

EVIDENCE REVIEW: Severe Combined Immunodeficiency (SCID)

**Prepared for: ADVISORY COMMITTEE ON HERITABLE DISORDERS IN
NEWBORNS AND CHILDREN**

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i. Abbreviations used

ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children
ACTB	Gene symbol for beta-actin
ADA deficiency	Adenosine deaminase deficiency
BMT	Bone marrow transplant
B+ SCID	Subgroup of severe combined immunodeficiency in which B lymphocytes are present
B- SCID	Subgroup of severe combined immunodeficiency in which B lymphocytes are absent
CD Antigens	Cluster of differentiation, nomenclature of leucocyte molecules
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
DNA	Deoxyribonucleic acid
ELISA	Enzyme-Linked ImmunoSorbent Assay
ERG	Evidence review group
ERT	Enzyme replacement therapy
G-CSF	Granulocyte-colony stimulating factor
GVHD	Graft versus host disease
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplant
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-7	Interleukin 7
IVIG	Intravenous immunoglobulin
JAK	Janus kinase
MeSH	National Library of Medicine medical subject heading
MMRD	Mismatched related donor
MUD	Matched unrelated donor
NIAID	National Institute of Allergy and Infectious Diseases

NK	Natural killer
PEG	Polyethylene glycol
PHA	Phytohemagglutinin
RID	Related identical
SCID	Severe Combined Immunodeficiency
SCIDA	Severe Combined Immunodeficiency, Athabascan-type
TREC	T-cell receptor excision circles
USIDNET	United States Immunodeficiency Network
XSCID	X-Linked Severe Combined Immunodeficiency
γc	Common cytokine receptor γ chain

I. Overview

Severe Combined Immunodeficiency (SCID) is a group of disorders characterized by the absence of both humoral and cellular immunity. Reported incidence is approximately 1/100,000 (Chan, Puck 2005, McGhee et al. 2005). Currently at least 15 genes are known to cause SCID when mutated (Puck, SCID Newborn Screening Working Group 2007). Although disease presentation varies (Buckley et al. 1997), as protection from maternal antibodies wanes during the first months of life, infants with SCID develop infections due to both common and opportunistic pathogens (Buckley et al. 1997). Treatment and prevention of infections can prolong life but are not curative actions (Buckley et al. 1999).

Early receipt of hematopoietic stem cell transplant (HSCT), prior to the onset of severe infections, offers the best chance of cure (Buckley et al. 1999). Although family history leads to early detection of some infants, the majority of infants with SCID are not detected until they develop clinical symptoms such as recurrent infections, failure to thrive and infection with opportunistic organisms (Buckley et al. 1997). The apparent value of early HSCT has led to a search for methods for pre-symptomatic identification of infants with SCID, including possible population-based newborn screening.

II. Rationale for Review

The Advisory Committee on Heritable Disorders in Newborns and Children has directed the Evidence Review Group to produce this report for the nominated condition of SCID. SCID has been nominated for the following reasons:

1. Without treatment, SCID leads to death in early childhood.
2. Earlier treatment, particularly before the onset of lung infection, decreases the mortality and morbidity associated with SCID and with HSCT for SCID.
3. Methods to screen infants for SCID, using quantitative PCR for T-cell receptor excision circles (TREC), have been developed.

III. Objectives of review

The objective of this review is to provide information to the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) to guide recommendations regarding screening newborns for SCID. Specifically, the Evidence Review Group's (ERG) goal was to summarize the evidence available from published studies, as well as critical unpublished data available from key investigators in the field.

IV. Main questions

We sought to answer the following questions, with a particular emphasis on the questions related to screening and the benefits of early treatment.

1. What is the natural history of SCID and are there clinically important phenotypic or genotypic variations?
2. What is the prevalence of SCID and its variations?
3. What methods exist to screen newborns for SCID? How accurate are those methods? What are their sensitivity and specificity? What methods exist to diagnose individuals with positive screens?

4. What benefit does treatment, particularly pre-symptomatic, confer?
5. What are the potential harms or risks associated with screening, diagnosis or treatment?
6. What costs are associated with screening, diagnosis, treatment and the failure to diagnose in the newborn period?

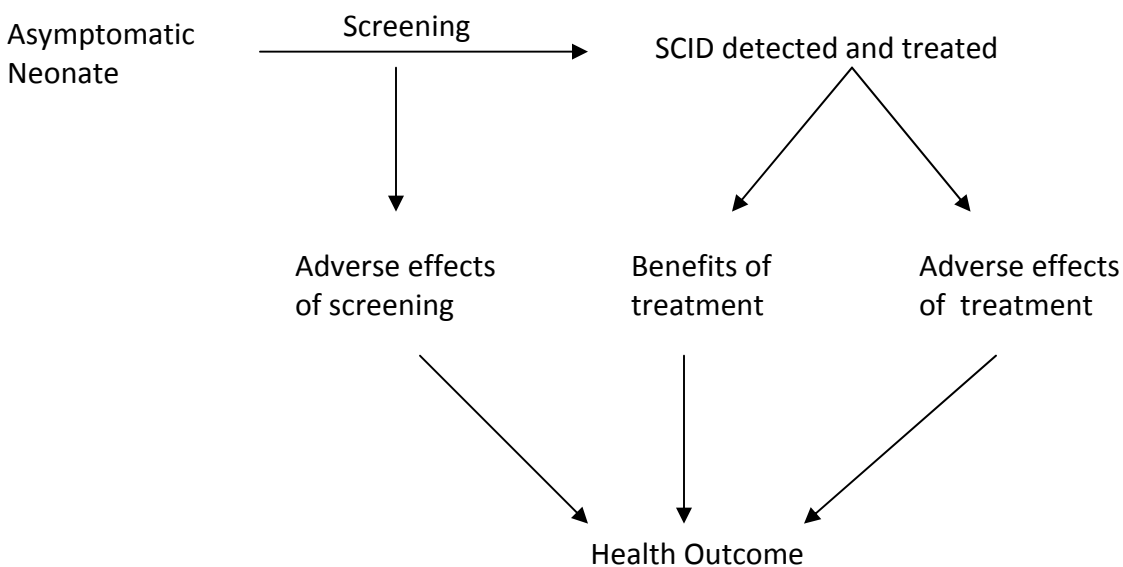
By answering these questions we hoped to provide the ACHDNC with answers to broader questions related to SCID screening. Specifically:

1. Do current screening tests effectively and efficiently identify cases of SCID?
2. Does pre-symptomatic or early symptomatic intervention in newborns or infants with SCID improve health outcomes? In other words, does early identification lead to better outcomes?
3. What is the cost-effectiveness of newborn screening for SCID?
4. What critical evidence appears lacking that may inform screening recommendations for SCID?

V. Conceptual framework

The conceptual framework illustrated below outlines the salient factors when considering newborn screening for any disorder, SCID in the case of this review. Children will develop SCID regardless of whether or not they are screened. The key decision points, therefore, are whether to screen newborns and what treatment to pursue for affected children. At either decision point, children may experience benefits from the decision but also are at risk of adverse effects, including false-positive or false-negative screening results and significant treatment side-effects. The combination of the baseline risk for SCID and the effects of the screening and treatment decisions lead to a state of health.

Figure 1- Conceptual framework.



VI. Methods

This evidence review provides information from two sources: a systematic literature review and interviews with experts in the field of SCID.

A. Systematic literature review

We searched MEDLINE for all relevant studies published over the 20 year period from January 1988 to October 2008. We completed searches combining the National Library of Medicine Medical Subject Heading (MeSH) “severe combined immunodeficiency” with each of the following MeSH terms: epidemiology, incidence, prevalence, disease progression, mass screening, neonatal screening, genetic screening, diagnosis, and therapeutics. In order to capture articles which have not yet been assigned MeSH terms, we also searched the following keywords within the OVID In-Process and Other Non-Indexed Citations database: severe combined immunodeficiency, severe immune deficiency, adenosine deaminase deficiency. We applied human studies and English language limitations to all searches. This search strategy resulted in a total of 725 articles.

All abstracts were reviewed by at least 2 readers (EL, JD, JP). Articles which were non-human data, reviews, editorials or other opinion pieces, case series of <4 patients, only contained adult subjects or did not address one or more of the key questions were eliminated. Disagreements were resolved through discussion with emphasis on inclusion of any potentially useful data. After this process 60 articles remained which were reviewed in detail.

Each article was evaluated, using standardized tools, for the quality of the study design (NHS Centre for Reviews and Dissemination, March 2001) and the quality of the evidence, as it relates to the category of evidence (Pandor et al. 2004, Pollitt et al. 1997). A given article received only one rating per reader for study design, but may have received multiple quality evaluations for the type of evidence. For example, a study that discusses prevalence and natural history would be evaluated for the quality of the evidence in each of those domains.

Data were abstracted from the articles by 2 reviewers (EL, SV). A subset of the papers, approximately 20%, was abstracted by both reviewers in order to check for agreement. There were no significant differences in the data extracted by the reviewers.

B. Interviews with experts

The ERG and the ACHDNC recognize that in a rapidly developing field, such as newborn screening for SCID, there may be crucial evidence that is either not yet ready for publication or has not been published for other reasons. As such, using our literature search and discussions with content experts, we identified a list of key investigators. This list was discussed among the members of the ERG, and additional names were added based on personal knowledge of the field by members of the ERG. This list (Table 1) was approved by the ERG and the experts were contacted via e-mail. Reminder e-mails were sent to non-responders approximately 2 weeks after the initial e-mail.

Experts were sent a letter (appendix C) explaining the purpose of the review, a conflict of interest form (appendix B) and an open-ended survey (appendix C). After receipt of the conflict of interest form and survey, phone interviews were scheduled between experts and members of

the ERG (EL, AK, JP), when clarification of the written survey was needed. The semi-structured phone interviews clarified information provided in the written survey. Information from the surveys and interviews is explicitly provided in this report when such information was not available in the published literature.

Table 1- List of experts contacted and degree of participation

Name	Title	Completed written survey	Telephone interview
Mei Baker	Assistant Professor, Department of Pediatrics, School of Medicine and Public Health, Science Advisor, Newborn Screening Program, Wisconsin State Laboratory of Hygiene, University of Wisconsin-Madison	✓	✓
Barbara Ballard	The SCID Family Network	✓	
Tony (Francisco) Bonilla	Program Director, Clinical Immunology Assistant in Medicine, Assistant Professor, Harvard Medical School and Children's Hospital, Boston, Massachusetts	✓*	
Marcia Boyle	President and Founder, Immune Deficiency Foundation	✓	
Rebecca Buckley	Professor of Pediatrics, Professor of Immunology, Duke University Medical Center, Durham, North Carolina	✓	✓
Anne Comeau	Deputy Director New England Newborn Screening Program University of Massachusetts Medical School	✓	✓
Lisa Filipovich	Medical Director, Hematology/Oncology Diagnostic Laboratory, Division of Hematology/ Oncology, Cincinnati Children's Hospital Medical Center, Ohio		
Alain Fischer	Professor of Pediatric Immunology and Head of the Pediatric Immunology Department and the INSERM Research Unit		
Alan P. Knutsen	Professor of Pediatrics, Allergy and Immunology, Director of Pediatric Clinical Immunology Laboratory, Department of Pathology, St Louis University Health Sciences Center		
Ronald Laessig	Professor of Population Health Sciences and Pathology at University of Wisconsin		✓ [^]
Edward McCabe	Clinical Biochemical Genetics, Clinical Genetics, Professor and Executive Chair of the UCLA Department of Pediatrics, and Physician-in-Chief of the Mattel Children's Hospital at UCLA, Los Angeles, California	✓**	

Sean McGhee	Assistant Clinical Professor of Pediatrics. Division of Pediatric Immunology, Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, California	✓	
Vicki Modell	Co-founder, Jeffrey Modell Foundation	✓	
Luigi Notarangelo	Professor of Pediatrics and Pathology, Harvard Medical School Director, Research and Molecular Diagnosis Program on Primary Immunodeficiencies, Division of Immunology, Children's Hospital Boston, Massachusetts	✓*	✓
Hans Ochs	Professor of Pediatrics and Immunology at the University of Washington, Seattle, Washington		
Sung-Yun Pai	Assistant Professor in Pediatrics, Pediatric Hematology/Oncology, Harvard Medical School and Children's Hospital, Boston, Massachusetts	✓*	
Ken Pass	Senior Research Scientist, Molecular Medicine, Wadsworth Center, New York State Department of Health, Albany, New York	✓	
Jennifer Puck	Professor, Department of Pediatrics and Institute for Human Genetics University of California, San Francisco	✓	✓
Robert Vogt	Centers for Disease Control and Prevention, Newborn Screening Quality Assurance Program, Atlanta, Georgia	✓	

*Responded as a group with one combined survey

**Dr. McCabe declined to answer and referred us to Dr. McGhee

^ Interviewed in conjunction with Dr. Baker

VII. Results

Case definition: For the purpose of this review, Severe Combined Immunodeficiency is defined based on the definition for the PubMed medical subheading. SCID is a “group of rare congenital disorders characterized by impairment of both humoral and cell-mediated immunity, leukopenia, and low or absent antibody levels. It is inherited as an X-linked or autosomal recessive defect.” (U.S. National Library of Medicine and the National Institutes of Health, 2008) Children with SCID universally have extremely low or absent T-cells and may or may not have B-cells. We have included some specific sub-types such as adenosine deaminase deficiency (ADA deficiency), reticular dysgenesis and Omenn syndrome in the definition of SCID because they are characterized by absence of T-cells, but we recognize that some groups consider these disorders distinct from SCID (WHO Scientific Group, 1995).

Table 2- Study design for abstracted articles

Study design	Number of papers
Experimental intervention	0
Cohort study	10
Case-control study	8
Case series total	39
Sample size \leq 10	11
Sample size 11 to 50	18
Sample size \geq 51	10
Economic evaluation	1
Other design	2*
Total	60

*Epidemiologic studies using retrospective record review (Jones et al. 1991) and telephone survey (Boyle & Buckley, 2007)

Evidence review: The remainder of this section of the report is dedicated to presentation of the evidence. Data are organized by key questions. A table indicating the quality of the evidence for that key question leads the section, followed by data from the systematic literature review. Finally, any additional information learned from surveying experts is provided at the end of each section.

