Allergy and Immunology, Duke University Medical Center, Durham;

[e]Department of Microbiology, Immunology & Molecular Genetics, Los Angeles, Los Angeles;

[f]Department of Pediatrics, University of California, Los Angeles, Los Angeles;

[g]Immune Deficiency Cellular Therapy Program, Center for Cancer Research, National Cancer Institute, Bethesda

[h]Division of Allergy Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda;

[i]Manitoba Blood and Marrow Transplant Program, CancerCare Manitoba, University of Manitoba, Winnipeg, Manitoba;

[j]Division of Pediatric Hematology-Oncology-BMT, University of Colorado, Aurora;

[k]Division of Pediatric Hematology, Oncology, Stem Cell Transplantation and Regenerative Medicine, Stanford School of Medicine, Palo Alto;

[l]Department of Pediatrics, Stem Cell Transplantation and Cellular Therapies Service, Memorial Sloan Kettering, New York;

Corresponding author: Christopher C. Dvorak, MD, UCSF Benioff Children's Hospital, 550 16th Street, 4th Floor, Box 0434, San Francisco, CA 94143. christopher.dvorak@ucsf.edu.

*Co-senior authors.

This article is dedicated to the memory of William T. Shearer, MD, PhD (1937–2018).

[m]Division of Pediatric Hematology and Oncology, Intermountain Primary Childrens Hospital, Huntsman Cancer Institute at the University of Utah, Salt Lake City;

[n]Department of Pediatrics, Alberta Children's Hospital, University of Calgary, Calgary, Alberta;

[o]Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus;

[p]Pediatric Immunology Allergy and Retrovirology, Baylor College of Medicine, Houston.

Abstract

Severe combined immunodeficiency (SCID) results from defects in the differentiation of hematopoietic stem cells into mature T lymphocytes, with additional lymphoid lineages affected in particular genotypes. In 2014, the Primary Immune Deficiency Treatment Consortium published criteria for diagnosing SCID, which are now revised to incorporate contemporary approaches. Patients with typical SCID must have less than 0.05×10^9 autologous T cells/L on repetitive testing, with either pathogenic variant(s) in a SCID-associated gene, very low/undetectable T-cell receptor excision circles or less than 20% of CD4 T cells expressing naive markers, and/or transplacental maternally engrafted T cells. Patients with less profoundly impaired autologous T-cell differentiation are designated as having leaky/atypical SCID, with 2 or more of these: low T-cell numbers, oligoclonal T cells, low T-cell receptor excision circles, and less than 20% of CD4 T cells expressing naive markers. These patients must also have either pathogenic variant(s) in a SCID-associated gene or reduced T-cell proliferation to certain mitogens. Omenn syndrome requires a generalized erythematous rash, absent transplacentally acquired maternal, elevated IgE, lymphadenopathy, engraftment, and 2 or more of these: eosinophilia hepatosplenomegaly. Thymic stromal defects and other causes of secondary T-cell deficiency are excluded from the definition of SCID. Application of these revised Primary Immune Deficiency Treatment Consortium 2022 Definitions permits precise categorization of patients with T-cell defects but does not imply a preferred treatment strategy.

Keywords

Severe combined immunodeficiency; SCID; typical SCID; leaky/atypical SCID; Omenn syndrome; newborn screening

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The Primary Immune Deficiency Treatment Consortium (PIDTC) was established to investigate natural history and outcomes for severe combined immunodeficiency (SCID) and other rare primary immune deficiencies by means of prospective and retrospective natural history studies. Criteria for the diagnosis of SCID, using tests commonly applied at participating centers, were developed for PIDTC protocols beginning in 2010.[1,2] The early diagnostic experience, codified by Dr William Shearer and collaborators in the PIDTC 2014 Criteria, proposed definitions for typical SCID, leaky SCID, and Omenn syndrome, with the goal of facilitating a rigorous analysis of consistent subtypes of SCID, independent of clinical factors such as infections or failure to thrive.[3] These definitions, based on review of the 332 patients with SCID enrolled in the retrospective PIDTC Protocol 6902 (NCT10346150), between 2000 and 2009, mainly considered T-cell numbers, naive

versus memory T cells, T-cell proliferative responses to PHA, and transplacentally acquired maternal engraftment (TME) of T cells.

Between 2014 and 2021, both clinical presentation and diagnosis of SCID have changed with widespread adoption of newborn screening (NBS) and improved availability of gene sequencing.[4–6] Current enrollment into the PIDTC Protocols for SCID has made possible analyses showing that the 2014 Criteria should now be refined to incorporate these and other contemporary advances. Universal NBS for SCID by enumerating T-cell receptor excision circles (TRECs) in dried blood spots collected at birth has radically altered how infants with SCID in the United States and most infants in Canada are now identified. NBS has also brought to attention a new category of patients: very young infants (typically aged <30 days) with low TRECs and T-cell lymphopenia in whom SCID is suspected, but not yet confirmed. Simultaneously, genetic sequencing has become faster, cheaper, and widely available, and so causative pathogenic gene variants are identified in more than 90% of patients with SCID.[7]

In recognition of these developments, the PIDTC has reexamined the PIDTC 2014 Criteria, using an analysis of patients enrolled onto PIDTC Protocol 6901 (NCT01186913), a prospective natural history study of outcomes after treatment for SCID (see accompanying article by Dvorak et al[8]). Although the fundamental structure and principles of the 2014 Criteria have been retained, the PIDTC 2022 Definitions (Table I) (1) accommodate infants identified in the first weeks of life by TREC-based NBS; (2) account for advances in genetic sequencing; and (3) consider reduced proliferative response to mitogens (PHA, anti-CD3, or anti-CD3/CD28) as needed to establish a diagnosis of leaky/atypical SCID; furthermore, we now (1) describe a new category of suspected SCID, applied to infants with low T cells who have not yet received a definitive diagnosis; and (2) formally define the date of diagnosis.

Although recent data indicate similar survival for patients with typical SCID compared with leaky/atypical SCID and Omenn syndrome,[9,10] differences in presentation indicate that continued distinctions between these categories are warranted to facilitate future analyses. To date, PIDTC natural history studies have recorded treatment regimens used by physicians at participating centers but have not been designed to establish rules for treatment of SCID. Although most patients meeting the criteria for leaky/atypical SCID or Omenn syndrome have received preparative regimens,[9,10] neither the original PIDTC 2014 Criteria nor these revised PIDTC 2022 Definitions should be viewed as dictating a particular therapeutic approach, but may help in the design and evaluation of future therapeutic trials.

SCID AS A PATHOPHYSIOLOGIC ENTITY

The PIDTC views SCID as a pathophysiologic entity, rather than simply a phenotype of low T-cell numbers with very low or absent B-cell numbers or function. We reserve the term SCID for patients with a defect intrinsic to hematopoietic stem cells (HSCs) that prevents their differentiation into phenotypically and functionally mature T cells. SCID may also have defects in B-cell differentiation and/or function and/or natural killer (NK)-cell differentiation. However, for all SCID subtypes, definitive therapy requires establishing an HSC population intrinsically capable of generating T cells, whether by allogeneic

hematopoietic cell transplantation (HCT) or by autologous cell transplantation with a corrected gene.

In contrast, patients with non-SCID conditions (Table II) may have defects in thymic function with deletions in chromosome 22q11.2 (DiGeorge syndrome), pathogenic variants in genes such as *FOXN1, FOXI3, TBX1*, *TBX2, CHD7*, or *PAX1*, or other underlying cause. These patients may resemble SCID in terms of lymphocyte phenotype and clinical phenotype to some extent, but for them HCT is unlikely to be curative because the error is in thymic stromal cell development.[11–13] Both SCID and primarythymic function defects may present with low/absent TRECs and benefit from strict isolation and anti-infectious prophylaxis until improvements in immunity are achieved.[14] No standard clinical tests distinguish HSC defects from thymic defects; however, research-level methods may eventually be translated into clinical use.[15,16] Some thymic defects may demonstrate spontaneous improvements in T-cell numbers, whereas others respond to cultured thymic tissue implantation.[17] Although some patients with defects in thymic function have undergone HCT with apparent benefit, possibly due to engraftment of donor T cells, most patients have not seen benefit, and therapies focusing on restoring thymic function would be preferred for these patients.[18,19]

Single-gene profound combined immunodeficiencies (CIDs) that predominantly affect T-cell function rather than development may overlap with SCID. One example is pathogenic variants in *ZAP70*.[20] These patients characteristically lack CD8 T cells but have CD4 T cells that are dysfunctional. Other genotypes that fit the definition of profound CID with T-cell dysfunction better than SCID include defects in *LCK*, *IKBKB*, and MHC class II deficiency.[21–23] Therare patients with CID who meet criteria 1, 3, and 4 (Table I) may be considered to have atypical SCID. The same applies to other single-gene CIDs that can present with a wide range of T-cell numbers, in which T cells are functionally impaired. Of note, patients with CID with profound T-cell dysfunction often have normal TRECs and escape detection by NBS.[24] Their clinical presentation with opportunistic infections is often as severe as cases of SCID in the pre-NBS era and may also require HCT.