A. What is the natural history of SCID and are there clinically important phenotypic or genotypic variations?

Table 3- Quality assessment of abstracted literature pertaining to natural history

Genotype/Phenotype correlation	12
Data from retrospective screening studies in U.S. or similar population.	0
Data from systematic studies other than whole population screening.	5
Estimated from the known clinical features of the condition as described for individual cases or short series.	7
Incidence (cases per 100,000), average within the U.S.	4
Data obtained from whole-population screening or comprehensive national surveys of clinically detected cases.	1
Ia. As in I but more limited in geographical coverage or methodology.	2
Extrapolated from class I data for non-U.S. populations.	0
Estimated from number of cases clinically diagnosed in U.S.	1

Adapted from Pandor et al. 2004, Pollitt et al. 1997

The term SCID refers to a group of slightly heterogeneous disorders which are all related by the absence of T-cells in affected individuals. Some subtypes are missing other lymphocyte subsets, such as B-cells or NK-cells, and others have associated non-immune manifestations such as neurocognitive deficits, hearing loss and skeletal abnormalities.

We describe below evidence related to the characteristic presentations of SCID, the natural history (without treatment), subtypes of SCID, and genotype/phenotype data. The main findings are: 1) with the exception of children diagnosed early in life, typically through prenatal testing initiated because of family history, most children are diagnosed after recurrent pulmonary infections or infections with opportunistic organisms; 2) this is true of all SCID subtypes, although the exact timing may vary; and 3) without treatment of the underlying immunodeficiency, children with SCID die in early childhood from infection.

General findings regarding natural history and associated clinical conditions -Systematic literature review

Several studies provide descriptive data regarding symptomatic presentation of children with SCID, almost all of which highlight pulmonary and opportunistic infections, leading to early childhood death, as the key complications of untreated SCID.

A chart review (Deerojanawong et al. 1997) found that all children who did not receive prenatal diagnoses of SCID (13/15) had pulmonary symptoms at presentation. Of 9 that died, 5 were due to pulmonary disease. Moreover, pulmonary infections, most commonly *Pneumocystis jirovecii* pneumonia (PJP), were the most common presenting sign of SCID, occurring in 10/15 children, at a median age of 4 months. Another case series (Stocks et al. 1999) found 14/18 of the children, over a 20-year time period, had otolaryngological signs or symptoms (including congestion, URI, thrush, oral ulcers, cervical adenopathy, otitis media; mastoiditis) prior to diagnosis with SCID.

An institutional case series (Stephan et al. 1993) of 117 patients treated for SCID between 1970 and 1992, found the median age at diagnosis, which did not change over the time period, was 4.6 months with an average of 2 months delay between clinical manifestations and diagnosis. The primary clinical manifestations included oral candida, skin erythema, diarrhea with growth impairment and interstitial pneumonitis.

Hague et al. (Hague et al. 1994) found that, among 32 children with no family history of SCID, the median age of diagnosis was 7 months, despite the median age of symptom onset being 5 weeks. In this group the median age of first hospital admission was 4 months with 22/32 presenting with respiratory infection, 9/32 with vomiting and diarrhea, 8/32 with candidal infection and 6/32 with failure to thrive.

Two papers discussed physical signs or symptoms that may occur with high prevalence in children with SCID but are not necessarily presenting signs of the disease, including gastroesophageal reflux (GER) (Boeck, Buckley & Schiff 1997) and rashes, particularly due to engraftment of maternal T-lymphocytes (Denianke et al. 2001).

Table 4 - Evaluated literature pertaining to natural history of SCID (alphabetical by author)

Study (Author, Date)	Population: Size and age by subgroups	Study type	Key findings
Bertrand et al. 1999	178 children total; B+ group: 122, mean age at BMT was 7 months B- group: 56, mean age at BMT was 6.5 months.	Cohort study	<ul style="list-style-type: none"> • B+ SCID has better prognosis than B- SCID following non-identical BMT. • Rate of engraftment not different between groups. • B- SCID had higher rates of both early and late death. • Deaths in both groups due primarily to infection.
Bertrand et al. 2002	10 children total; BMT at age 0.5 to 10 months.	Case series	<ul style="list-style-type: none"> • All children had reticular dysgenesis. • All presented with infection in first days of life. • HLA-non-identical HSCT resulted in three of the 10 patients surviving. • Deaths due primarily to graft failure.
Buckley et al. 1997	108 children total; Diagnosed at age birth to 21 months.	Case series	<ul style="list-style-type: none"> • Mean age at diagnosis of SCID was 201 days (6.59 months) and did not differ significantly among different genetic types. • 67 (76%) of the 88 families were white, 14 (16%) were black, and 7 (8%) Hispanic. • Abnormal serum immunoglobulin concentrations existed in all types of SCID. • Mean IgA levels were lowest in γc-deficient, Jak3-deficient and unknown types of SCID. • Mean IgM concentrations were lowest in ADA, γc-deficient and Jak3-deficient patients. • IgE was normal in all but 2 patients.
Buckley et al. 1999	89 children total; 22 less than 3.5 months old at transplant, 67 greater than or equal to 3.5 months at transplant.	Case series	<ul style="list-style-type: none"> • 72 (81%) alive 3 months-16.5 years post-transplant, with a median follow up of 5.6 years. • 65 survived greater than 1 year, 38 greater than 5 years and 21 greater than 10 years. • All 12 HLA-identical recipients survived. • Mean number of T/B/NK-cells varies by genotype; all genotypes had normal average in vitro mitogen response after transplant. • Poor B-cell function, with 45 kids requiring IVIG. • NK-cell activity low in γc-chain deficiency and JAK3 deficiency, normal in other SCID subtypes.

Cavazzana-Calvo et al. 2007	31 children total; 1-42 months old at HSCT, now 10-27 years later.	Case series	<ul style="list-style-type: none"> • Myeloablation patients more likely to have evidence of donor-derived granulocytes and persistent naïve T-cells, as measured by TREC. • At follow-up, 60% of TREC+ and 45% of TREC- had no clinical manifestations. • Average follow-up time in the TREC+ group was 13 years and in the TREC- was 16 years.
Gomez et al. 1995	9 children total; 0.5-5 months old (mean 2.8) with BMT for Omenn Syndrome between 1981 and 1989.	Case series	<ul style="list-style-type: none"> • Engraftment occurred in 4/5 HLA-identical transplants and 3/4 non-identical transplants. • Full chimerism occurred in all but one of the patients that engrafted. • Clinical manifestations of Omenn syndrome disappeared within days of BMT (likely due to pre-treatment with chemotherapy). • One patient died of CMV 50 days post-transplant, 3 developed interstitial pneumonia. • All survivors except one (who has chronic GVHD) have normal growth rates.
Laffort et al. 2004	41 patients total; at least 10 years after HSCT for SCID.	Case-control study	<ul style="list-style-type: none"> • 9/41 developed extensive chronic human papilloma virus. • 4 had lesions typical of a rare genodermatosis. • All with human papilloma virus had γc/Adenylate kinase- 3 (AK-3) deficiency, though only 9/18 with γc/JAK3 developed human papilloma virus.
Monafo et al. 1992	4 children total (2 sets of siblings); age 20 months, 4 months, 11 months, 24 months at the time of BMT.	Case series	<ul style="list-style-type: none"> • Presenting clinical signs of SCID included diarrhea, poor weight gain, oral ulcers, and PJP pneumonia but normal lymphocyte counts. • One child did not present until 1 year of age, with a previously undescribed phenotype. • CD8 cells were virtually absent and mononuclear cells did not proliferate normally in vitro.
O'Marcaigh et al. 2001	18 children total; Birth to 3 months of age at diagnosis; mean age of 17.5 months at first transplant.	Case series	<ul style="list-style-type: none"> • 12/18 developed oral/genital ulcers associated with SCIDA. • 16/18 children were well enough for transplant. • 15/16 achieved engraftment. • 11/16 developed normal T-cell function.

Roberts et al. 2004	170 total patients; 10 with JAK3 deficiency and 160 with other types of SCID.	Case series	<ul style="list-style-type: none"> • All patients had abnormal B-cell JAK3 dependent interleukin-2 induced signal transducer and activator of transcription 5 (STAT5) phosphorylation. • 9/10 patients with JAK3 deficiency were alive and well 4 to 18 years after stem cell transplant.
Rogers et al. 2001	22 children total; 1-51 months old at HSCT; 0.9-18 years old at follow-up; 11 children with ADA deficiency, 11 other SCID types.	Cohort study	<ul style="list-style-type: none"> • No significant difference in full-scale IQ between groups; children with ADA deficiency 2 standard deviations below mean. • Significant behavioral differences in children with ADA deficiency: more hyperactivity, higher scores for dysfunction in social, emotional and behavioral domains. • Abnormal behavior more evident in older children. • Children with ADA deficiency group with no abnormal motor function on gross neurological evaluation.

Genotype specific findings –Systematic literature review

Although as many as 15 different genes (Puck, SCID Newborn Screening Working Group 2007) are associated with SCID, the known phenotypic variation is less extensive. There is some phenotypic variation, as outlined below, in immunoglobulin levels, lymphocyte counts and lymphocyte function. More striking, however, a few phenotypes appear to have distinct characteristics at presentation. Specifically we found evidence supporting very early infections in children with reticular dysgenesis (Bertrand et al. 2002), neurologic symptoms in children with ADA deficiency (Stephan et al. 1993, Honig et al. 2007), and oral/genital ulcers associated with a distinct form of SCID known as SCIDA occurring among Athabaskan-speaking Native Americans (O'Marcaigh et al. 2001).

A case series (Buckley et al. 1997) of 108 infants examined the relationship between genotype and immune functional status. These patients ranged from birth to 21 months at diagnosis and children with less severe forms of combined immunodeficiency, such as Omenn syndrome, were excluded. The distribution of genotypes from this series is shown in table 5.

Table 5- Relative frequencies of different SCID genotypes from Buckley et al. 1997

Genotype	SCID Infants* (n=108)		SCID families* (n=88)	
	Number	Percent	Number	Percent
γ c deficiency	49	45.4	37	42
ADA deficiency	16	14.8	13	15
Jak3 deficiency	8	7.4	5	6
Autosomal Recessive (not ADA or Jak3 deficiency)	21	19.4	19	22
Reticular Dysgenesis	1	0.9	1	<1
Cartilage-hair hypoplasia	1	0.9	1	<1
Unknown	12	11.1	12	14

*table depicts genotype according to the 108 individual patients in the first column, and the 88 families of origin in the second column where siblings count as one unit

The authors found abnormal serum immunoglobulin concentrations in all types of SCID. Mean IgA levels were lowest in γ c-deficient, Jak3-deficient and unknown types of SCID. Mean IgM concentrations were lowest in ADA, γ c and Jak3 deficient patients. IgE was normal in all but 2 patients.

Lymphopenia was present in all categories of SCID but more severe in patients with ADA deficiency. 5 infants had elevated lymphocytes, of which 4 were due to the presence of maternal cells. Lymphocyte subpopulations varied between types of SCID. ADA-deficient children had the lowest mean number of B-cells and γ c and Jak3 the highest. Mean number of NK-cells was lowest in ADA, γ c, and Jak3 deficient patients. Lymphocyte response to mitogens was diminished in all patients.

B. What is the prevalence of SCID and its variations?

Most methods of determining the prevalence and incidence of a disorder depend on case ascertainment. As in other disorders with high risk of early death, the incidence of SCID may be higher than measured via case ascertainment because some patients may die prior to having a definitive diagnosis.

Incidence and Prevalence-Systematic literature review

In a study with a primary focus on SCID screening methods, Chan and Puck (Chan, Puck 2005) estimated the annual incidence as a minimum of 1/105,000 live births. This calculation was based on assuming an annual US birthrate of 4,000,000 that all children with XSCID in the U.S. had blood samples sent to the authors' laboratory for mutation detection (19 in one year) and that XSCID represents approximately half of all cases of SCID. A study (Stephan et al. 1993) of French children with SCID estimated a minimum incidence of 1/100,000 live births. This estimate is based on the number of French children referred to specialized units over a 5 year time period.

Some US populations, namely the Navajo, have a higher prevalence of SCID because of a founder mutation in the Artemis gene. The death records (Jones et al. 1991) of all Native American children in Arizona who died between 1969 and 1978 and Navajo children who died

between 1969 and 1982 in Arizona and New Mexico were reviewed. Subsequently the authors reviewed the hospital records of children who died from SCID, had signs of immunodeficiency or failure to thrive at the time of death or had unknown cause of death. They used this information to determine who may have had SCID. Based on this chart review the estimated prevalence of SCID is 52/100,000 live Navajo births.

Information from expert interviews

Dr. Buckley stated that in one year in North Carolina (where the birth rate is approximately 120,000/annually) there were 3 cases of SCID, for an incidence of 1/40,000. However, multi-year data confirming this incidence are not available.

Drs. Buckley and Notarangelo provided the distribution of genotypes among the SCID patients for which they have personally cared. Additionally, Drs. Pai, Bonilla, and Notarangelo provided subtype distribution information from both European and United States immunodeficiency collaboratives. These data corroborated the data from the published literature portion of this evidence review.

C. What methods exist to screen newborns for SCID? How accurate are those methods? What are their sensitivity and specificity? What methods exist to diagnose individuals with positive screens?

Table 6- Quality assessment of abstracted literature pertaining to screening test characteristics

Overall sensitivity and specificity of screening & false-positive rate	3
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than from whole population screening.	3
Estimated from the known biochemistry of the condition.	0
Repeat specimen rate	0
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than whole population screening.	0
Estimated from the known biochemistry of the condition.	0
Second-tier testing	1
Data obtained from screening programs in US population or similar.	0
Data from systematic studies other than whole population screening.	1
Estimated from the known biochemistry of the condition.	0

Adapted from Pandor et al. 2004, Pollitt et al. 1997

At least three different methods of screening for SCID have been proposed including 1) lymphocyte counts of whole blood, 2) quantitative polymerase chain reaction (qPCR), and 3) enzyme linked immunosorbent assay (ELISA) of dried blood spots. This section will review the evidence regarding screening. None of the proposed screening methods distinguish the various SCID genotypes and phenotypes.