The many other non-SCID causes of low TRECs and T-cell lymphopenia that—in their most extreme presentations—can mimic SCID include increased T-cell losses secondary to vascular leakage seen in various neonatal conditions, *in utero* exposure to maternal immunosuppressive medications, advanced congenital HIV infection, certain multisystem metabolic disorders (such as defects of folate transport and metabolism), and chromosomal aneuploidies.[25–27] Importantly, there are also non-SCID idiopathic T lymphopenias detected by NBS for which the value of HCT is unknown.

Suspected SCID

Suspected SCID is our term for patients who present with abnormally low numbers of T cells, often following an abnormal SCID NBS result, but in the pre-NBS era tested for low lymphocyte numbers because of a previously affected relative. Suspected SCID is generally a temporary assignment pending a definitive diagnosis of either SCID or a non-SCID disorder.

Suspected SCID is defined as follows:

1. Less than 0.3×10^9/L CD3 T cells, *OR* less than 20% of CD3/CD4 cells with naive cell surface markers (eg, CD3/CD4/CD45RA)

   AND 1 or more of:

   a. Abnormal TRECs on NBS or at presentation

   b. Family history of SCID

   c. Recurrent and/or opportunistic infection(s)

   OR

2. If TRECs not measured or not abnormal and no family history of SCID, then less than 0.3×10^9/L $CD3^+$ cells *AND* less than 20% of naive CD3/CD4 cells.

   OR

3. Features of Omenn syndrome, including

   a. More than 80% of CD3/CD4 cells with memory cell surface markers ($CD45RO^+$). $CD3^+$ cells may be more than 0.3×10^9/L

   b. Generalized skin rash

   c. Eosinophilia **OR** lymphadenopathy **OR** organomegaly

The date of diagnosis of suspected SCID is defined as the date that the first lymphocyte phenotyping panel was obtained that demonstrated the T-cell abnormalities as outlined above.

CLINICAL AND LABORATORY EVALUATION FOR PATIENTS WITH SUSPECTED SCID

To establish a diagnosis of SCID and eliminate other conditions with low T-cell numbers (Table II), a thorough evaluation should include the following[4]:

- History of infection, prematurity, other medical conditions (eg, congenital heart disease and lymphatic malformation), maternal comorbidities (eg, immunosuppressive therapy during pregnancy and diabetes[28]), and family history of immunodeficiency or early childhood deaths.
- Physical examination for features indicative of DiGeorge syndrome or other multisystem conditions; generalized rash, lymphadenopathy, hepatomegaly, and splenomegaly, as potential signs of either maternal graft-versus-host-disease (GvHD) or Omenn syndrome.
- Complete blood cell count with differential, including assessment of eosinophilia as a sign of maternal GvHD or Omenn syndrome.
- Lymphocyte phenotyping, including evaluation of:

  - T, B, and NK cells and T-cell subsets; naive and memory CD3/CD4 helper T cells. Evaluation of naive CD8 cytotoxic T cells may be performed, but CD4 cells are most reflective of thymic output.
  - Lymphocyte phenotyping should be repeated a minimum of 1 week after the first determination, and/or on confirmation of pathogenic SCID gene variant(s) by sequencing. If no genetic etiology is determined, at least 8 weeks should separate repeat lymphocyte phenotyping results to allow for improvement of transient T lymphopenia, unless an urgent HCT must be performed because of a clinical emergency.
  - All T-cell quantification should be interpreted against age-associated reference intervals.[29]