Table 7- Evaluated literature pertaining to SCID screening studies (alphabetical by author)

Study (Author, Date)	Population	Screening method	Sens, spec, PPV, NPV	Type of Evidence
Chan, Puck 2005	23 children with SCID, 2 children with non-SCID immunodeficiencies. 242 anonymized newborn screening cards.	<ul style="list-style-type: none"> • Used DNA amplification of TREC from dried blood spot. • Among the children known to have SCID, none had detectable levels of TREC and all had detectable β-actin. • The 2 children with non-SCID immunodeficiency had detectable TREC. • Had several presumed false-positives in which beta-actin could be amplified but TREC could not. • Estimated incidence of SCID to be 1/105,000 births, excluding patients who die before their immunodeficiency is recognized. 	<p>*False positive rate: 1.5% from routine nurseries; 5% from special-care nurseries. ^Sensitivity: 84%-100% ^Specificity: 97-97.1%</p>	Overall sensitivity and specificity of screening & false-positive rate
Hague et al. 1994	135 total children, 45 children with SCID, 90 children without SCID.	<ul style="list-style-type: none"> • Used first available lymphocyte count. • SCID children matched to asymptomatic children by age and to children with same presenting symptoms by age. • Children with SCID had significantly lower levels of lymphocytes. • Unlike the 5 control children with low lymphocyte count, low lymphocyte count persisted in children with SCID. 	<p>*False-positive rate: 8% ^Sensitivity: 86.3%, and ^Specificity: 94.4%</p>	Overall sensitivity and specificity of screening & false-positive rate

Hennewig et al. 2007	36 children with rotavirus gastroenteritis; 18 with SCID, 18 without SCID.	<ul style="list-style-type: none"> • Lymphocyte study. • SCID children were more likely to have: <ul style="list-style-type: none"> • Low white blood cell count: 10/18 vs. 0/18, • Eosinophilia: 12/18 vs. 0/18 • Relative lymphopenia: 17/18 vs. 10/18 • Absolute lymphopenia: 16/18 vs. 4/18 	^Sensitivity: 55.6% to 94.4% ^Specificity: 44.4% to 100%.	Second-tier testing
McGhee et al. 2005	13 children with SCID, 183 anonymized dried blood spots, presumed to be from children without SCID.	<ul style="list-style-type: none"> • Dried blood spot study. • A 2-tiered screening approach in which IL-7 is first measured and only those with elevated IL-7 would have TREC measured, although for this study researchers evaluated each test separately. • Of the 183 presumed normal children tested for TREC, 14 were undetectable. • Of the 3 SCID children tested for TREC, all were undetectable. 	*Combined specificity of 100% (confidence interval, 97-100%) *Combined sensitivity of at least 85%	Overall sensitivity and specificity of screening & false-positive rate

**Calculation stated in article*

^Our calculation using data provided in article

Systematic literature review

Lymphocyte studies: A case-control study (Hague et al. 1994) matched children who were both pre- and post-symptomatically diagnosed with SCID to either asymptomatic children (presenting for surgery or bilirubin screening) or children matched by age and presenting symptoms, in order to compare the earliest available lymphocyte counts. Children with SCID had significantly lower levels of lymphocytes. Also, unlike in the 5 control children with low lymphocyte counts, in SCID children the low lymphocyte count persisted. The authors calculated a false-positive rate of 8%, positive predictive value of 86% and negative predictive value of 100% among symptomatic children, and a positive and negative predictive value of 93% for all children. As part of the evidence review, we used all data contained within this article to calculate the sensitivity, 86.3%, and specificity, 94.4%, of “first lymphocyte count” using a cut-off of $2.8 \times 10^9/l$ as indicating SCID.

A cohort study (Hennewig et al. 2007) that included 36 children (18 with and 18 without SCID) with rotavirus gastroenteritis, also investigated white blood cell count as a screening tool for SCID. The researchers found that most of the children with SCID were younger than controls

when rotavirus was diagnosed. They also were more likely to have a low white blood cell count (10/18 vs. 0/18), eosinophilia (12/18 vs. 0/18) and relative lymphopenia (17/18 vs. 10/18) and absolute lymphopenia (16/18 vs. 4/18). From these numbers we calculated sensitivities from 55.6% to 94.4% and specificities from 44.4% to 100%.

DBS studies: Two studies published in 2005 evaluated screening methods that utilize dried blood spots. The first (McGhee et al. 2005) evaluated a 2-tiered screening approach in which IL-7 is first measured (Table 8A) and only those with elevated IL-7 would have TREC measured (Table 8B). For the study the researchers evaluated each test separately, rather than using a tiered approach. The investigators tested samples from 13 children with SCID (either dried blood spots [3] collected in immunology clinic or stored serum [10]) and 183 anonymized dried blood spots, presumed to be from children without SCID. They evaluated the levels of T-cell receptor excision circles (TREC) in both groups. However, TREC analysis cannot be done on serum, limiting that portion of the analysis to dried blood spot specimens.

Table 8A- Tier 1: Elevated IL-7 from McGhee et al. 2005

	Yes	No	Total
SCID	11	2	13
Control	4	110	114
Total	15	112	127

Authors calculated a specificity of 96.1% for IL-7 and a sensitivity of 85% (confidence interval, 55-98%).

Table 8B- Tier 2: Detectable TREC from McGhee et al. 2005

	Yes	No	Total
SCID	0	3	3
Control	169	14	183
Total	169	17	186

Authors calculated a specificity of 92.3% for TREC and a sensitivity that “approaches 100%.”

They evaluated the sensitivity and specificity of the proposed 2-tiered approach calculating a combined specificity of 100% (confidence interval, 97-100%) and combined sensitivity of at least 85%.

Among their sample of SCID patients was one child with Omenn syndrome, which is known to have detectable T-cells, and another patient with T-B- SCID of unknown cause that could theoretically have affected the IL-7 system. This high proportion of “unusual types” of SCID led the authors to suggest that the actual sensitivity of IL-7 may be higher than shown in this study.

In the second study (Chan, Puck 2005) investigating screening for SCID using dried blood spots, the sample included 23 children with SCID, 2 children with non-SCID immunodeficiencies, 242 anonymized newborn screening cards.

The researchers used DNA amplification as the screening method in which β -actin served as a control, indicating that DNA could be amplified from a given specimen, i.e., that the specimen was satisfactory for analysis; and TREC amplification served as the screening test.

Among the children known to have SCID, none had detectable levels of TREC and all had detectable β -actin. The 2 children with non-SCID immunodeficiency had detectable TREC.

The researchers assumed that the anonymized newborn screening cards came from children without SCID. In this group there were 7 (2 from routine nursery, 5 from special-care nursery) cards from which TREC could not be detected. Cards with detectable β -actin but not TREC were presumed to be false-positive. They calculated a false-positive rate of 1.5% among children discharged from routine nurseries and 5% among children discharged from special-care nurseries.

We combined the results from this study, except the cards from which β -actin could not be amplified, and calculated a sensitivity of 84% and specificity of 97.1% for undetectable TREC and sensitivity of 100% and specificity of 97% for TREC <30.

Additional data from expert interviews regarding screening:

Wisconsin implemented universal newborn screening for SCID on January 1, 2008. Their protocol involves TREC quantification. For samples with TREC <25/ μ l they repeat the testing in duplicate, using two new punches from the same newborn screening sample collection card, and also assess for β -actin. Approximately 1.5% of samples require a second test, and approximately 0.2% require a second newborn screen or confirmatory testing. The table below was provided by Dr. Baker as a summary of their screening reports.

Table 9- Summary of screening categories for Wisconsin’s newborn screening for SCID

Reporting Type	Situation	Action Plan
Normal	1. TRECs \geq 25 / ul in the first tier test	None
	2. TRECs \geq 25 / ul in one or both duplicates of the second tier test	None
Abnormal	TRECs < 25 / ul and ACTB > 10,000 / ul in full term babies	1. Phone Primary Care Provider and clinical consultant 2. Recommend confirmatory testing
	TRECs < 25 / ul and ACTB > 10,000 / ul in premature infants	1. Phone Primary Care Provider 2. Tracking second NBS*
Inconclusive	TRECs < 25 / ul and ACTB < 10,000 / ul in full term babies	Recommend repeating NBS
	TRECs < 25 / ul and ACTB < 10,000 / ul in premature infants	Tracking second NBS*

* The second and third NBS in premature infants is a standard practice in the Wisconsin newborn screening program, and no additional sample is requested for the SCID screening test.

As of December 31, 2008, Wisconsin had screened nearly 70,400 babies, of which 118 babies had inconclusive screens and 232 had abnormal screens (Table 10 and Table 11). To date, they have not identified any children with SCID.

Table 10- SCID screening results (Courtesy of Dr. Mei Baker, presented at the Newborn Screening Symposium, November, 2008; updated January, 2009)

• Number Screened:	70,397 (01/01/2008-12/31/2008)
o Premature (<37 weeks)	6487
o Full term	63910
• Abnormal Results:	32 (0.045%)
o Premature (<37 weeks)	20 (0.308%)
o Full term	12 (0.019%)
• Inconclusive Results	118 (0.168%)
o Premature (<37 weeks)	97 (1.50%)
o Full term	21 (0.033%)

Table 11- SCID screening confirmation results (Courtesy of Dr. Mei Baker, presented at the Newborn Screening Symposium, November, 2008; updated January, 2009)

Abnormal Results:	Inconclusive Results:
<p>-Full Term</p> <ul style="list-style-type: none"> 1 DiGeorge Syndrome 1 Downs Syndrome with sepsis at birth 1 Idiopathic T-cell lymphopenia 1 Neutrophil migration defect with RAC2 mutation 2 normal Flow Cytometry results 4 normal results on repeated newborn screening 1 pending case 1 expired case <p>-Premature</p> <ul style="list-style-type: none"> 1 DiGeorge Syndrome (36 weeks) 1 chylous effusions (chylothorax and chylous ascites) 3 normal Flow Cytometry results 9 normal results on repeated newborn screening 4 pending cases 2 expired cases 	<p>-Full Term</p> <ul style="list-style-type: none"> 1 Abnormal results on repeated NBS and abnormal Flow Cytometry (Idiopathic T-cell lymphopenia) 17 normal results on repeated newborn screening 1 pending cases 2 expired cases <p>-Premature</p> <ul style="list-style-type: none"> 1 DiGeorge Syndrome (36 weeks) 1 Abnormal results on repeated NBS and abnormal Flow Cytometry (gastrochisis) 72 normal results on repeated newborn screening 2 pending cases 21 expired cases

Two other investigators have definitive plans for newborn screening trials. In February 2009, Dr. Comeau and colleagues at the New England Newborn Screening Laboratory began a trial of

universal newborn screening for SCID in Massachusetts, with a small pilot program planned in Texas and potential extension to other New England states. Similarly, Dr. Puck will soon begin a screening trial at 2 hospitals on Navajo reservations in New Mexico and Arizona, a site chosen because of the high frequency of SCID in the Navajo population.

All three of these trials use PCR to detect both TREC and DNA from a housekeeping gene as the screening test and control, respectively. However, there are minor variations in the specific methodology currently in practice or planned for each trial. These include variations in specific primers and extraction methods used, as well as the degree of automation.

Additionally, correspondence with topic experts indicated other screening techniques currently under consideration or evaluation. Dr. Pass indicated that work is underway to develop a T-cell immunoassay that could target key T-cell antigens and serve as a quantitative assay. However, this technique is still under development and has not yet, to our knowledge, been validated. Dr. Comeau indicated that her laboratory has developed a multiplex assay that ensures integral quality assurance; TRECs and RNaseP from the same aliquot of blood are measured in the same reaction. Furthermore, the assay is amenable to measuring other markers such as key T-cell antigens and development of multi-analyte profiles for SCID. Proof of principle for the multianalyte assay has been demonstrated; specific non-DNA markers are still in development.

Feasibility/acceptability of screening

We found no articles for inclusion in this review that evaluated the feasibility or acceptability of screening for SCID.

Diagnostic testing

Review of the literature found no evidence that describes any specific diagnostic testing protocol for SCID. We suspect this reflects the time-frame used in the literature search and that diagnostic testing protocols were established prior to 1988.

Articles that make reference to diagnostic testing and the experts with whom we spoke all utilize flow cytometry, which allows for the differentiation and quantification of the various sub-types of white blood cells. As mentioned in conversation with Dr. Puck, the presence of maternal T-cells can confound standard flow cytometry results. However, further testing for T-cell response to mitogens allows for differentiation between the mother's cells, which do not respond to mitogens in vitro, and the child's cells.

Additionally, several researchers (Vogt, Puck, Buckley, Notarangelo, Pai and Bonilla) commented on gene sequencing. The current expert opinion seems to be that knowing the specific genotype, with the exception of ADA deficiency, has little clinical significance or implications for treatment. However, the possibility exists that better knowledge of how children with different genotypes respond to treatment may help tailor future treatment.

D. What benefit does treatment, particularly pre-symptomatic, confer?

Numerous studies document that treatment, mainly bone marrow transplant, substantially improves survival. We describe below the evidence regarding the key debates surrounding

forms of treatment and their relative efficacy. We also provide some focus on the evidence regarding early versus later treatment effects.