- TREC quantification or cycle threshold, with confirmation of detection of a suitable genomic control DNA segment, such as actin or RNaseP.
- Quantitative immunoglobulins, including IgE as a potential sign of Omenn syndrome.
- Genetic sequencing, now standard of care, often starting with a panel of genes associated with immunodeficiency. Additional sequencing of a whole exome or genome, preferably a trio analysis with the infant and parents, is warranted if initial testing nondiagnostic.
- Testing for TME in either whole blood or isolated CD3 T cells. For male patients, fluorescent *in situ* hybridization was historically used to detect a second X chromosome indicative of maternal (female) cells; however, in the modern era, more sensitive analysis—such as DNA typing with short tandem repeat markers—is preferred.
- Testing for T-cell receptor diversity if T cells are present, measured as T-cell receptor–Vβ usage by flow cytometry, or spectratyping or high-throughput sequencing of T-cell receptor–Vβ complementarity determining region 3.[30]
- Proliferative testing by mitogen stimulation with PHA, anti-CD3, or anti-CD3/CD28 antibodies may be performed, but may not be required to confirm the diagnosis if the patient otherwise meets criteria for typical SCID. Reduced proliferation may indicate either low T-cell numbers (which can be confirmed by standard lymphocyte subset enumeration) or dysfunctional/nonfunctional T cells despite normal numbers. Traditional radioactive assays do not address this issue because both low T cells and nonfunctional T cells will result as abnormal, whereas flow cytometry–based assays better differentiate between low T cells and nonfunctional T cells. Other stimuli of T-cell proliferation historically performed include specific antigens (*Candida* or tetanus), if previously exposed; however, these have been removed from the Revised 2022 Definitions and are not typically recommended.

- HIV testing by either nucleic acid amplification or protein determination in a patient sample, or by documentation that maternal HIV antibody testing is persistently negative.

SEVERE COMBINED IMMUNODEFICIENCY

Approximately 30% of patients with abnormal NBS will be found to have SCID.[25] The PIDTC 2014 Criteria recognized 4 major subtypes of SCID: typical SCID, leaky SCID, Omenn syndrome, and reticular dysgenesis (the latter due to pathogenic variants in *AK2*). Although patients with reticular dysgenesis present in a much different fashion (with severe neutropenia due to defects in myeloid cell development and sensorineural deafness) than do other patients with SCID,[31] the revised 2022 PIDTC Definitions now recommend classifying patients with *AK2* pathogenic variants according to how they fit into 1 of the 3 other major subtypes: typical SCID with very low T cells, leaky/atypical SCID with low T cells, or Omenn syndrome (Table I), recognizing that patients with *AK2* pathogenic variants require special planning of HCT to address their defects in myeloid as well as lymphoid differentiation.

Although the distinction between “typical” and “leaky/atypical” SCID has at times been used to determine which patients could receive an allogeneic HCT without conditioning, the 2022 Definitions are strictly descriptors of presenting findings and are not meant to imply that a particular type of treatment is indicated.

To assess morbidities before and outcomes after treatment, patients with SCID should be further classified according to first presentation (called the “trigger for diagnosis”):

a. *Family history:* Recognized SCID in a previously affected relative leading to lymphocyte subset enumeration or genotyping for known SCID-associated pathogenic variant(s). Testing may be done prenatally (via amniocentesis, chorionic villus sampling, or fetal blood sampling) or after birth. This category does not include patients for whom the history of a (possibly) affected family member is recognized after an abnormal NBS result or T-cell count has been obtained.

b. *Newborn screening*: Population-wide NBS via TREC analysis of dried blood spots (or rarely targeted DNA sequencing of very high-risk populations) reported to be abnormal before additional immunologic testing. This does not include patients who had NBS, but who also had additional immunologic evaluation commenced before return of the abnormal screening result (due to a recognized family history, signs of infection or Omenn syndrome, or other reasons).

c. *Infection*: Immunologic evaluation prompted following presentation with 1 or more microbiologically documented or suspected (eg, pneumonia or cellulitis) infections, particularly opportunistic infections.

d. *Noninfectious clinical signs*: Clinical manifestation (other than infection), such as a rash, autoimmunity, or syndromic features (eg, dwarfism in cartilage hair

hypoplasia, microcephaly, or oral and/or genital ulcers in some DNA repair defects) leading to immunologic evaluation.

e. *Incidental*: Rarely, a complete blood cell count done for reasons other than evaluation of immune function, indicating unexpected lymphopenia and prompting further immunologic evaluation.