Table 12- Quality assessment of abstracted literature pertaining to effectiveness of treatment

Effectiveness of treatment	47
I. Well-designed RCTs.	0
II-1. Well-designed controlled trials with pseudorandomization or no randomization.	0
II-2. Well-designed cohort studies:	8
A. prospective with concurrent controls	0
B. prospective with historical control	1
C. retrospective with concurrent controls.	7
II-3. Well-designed case-control (retrospective) studies.	0
III. Large differences from comparisons between times and/or places with and without intervention	4
IV. Opinions of respected authorities based on clinical experience, descriptive studies and reports of expert committees.	35

Adapted from Pandor et al. 2004, Pollitt et al. 1997

Over the last twenty years, three modes of treatment for SCID have been investigated: allogeneic hematopoietic stem cell transplant (HSCT), the most common subtype being bone marrow transplant (BMT), enzyme replacement therapy (ERT), and gene therapy. While HSCT is the most common treatment for SCID patients, ERT may be used for some patients with ADA deficiency. Lastly, small trials of gene therapy for SCID have been conducted. This section describes the evidence for each method of treatment.

Hematopoietic stem cell transplant-Systematic literature review

HSCT has been utilized as a treatment for SCID since its initial patient application in 1968 (Buckley et al. 1999). Since then, many researchers have investigated the efficacy, outcomes for different methods, and the long-term outcomes associated with HSCT. This evidence review focuses on answering the questions pertaining to the benefit of treatment: overall efficacy, efficacy early in life, efficacy for different genotypes and phenotypes of SCID, efficacy based on transplant method, and long-term follow-up including survival and immune reconstitution.

HSCT in the neonatal period and/or infancy

We found 2 studies that specifically addressed HSCT in the neonatal period. The first was a cohort study (Myers et al. 2002) and the other was a case series (Kane et al. 2001). In addition, Buckley et al. (Buckley et al. 1999) evaluated a group of patients receiving transplants within the first 3.5 months of life and a large case series from Europe (Antoine et al. 2003) distinguished children by age at transplant

Table 13- Abstracted literature pertaining to HSCT in the neonatal period and/or infancy (alphabetical by author)

Study (Author, Date)	Population	Key Findings	Quality of Evidence
Antoine et al. 2003 [^] Case series	475 patients (total of 566 transplants); 202 less than 6 months old at transplant, 184 between 6-11 months of age at transplant, from 37 European centers between 1968 and 1999.	<ul style="list-style-type: none"> • Children transplanted at less than 6 months of age had better 3-year survival rates than older cohorts. • Three-year survival with sustained engraftment was 77% for HLA-identical and 54% for HLA-non-identical transplants. • Survival has improved over time for both HLA-identical and HLA-non-identical transplant recipients. • Myeloablation prior to HLA-non-identical transplant trended towards improving survival among B- children but not B+ children. • ADA deficiency (n=51) 3-yr-survival was 81% for matched and 29% for unmatched transplants. • Reticular dysgenesis survival (n=12) was 75% for matched and 29% for unmatched transplants. 	II-2 C
Buckley et al. 1999* Case series	89 children total; 22 less than 3.5 months old at transplant, 67 greater than or equal to 3.5 months at transplant.	<ul style="list-style-type: none"> • 72 (81%) alive 3 months-16.5 years post-transplant, with a median follow up of 5.6 years. • 65 survived greater than 1 year, 38 greater than 5 years and 21 greater than 10 years. • All 12 HLA-identical recipients survived. • Mean number of T/B/NK-cells varies by genotype; all genotypes had normal average in vitro mitogen response after transplant. • Poor B-cell function with 45 kids requiring IVIG. • NK-cell activity low in γc-chain deficiency and JAK3 deficiency, normal in other SCID subtypes. 	IV
Kane et al. 2001 Case series	13 children total; transplanted between 7 and 68 days old.	<ul style="list-style-type: none"> • All patients alive and well 0.5-11.5 years after transplant (median 3 years). • 2 children developed chronic GVHD chronic. • 3 children required more than one transplant. • All children achieved neutrophil engraftment and normal levels of IgA. • 7 have normal IgG. • 12 have normal IgM. • 10/12 have normal neuro-development; 1/12 has trouble with communication and interactive skills, and 1/12 has motor delay. 	IV

Myers et al. 2002* Cohort study	21 children total; transplanted prior to 28 days of life (early treatment) and 96 children transplanted at a median age of 190 days (range: of 45-516 days) (late treatment).	<ul style="list-style-type: none"> • 20/21 (95%) early treatment children survived. • 71/96 (74%) late treatment children survived. • Mean time to significant T-cell function in all early treatment was 33 days and to normal T-cell function was 103 days. • Mean TREC value peaked earlier post-transplant for early treatment recipients but the 2 groups were indistinguishable by 5 years. • Early transplantation did not have an affect on B-cell function. 	II-2 C
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Potential patient overlap of Myers et al. 2002, Buckley et al. 1999

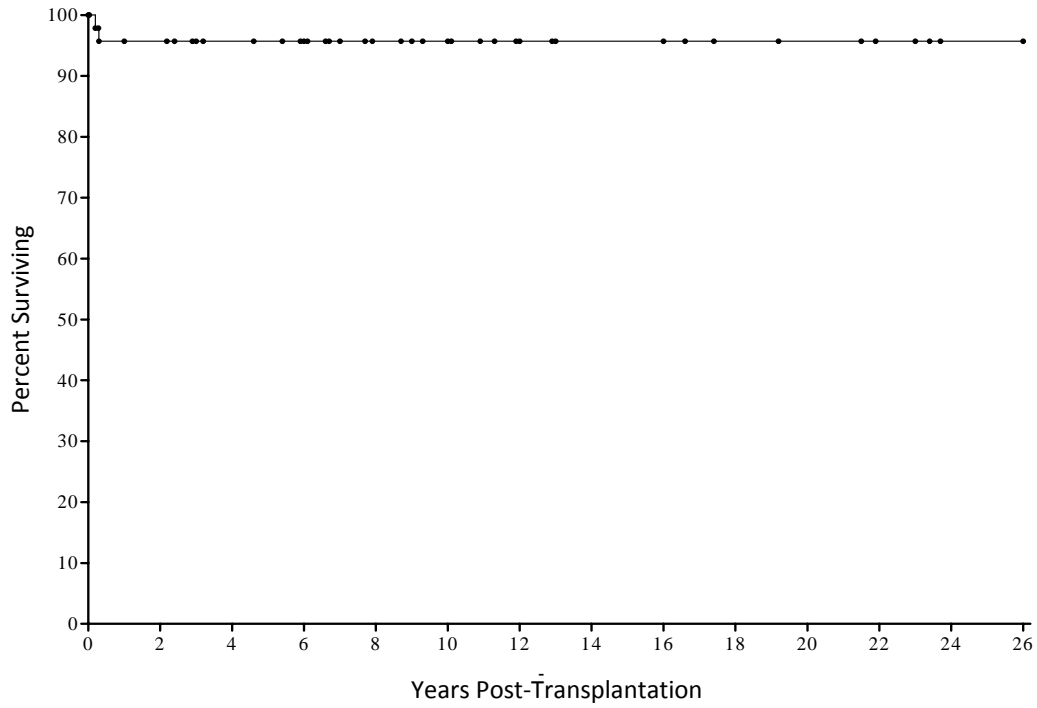
^A subset of patients in Fischer et al. 1990 are also included in Antoine et al. 2003

Information from expert interviews

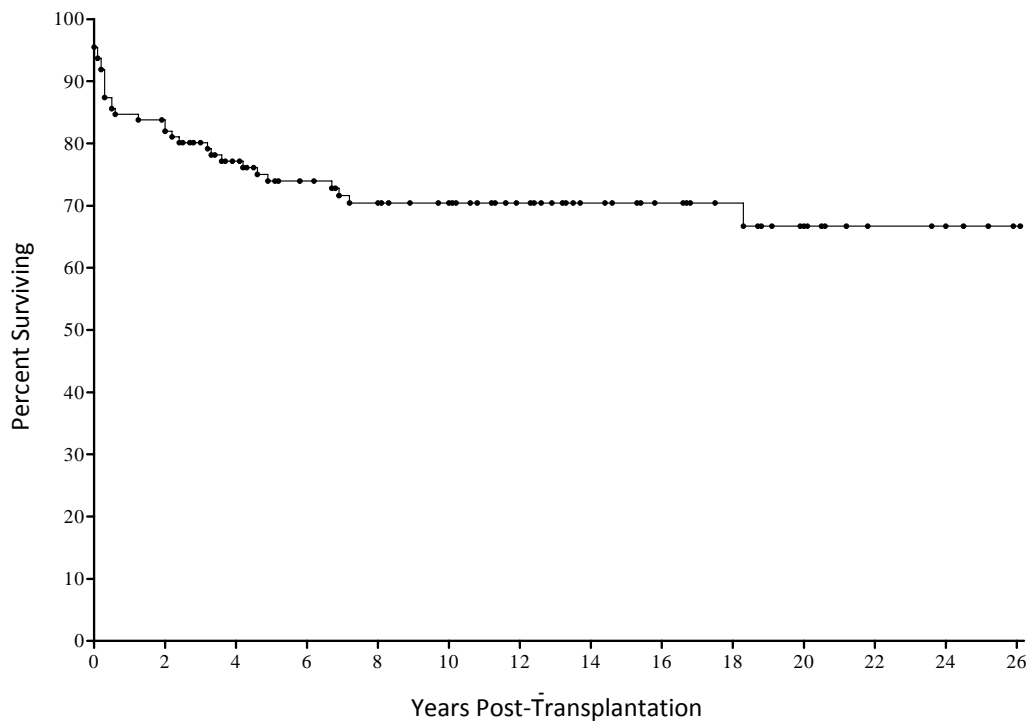
Dr. Buckley shared SCID treatment data with our group. They have transplanted 161 SCID infants over the past 26 years, of which 16 had an HLA-identical (genotypically HLA-identical) donor. The remaining 145 patients received half-matched (HLA-haplo-identical) transplants from their parents. She has documented an overall 26-year survival rate of 125/161 (78%). However, her data shows there is a survival difference when the population is divided by age at transplantation. The survival rate in those transplanted before 3.5 months of age is 96%, whereas the survival rate for those transplanted after later is only 71%. All transplants included in this data were done without pre-transplant chemotherapeutic conditioning or post-transplantation GVHD prophylactic immunosuppressive drugs. The Kaplan-Meier graphs from Dr. Buckley (with permission) for these data are below (Graphs 1A and 1B).

Additionally, Dr. Notarangelo reported that the European experience has also shown that early age at transplant is favored, particularly because that decreases the chance of pre-transplant infection which may negatively impact outcomes.

Graph 1A- Kaplan-Meier plot of 48 children with SCID transplanted at Duke University Medical Center in the first 3.5 months of life



Graph 1B- Kaplan-Meier plot of 113 children with SCID transplanted at Duke University Medical Center after the first 3.5 months of life



Overview of efficacy—large case series of HSCT

We found 3 case series that specifically addressed the efficacy of HSCT over time. In one series, 31 patients undergoing BMT for SCID were evaluated between 1968 and 1992 (van Leeuwen et al. 1994). In a similar large case series (Stephan et al. 1993) 117 patients were followed from 1970 to 1992. A single-center study (Buckley et al. 1999) followed 89 children between 1982 and 1998.

Table 14- Abstracted literature pertaining to efficacy in large case series studies of HSCT (alphabetical by author)

Study (Author, Date)	Population	Key findings	Quality of Evidence
Buckley et al. 1999 Case series	89 children total; 22 less than 3.5 months old at transplant, 67 greater than or equal to 3.5 months at transplant.	<ul style="list-style-type: none"> • 72 (81%) alive 3 months-16.5 years post-transplant, with a median follow up of 5.6 years. • 65 survived greater than 1 year, 38 greater than 5 years and 21 greater than 10 years. • All 12 HLA-identical recipients survived. • Mean number of T/B/NK-cells varies by genotype; all genotypes had normal average in vitro mitogen response after transplant. • Poor B-cell function with 45 kids requiring IVIG. • NK-cell activity low in γc-chain deficiency and JAK3 deficiency, normal in other SCID subtypes. 	IV
Stephan et al. 1993* Case series	117 patients total; treated for SCID between 1970 and 1992; 85 children were treated with BMT.	<ul style="list-style-type: none"> • Estimated SCID incidence: 1/ 100-150,000. • HLA-identical transplant from a related donor 21/25 (84% survived). • Pheno-identical transplant (HLA-genotypically haplo-identical) from related donor 2/5 (40% survived). • HLA-haplo-identical transplant without T-cell depletion 0/5 (0% survived). • T-cell depleted haplo-identical transplant 28/50 (56% survived). • 22 children did not receive any type of transplant and died. • 10 received fetal liver transplant, 9 died post transplant. 	IV

van Leeuwen et al. 1994 Case series	31 patients total; 1-94 months old at BMT.	<ul style="list-style-type: none"> • HLA-identical related 6/10 (60% survived) • HLA-haplo-identical related: 9/19 (47% survived). • HLA-matched unrelated: 0/2 (0% survived). • Major causes of death were graft and respiratory failure. • All who died of respiratory failure had a lung infection prior to transplant. • All children with sustained engraftment had evidence of humoral immunity. 	IV
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* Potential patient overlap with Stephan et al. 1993 and Wijnaendts et al. 1989

HSCT efficacy in different genotypes and phenotypes of SCID

Several studies examined HSCT for patients with specific pheno- or genotypes, including: B+ SCID vs. B- SCID, SCIDA, reticular dysgenesis, ADA deficiency, specific Jak3 mutations, and Omenn syndrome. Table 15 summarizes the results of these studies.