For analyzing outcomes, the date of definitive diagnosis of SCID is the date of laboratory testing that confirms meeting criteria for inclusion in a particular subtype, including the repeat T-cell count. In some cases, this may be when the genotype is confirmed; however, patients can fulfill sufficient criteria before, or in the absence of, identification of pathogenic gene variant(s). For example, in the absence of other supporting results returning before this date, a patient with typical SCID may definitively be diagnosed on the day that positive TME testing result was returned.

Typical SCID

Typical SCID describes patients with the most profound defects in host T-cell numbers, usually due to null pathogenic variant(s) in a gene whose product is essential for T-cell development (Table I). More than 15 such genes are known, though defects in 7 (*IL2RG, RAG1*, *RAG2*, *ADA*, *DCLRE1C*, *IL7R*, and *JAK3*) represent at least 80% of SCID cases (Table III). When novel sequence changes are found in known SCID genes, input from experts in variant interpretation is required to assess pathogenicity based on available evidence.

A pathognomonic finding in many genotypes of typical SCID is the presence of maternal T cells in peripheral blood, due to failure to reject transplacentally transferred cells.[32] The degree of TME required to be considered positive has not been definitively defined, and some reports suggest that maternal microchimerism may exist in normal children.[33–35] TME is found in approximately50% of patients with typical SCID but is somewhat less common in the genetic subtypes *ADA*, *RAG1*, *RAG2*, and *DCLRE1C* (see accompanying article by Dvorak et al[8]), possibly due to the ability of NK cells or residual host T cells to eliminate maternal cells. Furthermore, because transferred maternal T cells may require time to proliferate to a sufficient degree for detection, it is theoretically possible that a patient blood sample sent early in life that results in no detected TME may be followed by a positive TME test result if repeated weeks to months later, especially if T-cell numbers rise significantly.

TME may elevate total T-cell numbers in typical SCID. In the absence of TME, the original PIDTC 2014 Criteria defined the T-cell threshold for typical SCID as less than 0.3×10^9/L; this was lowered to less than 0.05×10^9/L CD3 T cells in the revised PIDTC 2022 Definitions to better reflect a population of patients with profound T lymphopenia with limited capacity to proliferate (see accompanying article by Dvorak et al[8]). Furthermore, T-cell enumeration (including naive/memory phenotyping) must be repeated at least once before immune restoring therapy is undertaken because rare infants with non-SCID conditions have low T-cell numbers in the first weeks of life that then increase.[5] In patients with an identified pathogenic variant, the interval between tests must be at least 1 week; in patients without an identified pathogenic gene variant, the T-cell number must remain

less than 0.05×10^9/L for at least 8 weeks to qualify as typical SCID due to the potential for spontaneous improvement, with a shorter interval only if urgent hematopoietic cell transplant is required before 8 weeks. The second value should be used for typical versus leaky/atypical SCID classification. As noted in the 2014 PIDTC Criteria, a finding of low T-cell numbers is not on its own sufficient for a diagnosis of SCID, because non-SCID disorders may also present with varying degrees of T-cell lymphopenia (Table II).[25]

In the era from 2010 to 2018, we note that approximately 95% of patients with typical SCID had pathogenic variant(s) identified in a gene required for T-cell development.[7] Without a demonstrated genetic defect, patients with repeated values of less than 0.05×10^9/L CD3 T cells at least 8 weeks apart (shorter only if HCT performed for clinical emergency) may now be classified as typical SCID if they also have abnormal TRECs or less than 20% of total CD3/CD4 T cells with naive cell surface markers. For these rare patients, particularly if a $T^-B^+NK^+$ phenotype is identified, disorders affecting T-cell numbers that are not caused by a defect in HSCs, such as thymic disorders, must be ruled out (Table III).

Leaky/atypical SCID

Leaky/atypical SCID is the term used for patients with partial defects in host T-cell numbers, diversity, and maturity (reduced naive T cells), either due to hypomorphic or "leaky" pathogenic variant(s) in the same genes responsible for typical SCID ("leaky SCID") or due to as-yet-unidentified defects ("atypical SCID"). Leaky/atypical SCID (Table I) requires at least 2 of the following: (1) low T-cell numbers for age (<0.6×10^9/L for any age, <0.8×10^9/L if aged 2–4 years, or <1.0×10^9/L if aged <2 years); (2) an oligoclonal T-cell population; and (3) low percentages of naive T cells and/or low or undetectable TRECs. When T-cell enumeration is repeated, the second (or final pretreatment) value is used to assign SCID subtype.