Table 15-Abstracted literature pertaining to HSCT efficacy in different SCID subgroups (alphabetical by author)

Study (Author, Date)	Population	Key findings	Quality of evidence
1) Albuquerque & Gaspar, 2004 Cohort study	ADA deficiency	1) <ul style="list-style-type: none"> • Compared 12 children with ADA deficiency to 16 children with other immunodeficiencies, all treated with HSCT. • 7/12 children with ADA deficiency had bilateral deafness, compared to 1/16 in the control group. 	1) II-B
2) Honig et al. 2007 Case series		2) <ul style="list-style-type: none"> • 12/15 survived, all with developmental delay. • 6/12 have significant neurocognitive deficits (learning disabilities, gait problems, hearing deficit, and/or hyperactivity). 	2) IV
3) Rogers et al. 2001 Cohort study		3) <ul style="list-style-type: none"> • No significant difference in full-scale IQ between groups; children with ADA deficiency 2 standard deviations below mean. • Significant behavioral differences in children with ADA deficiency: more hyperactivity, higher scores for dysfunction in social, emotional and behavioral domains. • Abnormal behavior more evident in older children. • Children with ADA deficiency group with no abnormal motor function on gross neurological evaluation. 	3) II-2 C

Bertrand et al. 1999 Cohort study	B+ SCID vs. B- SCID	<ul style="list-style-type: none"> • B+ SCID has better prognosis than B- SCID following non-identical BMT. • Rate of engraftment not different between groups. • B- SCID had higher rates of both early and late death. • Deaths in both groups due primarily to infection. 	II-2 C
Bertrand et al. 2002 Case series	Reticular Dysgenesis	<ul style="list-style-type: none"> • All children with reticular dysgenesis. • Presented with infection in first days of life. • HLA-non-identical HSCT resulted in three of the 10 patients surviving. • Deaths due primarily to graft failure. 	IV
Gomez et al. 1995 Case series	Omenn syndrome	<ul style="list-style-type: none"> • Engraftment occurred in 4/5 HLA-identical transplants and 3/4 non-identical transplants. • Full chimerism occurred in all but one of the patients that engrafted. • Clinical manifestations of Omenn syndrome disappeared within days of BMT (likely due to pre-treatment with chemo.) • One patient died of CMV 50 days post-transplant, 3 developed interstitial pneumonia. • All survivors except one (who has chronic GVHD) have normal growth rates. 	IV
O'Marcaigh et al. 2001 Case series	SCIDA	<ul style="list-style-type: none"> • 12/18 developed oral/genital ulcers associated with SCIDA. • 16/18 children were well enough for transplant. • 15/16 achieved engraftment. • 11/16 developed normal T-cell function. 	IV
Roberts et al. 2004 Case series	Jak3 mutations	<ul style="list-style-type: none"> • All patients had abnormal B-cell JAK3 dependent interleukin-2 induced signal transducer and activator of transcription 5 (STAT5) phosphorylation. • 9/10 patients with JAK3 deficiency were alive and well 4 to 18 years after stem cell transplant. 	IV

HSCT variation in transplant methods

Multiple studies compare various transplant methods and their outcomes. The main points of discussion surround the degree of matching between the donor and recipient, the extent of myeloablation prior to transplant and the method for T-cell depletion of the donor stem cells. In addition, investigators have considered the source of stem cells and the use of “booster transplants.”

The extent of matching between the donor and recipient is only partially under the control of physicians, as many patients lack an available matched related donor. This results in recipients requiring either a haplo-identical or mismatched transplant. Several studies have looked at the various types of transplants and their efficacy.

Table 16- Abstracted literature pertaining to HLA matching and efficacy of HSCT (alphabetical by author)

Study (Author, Date)	Population	Key findings	Quality of evidence
Dalal et al. 2000 Case series	16 children total, 9 with SCID; all lacked histocompatible siblings or closely matched related donors between 1989 and 1997.	<ul style="list-style-type: none"> • Mean age at diagnosis of SCID was 7.4 months. • Neutrophil engraftment was achieved in all patients at a mean of 15.4 days. • Serum IgM and IgA normalized in all patients within a mean of 3.5 and 6 months, respectively. • 12/16 patients survived. • 2/9 (22%) SCID patients died from GVHD complications. 	IV
Dal-Cortivo et al. 2004 Case series	38 children total; 25 children with no potential to exert NK-cell alloreactivity compared to 13 with such potential (defined by donor expression of inhibitory killer immunoglobulin-like receptor (KIR)), all receiving haplo-identical transplants.	<ul style="list-style-type: none"> • No difference in the rates of engraftment (64% vs. 61.5%). • Trend towards lower incidence of grade II-IV acute GVHD in the patients with potential NK-cell alloreactivity (37.5% vs. 50%, p=0.68). • One year survival was not significantly different between the two groups (52% vs. 61.5%). 	IV
Giri et al. 1994 Case series	11 children total; receiving HLA-non-identical BMT between 1985 and 1992, with a median age at time of BMT of 13 months (range: 3 weeks to 77 months).	<ul style="list-style-type: none"> • 9 patients engrafted (8 after first BMT, 1 after second BMT). • 4/9 developed GVHD. • 5 (46%) patients surviving 6-78 months post-BMT. 	IV

<p>Grunebaum et al. 2006</p> <p>Cohort study</p>	<p>Compared recipient outcomes between:</p> <ul style="list-style-type: none"> - related HLA-identical donors (RID, n=13), - HLA-matched unrelated donors (MUD, n= 41) - HLA-mismatched related donors (MMRD, n=40). 	<ul style="list-style-type: none"> • Median time to transplant was 1 month for RID, 2 months for MMRD and 4 months for MUD. • Highest survival was RID (92.3%), followed by MUD (80.5%) and MMRD (52.5%). • 0% of RID, 7.3% of MUD and 30% of MMRD had graft failure. • No statistical difference between MUD and MMRD lymphocyte subsets and lymphocyte function. • Patient sex and presence of B-cells has no impact on survival. • No respiratory complications in RID children; respiratory complications occurred in 7.3% of MUD and 35% of MMRD. • GVHD most common following MUD BMT (73.1%) or MMRD BMT (45%). 	<p>II-2 C</p>
<p>Smogorzewska et al. 2000</p> <p>Cohort study</p>	<p>48 children total; 11 children treated with histocompatible transplants from a sibling; 37 children treated with T-cell depleted haplo-identical parental bone marrow between 1984 and 1997.</p>	<ul style="list-style-type: none"> • 100% survival in histocompatible group. • 46% survival in haplo-identical group. • Mean age at transplant of children who survived: 7.5 months. • Mean age at transplant of children who died: 11.4 months. • All surviving children recovered T-cell function. • Recovery slower for children receiving haplo-identical transplants. 	<p>II-2 C</p>
<p>Wijnaendts et al. 1989*</p> <p>Case series</p>	<p>33 children treated with HST between 1972 and 1987 surviving a minimum of 6 months: 18 HLA-identical transplants and 15 HLA-non-identical transplants.</p>	<ul style="list-style-type: none"> • Development of immune function occurred faster in patients with HLA-identical transplants. • Development of T- and B-cell function occurred faster when chemotherapy preceded BMT. • Poor B-cell function was observed more frequently when chemotherapy was not used. 	<p>IV</p>

*Potential patient overlap with Stephan et al. 1993 and Wijnaendts et al. 1989

Table 17- Abstracted literature pertaining to the role of myeloablation prior to transplant (alphabetical by author)

Study (Author, Date)	Population	Key findings	Quality of evidence
Amrolia et al. 2000* Case series	8 patients total, 5 with SCID; Children ineligible for conventional myeloablation due to comorbidities.	<ul style="list-style-type: none"> All treated with non-myeloablative chemotherapy prior to transplant. The median duration of admission was 52 days compared to 54 days in a historical cohort of children undergoing conventionally conditioned HSCT 7/8 children survived. At median follow-up of 12 months: all 7 survivors have good recovery of T-cell numbers, 4 patients have normal IgM levels, and 2 patients have normal IgA levels. 	IV
Rao et al. 2005* Cohort study	52 children with primary immunodeficiency; 33 children receiving reduced intensity pre-transplant chemotherapy; 19 receiving myeloablation.	<ul style="list-style-type: none"> All children in both groups had primary engraftment. Reduced intensity group: 32/33 were alive at one month and 31/33 alive at one year Myeloablation group: 14/19 were alive at one month and 11/19 alive at one year. At one year: all in the myeloablative group had normal B-cell function, 5 of reduced intensity group still required IVIG. GVHD incidence not different between groups but limited chronic GVHD was more common in myeloablation group. Quality of life, measured by Lansky score, was similar between the groups (97 vs. 94). 	III
Veys, Rao & Amrolia 2005* Case series	81 children total; 0.1-17.6 years old, with congenital immunodeficiencies, 20 with SCID.	<ul style="list-style-type: none"> All subjects treated with HSCT with reduced-intensity conditioning. Survival rate 84% (68/81) with survival difference between SCID and non-SCID. Increase in reactivation of EBV compared to conventional BMT procedures. HSCT with reduced-intensity conditioning appeared to be well tolerated. 	IV

**Potential patient overlap of Amrolia et al. 2000, Rao et al. 2005, and Veys, Rao & Amrolia 2005*

Other variation in treatment methods

Three studies specifically investigated stem cell sources other than bone marrow. A small study (Knutson, Wall 2000) which included only 8 children with SCID evaluated transplants using umbilical cord blood derived stem cells and found neutrophil recovery time was the same as that

reported in BMT, while platelet recovery was delayed compared to BMT. A study from Turkey (Arpaci et al. 2008) used peripheral stem cells mobilized by treating donors with G-CSF. 21 patients, of whom 16 had SCID, received a total of 28 haplo- HSCTs. Median age at transplant was 12 months. At last follow-up 8/21 children were alive with the authors believing that delay in transplantation accounted for the poor outcomes compared to other studies. Finally, stem cells from fetal liver (Touraine et al. 2007) were used for transplants in 17 infants; in the 3 patients for whom information was available, they found normal antibody responses several years after transplant.

One study (Dror et al. 1993) reported on 24 patients who underwent a total of 36 transplants using lectin-treated T-cell-depleted haplo-compatible BMT. Of these 24 children durable T-cell engraftment was achieved in 19, although 6/19 required more than one transplant to achieve engraftment. Pre-transplant conditioning positively affected engraftment, while cell dose, patient’s age, and donor and patient sex had no observable effect on engraftment rates.

For patients that achieve engraftment but not adequate immune function, bone marrow boosts (Kline, Stiehm & Cowan 1996), in which additional stem cells from the same donor were given without pre-treatment, led to increased absolute lymphocyte counts in 5/9, increased mean CD3, CD4 and CD8 counts and improved mean T-cell function. Mentioned prior, the long-term follow up case series (Buckley et al. 1999) also included a total of 20/89 receiving “booster transplants” to overcome poor T/B-cell function or poor engraftment. Of those who received a booster transplant, immune function improved in all but 3.

HSCT long-term follow up, survival and immune reconstitution

Table 18- Abstracted literature pertaining to long-term follow-up and survival after HSCT (alphabetical by author)

Study (Author, Date)	Population	Key findings	Quality of evidence
Antoine et al. 2003 * Case series	475 patients (total of 566 transplants); 202 less than 6 months old at transplant, 184 between 6-11 months of age at transplant, from 37 European centers between 1968 and 1999.	<ul style="list-style-type: none"> • Children transplanted at less than 6 months of age had better 3-year survival rates than older cohorts. • Three-year survival with sustained engraftment was 77% for HLA-identical and 54% for HLA-non-identical transplants. • Survival has improved over time for both HLA-identical and HLA-non-identical transplant recipients. • B- SCID (36% 3-yr survival) had a poorer prognosis than B+ SCID (64% 3-yr survival). • Myeloablation prior to HLA-non-identical transplant trended towards improving survival among B- children but not B+ children. • ADA deficiency (n=51) 3-yr-survival was 81% for matched and 29% for unmatched transplants. • Reticular dysgenesis survival (n=12) was 75% for matched and 29% for unmatched transplants. 	II-2 C

Cavazzana-Calvo et al. 2007 Case series	31 children total; 1-42 months old at HSCT, evaluated 10-27 years later.	<ul style="list-style-type: none"> • 26/31 had T-cell count in normal range for age. • 30/31 had normal mitogen-induced T-cell proliferation. • 18/31 had normal TREC counts. • Presence of NK-cells not correlated with TREC. • Presence of TREC/naïve T-cells associated with significantly higher t-cell counts and better t-cell mitogen proliferation. 	IV
Fischer et al. 1990 * Case series	183 patients total; (HLA-identical BMT: 70; HLA-non-identical BMT: 113), mean age at transplantation 7.3 months, from 15 European centers between 1968 and 1989.	<ul style="list-style-type: none"> • Survival significantly better for HLA-identical (76% survival) than HLA-non-identical transplants (50% survival). • SCID phenotype was not associated with difference in survival. • Lung infection before HSCT and absence of a protective environment significantly affected outcome (multivariate analysis). • A total of 27% had acute GVHD of grade II or higher and 25% developed chronic GVHD. • 97% survival in those treated since 1983. 	IV
Friedrich, Honig & Muller 2007 Cohort study	32 children total; 7 children with SCID with HLA-identical transplant, 25 children with SCID with HLA-haplo-identical transplant, all at least 10 years out from transplant.	<ul style="list-style-type: none"> • Most patients had normal and stable T-cell numbers and functions. • 3 patients' had decreasing T-cell numbers. • 4 patients' had decreasing PHA responses (all in HLA-haplo-identical group and no chemotherapy). • HLA-haplo-identical with no conditioning had lower levels of naïve CD4+ cells and impaired B-cell functioning. 	IV
Gennery et al. 2001 Case series	30 children total; 1987-1998 using CAMPATH-1MT depleted BMT for SCID.	<ul style="list-style-type: none"> • 19/30 (63%) children survived longer than 1 year post-BMT; median follow-up of 5.3 years (range 1.33–12 years); 11/30 (37%) died. • 18/30 showed evidence of successful engraftment (49%). • 17/30 had normal immune function following transplantation. • The overall engraftment rate was 59% (22/37 BMT procedures). • Most deaths attributed to pre-existing infection. 	IV

Haddad et al. 1998 Case series	193 patients total; from 18 European centers between 1982 and 1993.	<ul style="list-style-type: none"> • 116 alive with evidence of engraftment 5 months after BMT; 24 later died (20%). • T-cell function improved during the 2 years after BMT and continued to be better than B-cell function. • Poor outcomes associated with: absence of T-cell reconstitution, presence of chronic GVHD 6 months after transplant, B- SCID (multivariate analysis). • At last follow up (median, 6 years after transplant), 93% of survivors had normal T-cell function and 68% had normal B-cell function. 	IV
Slatter et al. 2008 Cohort study	36 children total; 2 months to 2 years old, treated with BMT with depletion of T-cells from a non-identical donor and followed for 1-19 years.	<ul style="list-style-type: none"> • No significant survival difference between children receiving transplants depleted of T-cells using anti-CD52 or anti-CD34 antibodies. • 5 patients in the anti-CD52 group and 2 in anti-CD34 group developed GVHD. 	II-2 C