Almost 90% of patients with leaky/atypical SCID have a pathogenic gene variant identified and can be referred to as leaky SCID.[7] Defects in *RAG1*, *RAG2, ADA*, and *RMRP* are overrepresented in leaky SCID (Table III). In the absence of an identified pathogenic variant, it is critical to test for TME, because maternal T cells would instead classify a patient as typical SCID. In the absence of available TME testing, atypical SCID criteria may be fulfilled via demonstration of impaired proliferation to PHA, anti-CD3, or anti-CD28 to less than 50% of the lower limit of the reference range. Finally, many laboratory findings of atypical SCID are also seen in certain forms of CID due to syndromes, thymic defects, or defects in non-SCID genes such as *CD40L* or *WASP*.[3,6,36] Thus, patients without an identified pathogenic variant in a known SCID gene, particularly those with a B^+NK^+ lymphocyte profile, must be tested to rule out known non-SCID conditions (Table II).

Omenn syndrome

Omenn syndrome is a form of leaky SCID characterized by expanded memory T cells of host origin that infiltrate the skin and other tissues, and produce a characteristic generalized erythematous rash, often associated with lymphadenopathy, hepatosplenomegaly, and other clinical features. The rash of Omenn syndrome can resemble the rash of GvHD; therefore,

exclusion of TME and maternal GvHD near the time of development of rash is essential to make the diagnosis of Omenn syndrome.

The PIDTC 2014 Criteria required that a patient with Omenn syndrome have more than 0.3 × 10^9/L T cells; however, the Revised 2022 Definitions recognize that any number of T cells in peripheral blood is possible (see accompanying article by Dvorak et al[8]). Furthermore, the diagnostic features of Omenn syndrome now require, along with a generalized rash and absence of TME, that more than 80% of the patient's CD4 T cells bear the memory marker CD45RO. In the era of NBS, Omenn syndrome has evolved in patients who initially met criteria for typical or leaky SCID[37]; thus, patients should be monitored for development of Omenn syndrome over time.

Historically some patients with Omenn syndrome may not have had an identified pathogenic SCID gene variant; however, in the current era, confirmation of genotype is required for diagnosing Omenn syndrome, with most cases having pathogenic variants in *RAG1* or *RAG2*, though additional genotypes occur (Table III).[38] This is to avoid confusion with other causes of neonatal erythroderma, including Netherton and DiGeorge syndromes.[39] Furthermore, patients with Omenn syndrome must have at least 2 other supporting features: (1) abnormal TRECs (normal numbers of TRECs exclude Omenn syndrome); (2) elevated number of eosinophils for performing laboratory tests (upper limit of normal for infants is ~0.8–1 × 10^9/L)[40]; (3) elevated IgE level for performing laboratory tests (1 reported upper limit of normal for children younger than 1 year is 34 IU/mL)[41]; (4) lymphadenopathy; (5) organomegaly (hepatomegaly and/or splenomegaly); (5) oligoclonal (restricted diversity) T cells (Table I).

The PIDTC 2014 Criteria considered proliferative responses to antigens, but these have been removed from the PIDTC 2022 Definitions due to unreliability in infants younger than age 3 months.

CONCLUSIONS

Before the development of the PIDTC 2014 Criteria, a lack of consensus regarding the diagnosis of SCID hampered multi-institutional analyses of these rare disorders. The original PIDTC criteria facilitated prospective studies to investigate factors that contribute to immune reconstitution and survival in patients with SCID.[10] The revised PIDTC 2022 SCID Definitions represent a significant enhancement and modernization of SCID definitions, incorporating collected patient data as well as NBS and improved diagnostic techniques. The distinction between typical and leaky/atypical SCID in the revised PIDTC 2022 Definitions is more precise but does not imply a specific treatment strategy. Furthermore, NBS has revealed that Omenn syndrome can develop over time from either typical or leaky SCID, highlighting previously unappreciated biological variation that demands nuance in the application of diagnostic criteria. Assessment of future patients with SCID using the revised PIDTC 2022 Definitions will continue to advance multinational collaborative studies and ultimately improve outcomes for these rare disorders.