**A subset of patients in Fischer et al. 1990 are also included in Antoine et al. 2003*

Table 19- Abstracted literature pertaining to long-term immune reconstitution after HSCT (alphabetical by author)

Study (Author, Date)	Population	Key findings	Quality of evidence
Borghans et al. 2006 Case-control study	192 patients total; 19 children with SCID 1 month to 33 months old at time of BMT (follow-up now 5-32 years post BMT) compared to 173 healthy controls.	<ul style="list-style-type: none"> • Median number of T-cells was lower than in healthy matched controls: 11 SCID patients had normal T-cell counts. • 8 SCID patients who had low T-cell counts at last follow-up also had low counts early (1-4 years after BMT). • Predictors of low T-cell count included NK+ SCID, B- SCID, earlier transplant. • No significant difference in late clinical outcomes found between patients with and without “good” immune reconstitution. 	III
Brugnoni et al. 1998 Case series	8 children treated with BMT from unrelated donors.	<ul style="list-style-type: none"> • Number of activated T-cells decreased in the months after BMT. • Proliferative response to PHA initially decreased and then increased to normal by 18 months post-transplant. 	IV

Mazzolari et al. 2007 Case series	58 children total; treated with HSCT (in-utero to 34 months old at time of transplant).	<ul style="list-style-type: none"> • 42/58 (72.4%) survived at least 5 years (median follow-up of 132 months). • 85% produced antibodies to tetanus toxoid or hepatitis B vaccines. • 26/28 immunized with Measles, Mumps and Rubella vaccine had evidence of anti-measles antibodies. • Most children had height (77.5%) and weight (82.5%) in the normal range. • At last follow-up, 24/40 required no treatment, 6 required IVIG and/or antibiotics; 5 are on thyroid replacement; 3 receive anti-epileptics; 1 treated for portal hypertension. 	IV
Patel et al. 2000 Case series	173 total patients; 83 SCID with a mean age of transplant of 0.5 ±0.4 years; 90 healthy controls from less than 1 to 79 years old.	<ul style="list-style-type: none"> • Non-thymus-dependent cells predominated in the first 100 days after transplant. • 140-180 days after transplant thymus-dependent cells predominated. • After transplant thymus-dependent cells peaked at approximately one year but then diminished over the next 14. • Controls showed a decline in thymus-dependent cells from birth to 79 years old. 	IV
Vossen et al. 1993 Case series	14 children evaluated; 1-23 years after BMT.	<ul style="list-style-type: none"> • All children who survived greater than 1 year had some donor T-cell engraftment. • Cellular immunity was quantitatively low but mostly qualitatively normal. 	IV

Information from expert interviews

Consultation with experts pertaining to treatment of SCID corroborated the data from the published literature portion of this evidence review. Experts concurred that major challenges to treating SCID are due to complications prior to diagnosis and treatment (such as infections), and a lack of a uniform approach for treatment. Drs. Buckley and Notarangelo provided information on development of two SCID consortia: United States Immunodeficiency Network (USIDNET) Registry sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and Center for International Blood and Marrow Transplant Research (CIBMTR). While USIDNET is focused on the registry of primary immune deficiencies, reporting of all BMT procedures to the CIBMTR registry has been mandatory since December. Data from these consortiums may, in the future, provide more data on treatment outcomes for patients with SCID.

Dr. Buckley and Ms Boyle, from the Immune Deficiency Foundation, report there are 15 major and 34 minor centers in the U.S. and Canada currently performing stem cell transplantation for SCID. Drs. Notarangelo, Bonilla and Pai stated that an informal survey performed under the auspices of the NIAID/Rare Diseases workshop identified 34 centers in the United States and Canada that currently perform HSCT for SCID (unpublished data, NIAID May 12-13, 2008 HCT for Primary Immune Deficiency Diseases workshop). Additionally, Ms Ballard from the SCID

Family Network corroborated the information about limited treatment availability in telling us about her son's transfer from a Washington, DC, area hospital to Duke, in order to receive HSCT for SCID.

Enzyme replacement therapy-Systematic literature review

Enzyme replacement therapy has been a therapeutic option for patients with ADA deficiency, a specific type of SCID. Although multiple case studies examining the use of polyethylene glycol-adenosine deaminase (PEG-ADA) have been published, our examination of the literature found only one study meeting criteria for inclusion in this evidence review.

A long-term follow up study by Chan et al (Chan et al. 2005), evaluated outcomes in 9 children treated with PEG-ADA. These children were diagnosed with ADA deficiency at ages ranging from birth to 6.5 years and were followed on intramuscular PEG-ADA for 5-12 years. Some patients also received other treatments. One child died after 9 yrs of PEG-ADA treatment and a failed bone marrow transplant. The remaining 8 children attended school without protective precautions although 2 children have disabilities thought to be related to early, severe infections. Lymphocyte counts (T, B and NK) and function increased significantly following initiation of PEG-ADA and peaked at 1-3 years after treatment initiation. Over time lymphocyte counts and T-cell function, as measured by PHA mitogen stimulation have diminished.

Gene therapy-Systematic literature review

Gene therapy using viral vectors has been tried for the treatment of X-linked SCID and ADA deficiency SCID. Two case series of patients treated with gene therapy were included in this evidence review.

In 2002, Hacein-Bey-Abina et al (Hacein-Bey-Abina et al. 2002) published a report of 5 boys with X-linked SCID due to a mutation in the common γ c-chain gene who were treated by infusing them with their own bone marrow which had previously been extracted and transduced with a vector containing γ c-chain derived from a defective Moloney murine leukemia virus. 4/5 had clinical improvement including resolution of infections, diarrhea and skin lesions. At follow-up 0.7-2.5 years later those 4 were well with normal growth. The fifth patient never had reconstitution of T-cells following gene therapy and underwent a bone marrow transplantation 8 months later. With regards to immunologic function, 3/5 patients had normal T-cell values 3 to 4 months after gene therapy. At last follow up, T-cells from 4/5 patients exhibited normal proliferative responses to in vitro stimulation with phytohemagglutinin and anti-CD3 antibody.

Schmidt et al (Schmidt et al. 2005) reported on a series of 10 patients (5 of whom were included in the Hacein-Bey-Abina paper) with a focus on longer-term follow-up after gene therapy. They found polyclonal T-cell repertoires, in the 9/10 patients who developed normal T-cell counts after treatment, indistinguishable from those of age-matched controls. In long-term follow up, 2/9 developed monoclonal lymphoproliferation 2.5 years post transplant. Additionally, the number of circulating naïve T-cells was similar to that for age-matched controls.

E. Benefits of treatment in screen positive children

We found no evidence related to the benefits of treatment in children who screen positive for SCID. The relative outcomes for early treatment versus late treatment of children with SCID provide evidence of improved outcomes with earlier treatment.

F. Harms of SCID screening

We found no evidence related to the harms associated with screening for SCID.

G. Harms of SCID diagnosis

We found no evidence related to the harms associated with diagnosing SCID.

H. Harms of SCID treatment

We found two papers specifically focused on harms associated with treatment of SCID. The first (Horn et al. 1999) analyzed the rates of auto-immune hemolytic anemia in children undergoing HSCT for SCID. 8/41 children developed auto-immune hemolytic anemia, 3 died from its complications. This was a higher rate of auto-immune hemolytic anemia than previously reported and higher than the rate, in the same institution, among patients undergoing HSCT for non-SCID diseases. Among several potential predictors for the development of auto-immune hemolytic anemia that were analyzed, only peripheral blood as source of stem cells was found to be related to increased risk of developing auto-immune hemolytic anemia.

Work by Hacein-Bey-Abina et al (Hacein-Bey-Abina et al. 2008) documented a total of 4 children (of the 9/10 who had successful treatment with gene therapy) who developed leukemia between 30 and 68 months after gene therapy. All cases were associated with vector insertion near genes associated with cancer development. 3/4 kids were successfully treated with chemotherapy and regained poly-clonal T-cell populations; the 4th child underwent 2 BMTs and ultimately died 60 months after gene therapy and 26 months after leukemia diagnosis.

I. Cost-effectiveness

Table 20- Quality Assessment of abstracted literature pertaining to economic evidence

Economic evidence	1
I. Evaluation of important alternative interventions comparing all clinically relevant outcomes against appropriate cost measurement and including a clinically sensible sensitivity analysis.	0
II. Evaluation of important alternative interventions comparing a limited number of outcomes against appropriate cost measurement, but including a clinically sensible sensitivity analysis.	0
III. Evaluation of important alternative interventions comparing all clinically relevant outcomes against inappropriate cost measurement, but including a clinically sensible sensitivity analysis.	1
IV. Evaluation without a clinically sensible sensitivity analysis	0
V. Expert opinion with no explicit critical appraisal, based on economic theory	0

Adapted from NHS Centre for Reviews and Dissemination Report 4, March 2001

We found one study (McGhee, Stiehm & McCabe 2005) that addressed the cost-effectiveness of SCID screening, as it would apply to the United States population. Using a deterministic decision-tree model, comparing universal and targeted screening approaches, the authors assessed the thresholds at which screening would be cost-effective from a health care system perspective. They noted a significant amount of uncertainty in their model parameters due, in part, to the lack of SCID screening studies. Additionally, utility estimates were based on information from patients receiving HSCT for oncologic processes. The authors found that, at a threshold of \$100,000 per quality adjusted life year, there is 86% likelihood of screening being cost-effective, but details of the Monte Carlo simulation used to arrive at this estimate were not provided in the paper.

Data from experts regarding cost-effectiveness

None of the experts with whom we had contact provided any specific cost-effectiveness information. However, several (Bonilla, Pai, Notarangelo, and Buckley) had collected some unpublished hospital cost or charge data for patients undergoing HSCT for SCID. These costs or charges provide a cost-estimate that is at least two to three times higher than the cost estimate used by McGhee et al in their base-case analysis. With regard to testing, from the Wisconsin trial and Dr. Puck's planned trial, estimates of the marginal costs of SCID screening, exclusive of capital expenses associated with new equipment, are \$6-9 per child tested for non-automated testing. The Wisconsin cost for diagnostic testing, namely flow cytometry, is approximately \$120 per test. These costs are relatively consistent with the base-case analysis costs of testing suggested by McGhee et al.

VIII. Summary

Key findings:

Severe Combined Immunodeficiency (SCID) affects at least 1/100,000 newborns within the United States. However, experts believe that with systematic case-finding the prevalence may be higher (perhaps as high as 1/40,000) due to earlier diagnosis of infants who would otherwise die prior to confirming a diagnosis of SCID. Although several population-based screening trials are underway (Wisconsin) or planned (Massachusetts, Navajo Reservation in Arizona and New Mexico), to date no population-based screening trial has been completed.

Without curative treatment, newborns with SCID develop severe, often opportunistic, infections which lead to early death. Studies indicate that treatment, most commonly with hematopoietic stem cell transplant, is effective in decreasing both the morbidity and mortality associated with SCID. Given the seriousness of SCID, it does not lend itself to randomized controlled trials of treatment. The current evidence supports the notion that earlier treatment leads to better outcomes.

Regarding the key questions:

- **Do current screening tests effectively and efficiently identify cases of SCID?**

Various screening methods ranging from targeted use of lymphocyte counts in hospitalized children to population based newborn screening using IL-7, TREC or a combination have been studied. Both IL-7 and TREC have been investigated using anonymized dried-blood spots. These studies allow for estimations of sensitivity and specificity, but due to the anonymous nature there is no way to prove which test results are true.

The state of Wisconsin began a trial of population-based screening for SCID, using low TREC as the marker of SCID, in January 2008. As of December 31, 2008, they had screened 70,397 newborns of which 118 (0.168%) had initially inconclusive results requiring a second newborn screening sample and 32 (0.045%) had abnormal results requiring either a second newborn screening sample or diagnostic testing. The rates for both inconclusive and abnormal results are higher in premature than in full-term infants. As of December 31, 2008, the investigators have not detected any cases of SCID.

- **Does pre-symptomatic or early symptomatic intervention in newborns or infants with SCID improve health outcomes?**

The most common, and well-studied, treatment modality for SCID is hematopoietic stem cell transplant which appears to be effective in significantly decreasing the morbidity and mortality associated with SCID. Within HSCT there are numerous variables which may contribute to the effectiveness. The most studied of these are the degree of haplotype matching between donor and recipient and the type of pre-conditioning the recipient receives. There is no clear evidence as to the best method for HSCT. However, despite the lack of randomized controlled trials of SCID treatment, the evidence from large case series indicates that HSCT is effective in treating SCID.

Furthermore, there is evidence, primarily from the early detection of siblings of known SCID cases, that earlier treatment may be more effective. Specifically, the existing evidence

indicates that undergoing HSCT prior to the onset of lung infection has higher likelihood of success.

In addition to HSCT, there is limited evidence that for children with ADA deficiency enzyme replacement may be effective in reconstituting their immune function.

- **What is the cost-effectiveness of newborn screening for SCID?**

The cost-effectiveness data reviewed were very limited and may not reflect current costs of treatment.

- **What critical evidence appears lacking that may inform screening recommendations for SCID?**

We identified several areas with deficient data:

- **Prevalence of SCID**

There is limited evidence regarding the true prevalence of SCID. A systematic method of case finding is needed in order to accurately determine the prevalence. Of note, the new consortium of treatment centers (USIDNET) that has recently been established may serve as a method of more systematic case-finding.

- **Accuracy of screening**

Initial pilot screening data from Wisconsin suggests that the false-positive rate will be relatively low. However, these data are limited at this time. Data regarding the accuracy of other screening methods, when applied in population-based protocols, are not available.

- **Feasibility of screening**

Wisconsin and Massachusetts have been able to implement universal newborn screening for SCID, at least on a pilot basis. Data are needed regarding the ability of other newborn screening laboratories to offer SCID screening

- **Acceptability of screening**

There are no data available regarding consumer or physician acceptance of newborn screening for SCID.

- **Cost-effectiveness**

Cost-effectiveness analyses utilizing measured costs and utilities, as well as applicable sensitivity analyses, are needed.

- **Adequacy of available treatment centers**

There are no data addressing variation in treatment success between centers or the number of centers in the United States and their capacity to provide treatment for SCID. Data from USIDNET and CIBMTR may, in the future, provide evidence on this topic.

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X. Appendix A- SCID evidence tables

Natural History of Disease (alphabetical by last name of first author) Author(s) , Year, Title of Paper & Study Design	Population	Significant Findings
<p>Bertrand, Y., Landais, P., Friedrich, W., Gerritsen, B., Morgan, G., Fasth, A., Cavazzana-Calvo, M., Porta, F., Cant, A., Espanol, T., Muller, S., Veys, P., Vossen, J., Haddad, E. & Fischer, A. 1999, "Influence of severe combined immunodeficiency phenotype on the outcome of HLA- non-identical, T-cell-depleted bone marrow transplantation: a retrospective European survey from the European group for bone marrow transplantation and the European society for immunodeficiency", <i>The Journal of Pediatrics</i>, vol. 134, no. 6, pp. 740-748.</p>	<p>178 children total; B+ group: 122, mean age at BMT was 7 months B- group: 56, mean age at BMT was 6.5 months.</p>	<ul style="list-style-type: none"> • B+ SCID has better prognosis than B- SCID following non-identical BMT. • Rate of engraftment not different between groups. • B- SCID had higher rates of both early and late death. • Deaths in both groups due primarily to infection.
Cohort study*		
<p>Bertrand, Y., Muller, S.M., Casanova, J.L., Morgan, G., Fischer, A. & Friedrich, W. 2002, "Reticular dysgenesis: HLA- non-identical bone marrow transplants in a series of 10 patients", <i>Bone Marrow Transplantation</i>, vol. 29, no. 9, pp. 759-762.</p>	<p>10 children total; BMT at age 0.5 to 10 months.</p>	<ul style="list-style-type: none"> • All children had reticular dysgenesis. • All presented with infection in first days of life. • HLA-non -identical HSCT resulted in three of the 10 patients surviving. • Deaths due primarily to graft failure.
Case series *		
<p>Boeck, A., Buckley, R.H. & Schiff, R.I. 1997, "Gastroesophageal reflux and severe combined immunodeficiency", <i>The Journal of Allergy and Clinical Immunology</i>, vol. 99, no. 3, pp. 420-424.</p>	<p>194 children total; age at diagnosis ranged from 3 months to 5 years.</p>	<ul style="list-style-type: none"> • Significantly increased incidence of gastroesophageal reflux in patients with SCID (20.5%), compared with that reported in the normal population (0.3% to 0.1%, $p < 0.001$).
Case-control study		
<p>Boyle, J.M. & Buckley, R.H. 2007, "Population prevalence of diagnosed primary immunodeficiency diseases in the United States", <i>Journal of Clinical Immunology</i>, vol. 27, no. 5, pp. 497-502.</p>	<p>10,005 households were contacted (response rate of 80%)</p>	<ul style="list-style-type: none"> • 131/10,005 households said that someone had been diagnosed with a primary immunodeficiency. • Specific Primary Immunodeficiency (PID) diagnoses given: 9% SCID, 9% IgG, 26% IgA, 35% Common variable immunodeficiency, 9% chronic granulomatous disease, 13% Alpha gamma. • 4/6773 kids were reported to have a primary immunodeficiency (PID). • Population prevalence of diagnosed PID: 1/1200 for adults, 1/2000 for kids, 1/600 for households.
Other- Telephone survey		

<p>Buckley, R.H., Schiff, R.I., Schiff, S.E., Markert, M.L., Williams, L.W., Harville, T.O., Roberts, J.L. & Puck, J.M. 1997, "Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants", <i>The Journal of Pediatrics</i>, vol. 130, no. 3, pp. 378-387.</p>	<p>108 children total; Diagnosed at age birth to 21 months.</p>	<ul style="list-style-type: none"> • Mean age at diagnosis of SCID was 201 days (6.59 months) and did not differ significantly among different genetic types. • 67 (76%) of the 88 families were white, 14 (16%) were black, and 7 (8%) Hispanic. • Abnormal serum immunoglobulin concentrations existed in all types of SCID. • Mean IgA levels were lowest in γc-deficient, Jak3-deficient and unknown types of SCID. • Mean IgM concentrations were lowest in ADA, γc-deficient and Jak3-deficient patients. • IgE was normal in all but 2 patients.
<p>Case series</p>		
<p>Buckley, R.H., Schiff, S.E., Schiff, R.I., Markert, L., Williams, L.W., Roberts, J.L., Myers, L.A. & Ward, F.E. 1999, "Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency", <i>The New England Journal of Medicine</i>, vol. 340, no. 7, pp. 508-516.</p>	<p>89 children total; 22 less than 3.5 months old at transplant, 67 greater than or equal to 3.5 months at transplant.</p>	<ul style="list-style-type: none"> • 72 (81%) alive 3 months-16.5 years post-transplant, with a median follow up of 5.6 years. • 65 survived greater than 1 year, 38 greater than 5 years and 21 greater than 10 years. • All 12 HLA-identical recipients survived. • Mean number of T/B/NK-cells varies by genotype; all genotypes had normal average in vitro mitogen response after transplant. • Poor B-cell function with 45 kids requiring IVIG. • NK-cell activity low in γc-chain deficiency and JAK3 deficiency, normal in other SCID subtypes.
<p>Case series ^Potential patient overlap of Myers et al. 2002, Buckley et al. 1999</p>		
<p>Cavazzana-Calvo, M., Carlier, F., Le Deist, F., Morillon, E., Taupin, P., Gautier, D., Radford-Weiss, I., Caillat-Zucman, S., Neven, B., Blanche, S., Cheynier, R., Fischer, A. & Hacein-Bey-Abina, S. 2007, "Long-term T-cell reconstitution after hematopoietic stem-cell transplantation in primary T-cell-immunodeficient patients is associated with myeloid chimerism and possibly the primary disease phenotype", <i>Blood</i>, vol. 109, no. 10, pp. 4575-4581.</p>	<p>31 children total; 1-42 months old at HSCT, now 10-27 years later.</p>	<ul style="list-style-type: none"> • Myeloablation patients more likely to have evidence of donor-derived granulocytes and persistent naïve T-cells, as measured by TREC. • At follow-up, 60% of TREC+ and 45% of TREC- had no clinical manifestations. • Average follow-up time in the TREC+ group was 13 years and in the TREC- was 16 years.
<p>Case series *</p>		

<p>Chan, K. & Puck, J.M. 2005, "Development of population-based newborn screening for severe combined immunodeficiency", <i>The Journal of Allergy and Clinical Immunology</i>, vol. 115, no. 2, pp. 391-398.</p>	<p>23 children with SCID; 2 children with non-SCID immunodeficiencies; 242 anonymized newborn screening cards.</p>	<ul style="list-style-type: none"> • Used DNA amplification of TREC from dried blood spot. • Among the children known to have SCID, none had detectable levels of TREC and all had detectable β-actin. • The 2 children with non-SCID immunodeficiency had detectable TREC. • Had several presumed false-positives in which beta-actin could be amplified but TREC could not. • Estimated incidence of SCID to be 1/105,000 births, excluding patients who die before their immunodeficiency is recognized.
<p>Case-control study</p>		
<p>Deerojanawong, J., Chang, A.B., Eng, P.A., Robertson, C.F. & Kemp, A.S. 1997, "Pulmonary diseases in children with severe combined immune deficiency and DiGeorge syndrome", <i>Pediatric Pulmonology</i>, vol. 24, no. 5, pp. 324-330.</p>	<p>15 children with SCID; 3 weeks to 8 months old.</p>	<ul style="list-style-type: none"> • 13/15 presented with pulmonary findings, while the two others were prenatally diagnosed. • Median age of pulmonary manifestation was 4 months. • Pulmonary infection remained a significant cause of morbidity and mortality in those that did not undergo BMT. • 9/13 died; for 5/9, pulmonary disease was the cause of death.
<p>Case series *</p>		
<p>Denianke, K.S., Frieden, I.J., Cowan, M.J., Williams, M.L. & McCalmont, T.H. 2001, "Cutaneous manifestations of maternal engraftment in patients with severe combined immunodeficiency: a clinicopathologic study", <i>Bone Marrow Transplantation</i>, vol. 28, no. 3, pp. 227-233.</p>	<p>21 children total; 0-16 months old at rash onset and 0-2.1 years of age at BMT.</p>	<ul style="list-style-type: none"> • Divided subjects into two groups comparing cases with evidence of maternal engraftment and rash prior to BMT, to controls that did not have evidence of maternal engraftment or rash pre-BMT but developed rash post BMT. • The parameters that showed statistical significance between the two groups were psoriasiform hyperplasia ($P < 0.04$), parakeratosis ($P < 0.01$), spongiosis ($P < 0.04$), necrotic keratinocytes ($P < 0.04$) and lichenoid infiltrate ($P < 0.04$).
<p>Case-control study</p>		
<p>Gomez, L., Le Deist, F., Blanche, S., Cavazzana-Calvo, M., Griscelli, C. & Fischer, A. 1995, "Treatment of Omenn syndrome by bone marrow transplantation", <i>The Journal of Pediatrics</i>, vol. 127, no. 1, pp. 76-81.</p>	<p>9 children total; 0.5-5 months old (mean 2.8) with BMT for Omenn Syndrome between 1981 and 1989.</p>	<ul style="list-style-type: none"> • Engraftment occurred in 4/5 HLA-identical transplants and 3/4 non-identical transplants. • Full chimerism occurred in all but one of the patients that engrafted. • Clinical manifestations of Omenn syndrome disappeared within days of BMT (likely due to pre-treatment with chemo.) • One patient died of CMV 50 days post-transplant, 3 developed interstitial pneumonia. • All survivors except one (who has chronic GVHD) have normal growth rates.
<p>Case series *</p>		

<p>Honig, M., Albert, M.H., Schulz, A., Sparber-Sauer, M., Schutz, C., Belohradsky, B., Gungor, T., Rojewski, M.T., Bode, H., Pannicke, U., Lippold, D., Schwarz, K., Debatin, K.M., Hershfield, M.S. & Friedrich, W. 2007, "Patients with adenosine deaminase deficiency surviving after hematopoietic stem cell transplantation are at high risk of CNS complications", <i>Blood</i>, vol. 109, no. 8, pp. 3595-3602.</p>	<p>15 children total; Treated with BMT for ADA deficiency, focus on neurologic symptoms.</p>	<ul style="list-style-type: none"> • 12/15 survived, all with developmental delay. • 6/12 have significant neurocognitive deficits (learning disabilities, gait problems, hearing deficit, and/or hyperactivity).
<p>Case series*</p>		
<p>Jones, J.F., Ritenbaugh, C.K., Spence, M.A. & Hayward, A. 1991, "Severe combined immunodeficiency among the Navajo. I. Characterization of phenotypes, epidemiology, and population genetics", <i>Human Biology; an International Record of Research</i>, vol. 63, no. 5, pp. 669-682.</p>	<p>248 patients total; birth to 15 months old at presentation.</p>	<ul style="list-style-type: none"> • Cases were spaced evenly both geographically and temporally. • Minimum SCID incidence rate calculated as 52/100,000 live Navajo births; gene frequency estimated at 2.25%. • SCID accounted for about 7% of deaths in children under 2. • Segregation analysis showed that it was not multifactorial inheritance but exact inheritance pattern could not be determined.
<p>Other- Cross Sectional review of death records and hospital records, followed by family interviews and genetic segregation analysis</p>		
<p>Laffort, C., Le Deist, F., Favre, M., Caillat-Zucman, S., Radford-Weiss, I., Debre, M., Fraitag, S., Blanche, S., Cavazzana-Calvo, M., de Saint Basile, G., de Villartay, J.P., Giliani, S., Orth, G., Casanova, J.L., Bodemer, C. & Fischer, A. 2004, "Severe cutaneous papillomavirus disease after haemopoietic stem-cell transplantation in patients with severe combined immune deficiency caused by common gammac cytokine receptor subunit or JAK-3 deficiency", <i>Lancet</i>, vol. 363, no. 9426, pp. 2051-2054.</p>	<p>41 patients total; at least 10 years after HSCT for SCID.</p>	<ul style="list-style-type: none"> • 9/41 developed extensive chronic human papilloma virus. • 4 had lesions typical of a rare genodermatosis. • All with human papilloma virus had γc/Adenylate kinase- 3 (AK-3) deficiency, though only 9/18 with γc/JAK3 developed human papilloma virus.
<p>Case-control study*</p>		
<p>Mazzolari, E., Forino, C., Guerci, S., Imberti, L., Lanfranchi, A., Porta, F. & Notarangelo, L.D. 2007, "Long-term immune reconstitution and clinical outcome after stem cell transplantation for severe T-cell immunodeficiency", <i>The Journal of Allergy and Clinical Immunology</i>, vol. 120, no. 4, pp. 892-899.</p>	<p>58 children total; treated with HSCT (in-utero to 34 months old at time of transplant).</p>	<ul style="list-style-type: none"> • 42/58 (72.4%) survived at least 5 years (median follow-up of 132 months). • 85% produced antibodies to tetanus toxoid or hepatitis B vaccines. • 26/28 immunized with Measles, Mumps and Rubella vaccine had evidence of anti-measles antibodies. • Most children had height (77.5%) and weight (82.5%) in the normal range. • At last follow-up, 24/40 required no treatment, 6 required IVIG and/or antibiotics; 5 are on thyroid replacement; 3 receive anti-epileptics; 1 treated for portal hypertension.
<p>Case series*</p>		