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C. C. Dvorak is an author for UpToDate, is on the Data Safety Monitoring Board for Chiesi, and consultant for Orchard Therapeutics. E. Haddad is a consultant for Jasper, Takeda, and CSL Behring. J. Heimall is an author for UpToDate, received an investigator-initiated grant from CSL Behring, and is a consultant for ADMA, CIRM, and Horizon. D. B. Kohn is an author for UpTo Date, is on the Data Safety Monitoring Board for Chiesi, and is a consultant/Scientific Advisory Board (SAB) member for ImmunoVec. M. J. Cowan is an author for UpToDate and SAB for Homology Medicine. G. D. E. Cuvelier is a consultant for Miltenyi. A. J. Shah is a consultant for Orchard. M. A. Pulsipher reports study support from Adaptive and Miltenyi, working as an advisor for Vertex, Medexus, Equillium, Novartis, and Mesoblast, and receives educational honoraria from Novartis and Miltenyi. R. S. Abraham is an advisor for Enzyvant. L. F. Satter is a consultant for ADMA, Grifols, Takeda, Horizon, Enzyvant, and Orchard. J. M. Puck is an author for UpToDate and has a family member employed by Invitae. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used

CID	Combined immune deficiency
GvHD	Graft-versus-host-disease
HCT	Hematopoietic cell transplantation
HSC	Hematopoietic stem cell
NBS	Newborn screening
NK	Natural killer
PIDTC	Primary Immune Deficiency Treatment Consortium

SCID	Severe combined immunodeficiency
TME	Transplacentally acquired maternal engraftment
TREC	T-cell receptor excision circle

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TABLE I.

PIDTC 2022 Definitions for SCID

SCID subtype	Diagnosis requires	Criterion 1	Criterion 2	Criterion 3	Criterion 4
Typical SCID (very low autologous T cells)	Criteria 1 & 2 **OR** Criteria 1 & 3 **OR** Criterion 4	Very low T cells (<0.05 × 10^9/L) *	Pathogenic gene variant(s) †	No alternate explanation for low T-cell count ‡ **AND, EITHER:** Undetectable or low TRECs § **OR** <20% of $CD4^+$ T cells have naive cell surface markers ‖	Presence of TME ¶
Leaky/atypical SCID (low T cells)	Criteria 1 & 2 & 4 **OR** Criteria 1 & 3 & 4	Two or more of: • Low T-cell number for age (0.05–1.0 × 10^9/L) # • Oligoclonal T cells ** • Abnormal TRECs **OR** <20% of $CD4^+$ T cells are naive	Pathogenic gene variant(s)	Reduced proliferation ††	Does not have: • Other SCID subtype • CID with known genotype • Thymic disorder • Other disorder with low T-cell numbers ‡‡
Omenn syndrome	All 4 Criteria	>80% of $CD4^+$ T cells have $CD45RO^+$ memory phenotype	Pathogenic gene variant(s)	Generalized rash **AND** Absence of TME	Two or more of: • Eosinophilia (>0.8 × 10^9/L) • Elevated IgE • Abnormal TRECs • Lymphadenopathy • Hepatomegaly and/or splenomegaly • Oligoclonal T cells

* T-cell subset determination (with naive/memory phenotyping) should be repeated at least once, with the second test used as the criterion value. In patients with an identified pathogenic variant, the interval between tests must be at least 1 wk; however, in patients without an identified pathogenic gene variant, the T-cell number must remain <0.05 × 10^9/L for at least 8 wk to qualify as typical SCID due to the potential for spontaneous improvement, with a shorter interval only if urgent hematopoietic cell transplant is required before 8 wk.

† Pathogenic variant(s) identified in a gene whose product is known to be essential for T-cell development (examples in Table III).

‡ Alternate explanations for low T-cell counts include those listed in Criterion 4 of leaky/atypical SCID.

§ Number of TRECs below the normal cutoff, or cycle threshold value above the normal cutoff defined as consistent with SCID by performing laboratory.

‖ Naive T cells should be measured via CD3/CD4/CD45RA, or with additional naive markers.

[¶] Best performed by DNA analysis, such as with short tandem repeats, from whole blood or CD3-seperated cells, with any level of detection considered positive. Documented TME classifies patients as typical SCID; TME testing is strongly recommended for patients considered to possibly have leaky/atypical SCID.

[#] Low T-cell numbers for age defined as $<0.6 \times 10^9$/L (any age), $<0.8 \times 10^9$/L if aged 2–4 y, or $<1.0 \times 10^9$/L if younger than 2 y.

[**] Oligoclonal T cells as defined by laboratory performing testing, eg, <5 peaks in ≥4 T-cell receptor (TCR) Vbeta families on spectratyping, evidence of expansion of ≥2 TCR Vbeta families to >2 × the upper limit of normal for those families, or low Shannon [H] entropy index on high-throughput sequencing of TCR Vbeta variable regions.

[††] Reduced proliferation is defined as a proliferative response to PHA, anti-CD3, or anti-CD3/CD28 <50% lower limit of reference range for laboratory.

[‡‡] See Table II.

TABLE II.

Non-SCID disorders with low T-cell numbers potentially identified by TREC-based newborn screening

Disorder
Combined immunodeficiency, including single-gene and syndromic disorders of T-cell development, such as the following: • Ataxia-telangiectasia • Disorders of folate absorption or metabolism • MHC class I and II defects • Nijmegen breakage syndrome • Trisomy 21 and other chromosomal aneuploidies
Disorders of thymic stromal cell development, such as the following: • CHARGE syndrome • DiGeorge syndrome (complete or partial) • Other disorders of thymic stromal cell development (eg, pathogenic variants in genes such as *FOXN1, FOXI3, TBX1, TBX2, CHD7,* or *PAX1*)
Idiopathic T-cell lymphopenia
Secondary T-cell lymphopenia due to: • Advanced *in utero* HIV infection • Chylous effusions, spontaneous or postsurgery • Gastrointestinal or cardiac malformations • Hydrops • Maternal immunosuppressive medications • Preterm birth, very low birth weight

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TABLE III.

Genotypes and associated SCID subtypes

Genotype	Overall frequency*	SCID subtype		
		Typical SCID (69% of total)	Leaky/atypical SCID (26% of total)	Omenn syndrome (5% of total)
IL2RG†	~30%	Most common (42%)‡	Common	
RAG1	~17%	Common	Most common (26%)	Most common (79%)
ADA	~12%	Common	Common	
IL7R	~7%	Common		Very rare
DCLRE1C	~7%	Common	Rare	
JAK3	~5%	Common	Unusual	
RAG2	~4%	Unusual	Common	Common
RMRP	<4%	Very rare	Common	Possible
CD3D	<2%	Unusual	Rare	
AK2	<2%	Unusual		Very rare
PNP	<1%	Very rare	Rare	
MSN†	<1%	Very rare	Very rare	
LIG4	<1%		Rare	
NHEJ1	<1%		Rare	
BCL11B†	<1%		Very rare	
MAN2B2	<1%		Very rare	
RAC2†	<1%		Very rare	
TTC7A	<1%		Very rare	

*Of all SCIDs, including 7% without identified pathogenic variant(s). Data derived from 346 patients (diagnosed 2010–2021) from the PIDTC 6901 prospective natural history study (see accompanying article by Dvorak et al[8]). Other rare genotypes that might produce a phenotype overlapping with SCID include *CD3E*, *CD3Z*, *CORO1A*, *DIAPH1*, *DOCK2*, *EPG5*, *EXTL3*, *FCHO1*, *ICOSLG*, *IKBKB*, *ITPKB*, *LAT*, *LCK*, *LIG1*, *MYSM1*, *POLE1*, *POLE2*, *PRKDC*, *SLP76*, *SMARCAL1*, *TRAC*, and *ZAP70*.

†*IL2RG and MSN* mutations are X-linked recessive; *BCL11B* and *RAC2* are autosomal- dominant; all others are autosomal-recessive. A hemizygous pathogenic variant in a gene on the X chromosome is required for male patients. A heterozygous variant with dominant function is required for autosomal-dominant genes. Autosomal-recessive genes require 2 compound heterozygous variants or a single homozygous pathogenic variant. Abnormal adenosine deaminase or purine nucleoside phosphorylase enzyme activity is also acceptable.

‡Frequency of genotypes within a particular SCID subtype. Common genotypes are those found in >5% of cases within that subtype; unusual genotypes are those found in 2%−5% of cases; rare genotypes are those found in more than 1 patient; very rare genotypes are those seen in only a single patient; possible genotypes have been reported in the literature, but not found among PIDTC 6901 prospective natural history cases.