<p>Monafo, W.J., Polmar, S.H., Neudorf, S., Mather, A. & Filipovich, A.H. 1992, "A hereditary immunodeficiency characterized by CD8+ T lymphocyte deficiency and impaired lymphocyte activation", <i>Clinical and Experimental Immunology</i>, vol. 90, no. 3, pp. 390-393.</p>	<p>4 children total (2 sets of siblings); age 20 months, 4 months, 11 months, 24 months at the time of BMT.</p>	<ul style="list-style-type: none"> • Presenting clinical signs of SCID included diarrhea, poor weight gain, oral ulcers, and PJP pneumonia but normal lymphocyte counts. • One child did not present until 1 year of age, with a previously undescribed phenotype. • CD8 cells were virtually absent and mononuclear cells did not proliferate normally in vitro.
<p>Case series</p>		
<p>O'Marcaigh, A.S., DeSantes, K., Hu, D., Pabst, H., Horn, B., Li, L. & Cowan, M.J. 2001, "Bone marrow transplantation for T-B- severe combined immunodeficiency disease in Athabaskan-speaking native Americans", <i>Bone Marrow Transplantation</i>, vol. 27, no. 7, pp. 703-709.</p>	<p>18 children total; Birth to 3 months of age at diagnosis; mean age of 17.5 months at first transplant.</p>	<ul style="list-style-type: none"> • 12/18 developed oral/genital ulcers associated with SCIDA. • 16/18 children were well enough for transplant. • 15/16 achieved engraftment. • 11/16 developed normal T-cell function.
<p>Case series</p>		
<p>Roberts, J.L., Lengi, A., Brown, S.M., Chen, M., Zhou, Y.J., O'Shea, J.J. & Buckley, R.H. 2004, "Janus kinase 3 (JAK3) deficiency: clinical, immunologic, and molecular analyses of 10 patients and outcomes of stem cell transplantation", <i>Blood</i>, vol. 103, no. 6, pp. 2009-2018.</p>	<p>170 total patients; 10 with JAK3 deficiency and 160 with other types of SCID.</p>	<ul style="list-style-type: none"> • All patients had abnormal B-cell JAK3 dependent interleukin-2 induced signal transducer and activator of transcription 5 (STAT5) phosphorylation. • 9/10 patients with JAK3 deficiency were alive and well 4 to 18 years after stem cell transplant.
<p>Case series</p>		
<p>Rogers, M.H., Lwin, R., Fairbanks, L., Gerritsen, B. & Gaspar, H.B. 2001, "Cognitive and behavioral abnormalities in adenosine deaminase deficient severe combined immunodeficiency", <i>The Journal of Pediatrics</i>, vol. 139, no. 1, pp. 44-50.</p>	<p>22 children total; 1-51 months old at HSCT; 0.9-18 years old at follow-up; 11 children with ADA deficiency, 11 other SCID types.</p>	<ul style="list-style-type: none"> • No significant difference in full-scale IQ between groups; children with ADA deficiency 2 standard deviations below mean. • Significant behavioral differences in children with ADA deficiency: more hyperactivity, higher scores for dysfunction in social, emotional and behavioral domains. • Abnormal behavior more evident in older children. • Children with ADA deficiency group with no abnormal motor function on gross neurological evaluation.
<p>Cohort study*</p>		

<p>Stephan, J.L., Vlekova, V., Le Deist, F., Blanche, S., Donadieu, J., De Saint-Basile, G., Durandy, A., Griscelli, C. & Fischer, A. 1993, "Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 patients", <i>The Journal of Pediatrics</i>, vol. 123, no. 4, pp. 564-572.</p>	<p>117 patients total; treated for SCID between 1970 and 1992; 85 children were treated with BMT.</p>	<ul style="list-style-type: none"> • Estimated SCID incidence: 1/ 100-150,000. • HLA-identical transplant from a related donor 21/25 (84% survived). • Pheno-identical transplant (HLA-genotypically haplo-identical) from related donor 2/5 (40% survived). • HLA- haplo-identical transplant without T-cell depletion 0/5 (0% survived). • T-cell depleted haplo-identical transplant 28/50 (56% survived). • 22 children did not receive any type of transplant and died. • 10 received fetal liver transplant, 9 died post transplant.
<p>Case series* ^Potential patient overlap with Stephan et al. 1993 and Wijnaendts et al. 1989</p>		
<p>Stocks, R.M., Thompson, J.W., Church, J.A., Kun, S. & Simms, E. 1999, "Severe combined immunodeficiency: otolaryngological presentation and management", <i>The Annals of Otolaryngology, Rhinology, and Laryngology</i>, vol. 108, no. 4, pp. 403-407.</p>	<p>18 children total; prenatal to 8 months old at diagnosis.</p>	<ul style="list-style-type: none"> • Children presented with many ENT findings including congestion, URI, thrush, oral ulcers, cervical adenopathy, otitis media; mastoiditis. • Greater than 70% of this series had an otolaryngological presentation prior to diagnosis.
<p>Case series</p>		

* Study conducted outside the United States

<p>Screening Test Characteristics (alphabetical by last name of first author) Author(s) , Year, Title of Paper & Study Design</p>	<p>Population</p>	<p>Significant Findings</p>
<p>Chan, K. & Puck, J.M. 2005, "Development of population-based newborn screening for severe combined immunodeficiency", <i>The Journal of Allergy and Clinical Immunology</i>, vol. 115, no. 2, pp. 391-398.</p> <p>Case-control study</p>	<p>23 children with SCID, 2 children with non-SCID immunodeficiencies. 242 anonymized newborn screening cards.</p>	<ul style="list-style-type: none"> • Used DNA amplification of TREC from dried blood spot. • Among the children known to have SCID, none had detectable levels of TREC and all had detectable β-actin. • The 2 children with non-SCID immunodeficiency had detectable TREC. • Had several presumed false-positives in which beta-actin could be amplified but TREC could not. • Estimated incidence of SCID to be 1/105,000 births, excluding patients who die before their immunodeficiency is recognized.
<p>Hague, R.A., Rassam, S., Morgan, G. & Cant, A.J. 1994, "Early diagnosis of severe combined immunodeficiency syndrome", <i>Archives of Disease in Childhood</i>, vol. 70, no. 4, pp. 260-263.</p> <p>Case-control study*</p>	<p>135 total children, 45 children with SCID, 90 children without SCID.</p>	<ul style="list-style-type: none"> • Used first available lymphocyte count. • SCID children matched to asymptomatic children by age and to children with same presenting symptoms by age. • Children with SCID had significantly lower levels of lymphocytes. • Unlike the 5 control children with low lymphocyte count, low lymphocyte count persisted in children with SCID.

<p>Hennewig, U., Schulz, A., Adams, O., Friedrich, W., Gobel, U. & Niehues, T. 2007, "Severe combined immunodeficiency signalized by eosinophilia and lymphopenia in rotavirus infected infants", <i>Klinische Padiatrie</i>, vol. 219, no. 6, pp. 343-347.</p>	<p>36 children with rotavirus gastroenteritis; 18 with SCID, 18 without SCID.</p>	<ul style="list-style-type: none"> • Lymphocyte study. • SCID children were more likely to have: <ul style="list-style-type: none"> ○ Low white blood cell count:10/18 vs. 0/18, ○ Eosinophilia: 12/18 vs. 0/18 ○ Relative lymphopenia: 17/18 vs. 10/18 ○ Absolute lymphopenia:16/18 vs. 4/18
<p>Cohort study*</p>		
<p>McGhee, S.A., Stiehm, E.R., Cowan, M., Krogstad, P. & McCabe, E.R. 2005, "Two-tiered universal newborn screening strategy for severe combined immunodeficiency", <i>Molecular Genetics and Metabolism</i>, vol. 86, no. 4, pp. 427-430.</p>	<p>13 children with SCID, 183 anonymized dried blood spots, presumed to be from children without SCID.</p>	<ul style="list-style-type: none"> • Dried blood spot study. • A 2-tiered screening approach in which IL-7 is first measured and only those with elevated IL-7 would have TREC measured, although for this study researchers evaluated each test separately. • Of the 183 presumed normal children tested for TREC, 14 were undetectable. • Of the 3 SCID children tested for TREC, all were undetectable.
<p>Case-control study</p>		

* Study conducted outside the United States

Treatment	Population	Significant Findings
(alphabetical by last name of first author)		
Author(s) , Year, Title of Paper & Study Design		
<p>Albuquerque, W. & Gaspar, H.B. 2004, "Bilateral sensorineural deafness in adenosine deaminase-deficient severe combined immunodeficiency", <i>The Journal of Pediatrics</i>, vol. 144, no. 2, pp. 278-280.</p>	<p>28 children total; 1-20 months of age; 12 with ADA deficiency and 16 with other immunodeficiencies.</p>	<ul style="list-style-type: none"> • Compared 12 children with ADA deficiency to 16 children with other immunodeficiencies, all treated with HSCT. • 7/12 children with ADA deficiency had bilateral deafness, compared to 1/16 in the control group.
<p>Cohort study*</p>		
<p>Amrolia, P., Gaspar, H.B., Hassan, A., Webb, D., Jones, A., Sturt, N., Mieli-Vergani, G., Pagliuca, A., Mufti, G., Hadzic, N., Davies, G. & Veys, P. 2000, "Nonmyeloablative stem cell transplantation for congenital immunodeficiencies", <i>Blood</i>, vol. 96, no. 4, pp. 1239-1246.</p>	<p>8 patients total, 5 with SCID; Children ineligible for conventional myeloablation due to comorbidities.</p>	<ul style="list-style-type: none"> • All treated with non-myeloablative chemotherapy prior to transplant. • The median duration of admission was 52 days compared to 54 days in a historical cohort of children undergoing conventionally conditioned HSCT • 7/8 children survived. • At median follow-up of 12 months: all 7 survivors have good recovery of T-cell numbers, 4 patients have normal IgM levels, and 2 patients have normal IgA levels.
<p>Case series*</p>		
<p>[^]Potential patient overlap of Amrolia et al. 2000, Rao et al. 2005, and Veys, Rao & Amrolia 2005</p>		

<p>Antoine, C., Muller, S., Cant, A., Cavazzana-Calvo, M., Veys, P., Vossen, J., Fasth, A., Heilmann, C., Wulffraat, N., Seger, R., Blanche, S., Friedrich, W., Abinun, M., Davies, G., Bredius, R., Schulz, A., Landais, P., Fischer, A., European Group for Blood and Marrow Transplantation & European Society for Immunodeficiency 2003, "Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: report of the European experience 1968-99", <i>Lancet</i>, vol. 361, no. 9357, pp. 553-560.</p>	<p>475 patients (total of 566 transplants); 202 less than 6 months old at transplant, 184 between 6-11 months of age at transplant, from 37 European centers between 1968 and 1999.</p>	<ul style="list-style-type: none"> • Children transplanted at less than 6 months of age had better 3-year survival rates than older cohorts. • Three-year survival with sustained engraftment was 77% for HLA-identical and 54% for HLA-non-identical transplants. • Survival has improved over time for both HLA-identical and HLA-non-identical transplant recipients. • B- SCID (36% 3-yr survival) had a poorer prognosis than B+ SCID (64% 3-yr survival). • Myeloablation prior to HLA-non-identical transplant trended towards improving survival among B- children but not B+ children. • ADA deficiency (n=51) 3-yr-survival was 81% for matched and 29% for unmatched transplants. • Reticular dysgenesis survival (n=12) was 75% for matched and 29% for unmatched transplants.
<p>Case series* ^A subset of patients in Fischer et al. 1990 are also included in Antoine et al. 2003</p>		
<p>Arpaci, F., Tezcan, I., Kuzhan, O., Yalman, N., Uckan, D., Kurekci, A.E., Ikinciogullari, A., Ozet, A. & Tanyeli, A. 2008, "G-CSF-mobilized haplo-identical peripheral blood stem cell transplantation in children with poor prognostic nonmalignant disorders", <i>American Journal of Hematology</i>, vol. 83, no. 2, pp. 133-136.</p>	<p>21 children total, 16 with SCID; Overall median age 12 months (range: 2.7 months to 12.5 years).</p>	<ul style="list-style-type: none"> • 21 kids received 28 haplo-identical HSCT. • The rate of engraftment was 66%. • Of the 12 patients with engraftment, 7 (58%) had no signs of GvHD. • 8 of 21 patients were still alive at last follow up; median follow up was 167 days (range: 14-2,204 days). • Transplant related mortality was 14.2% (3/21). • Projected 6-year-survival was 32% for all patients and 29.76% for SCID patients. • Causes of death were infection, GVHD, VOD and bleeding.
<p>Case series*</p>		
<p>Bertrand, Y., Landais, P., Friedrich, W., Gerritsen, B., Morgan, G., Fasth, A., Cavazzana-Calvo, M., Porta, F., Cant, A., Espanol, T., Muller, S., Veys, P., Vossen, J., Haddad, E. & Fischer, A. 1999, "Influence of severe combined immunodeficiency phenotype on the outcome of HLA- non-identical, T-cell-depleted bone marrow transplantation: a retrospective European survey from the European group for bone marrow transplantation and the european society for immunodeficiency", <i>The Journal of Pediatrics</i>, vol. 134, no. 6, pp. 740-748.</p>	<p>178 children total; B+ group: 122, mean age at BMT 7 months B- group: 56, mean age at BMT 6.5 months.</p>	<ul style="list-style-type: none"> • B+ SCID has better prognosis than B- SCID following non-identical BMT. • Rate of engraftment not different between groups. • B- SCID had higher rates of both early and late death. • Deaths in both groups due primarily to infection.
<p>Cohort study*</p>		

<p>Bertrand, Y., Muller, S.M., Casanova, J.L., Morgan, G., Fischer, A. & Friedrich, W. 2002, "Reticular dysgenesis: HLA- non- identical bone marrow transplants in a series of 10 patients", <i>Bone Marrow Transplantation</i>, vol. 29, no. 9, pp. 759-762.</p>	<p>10 children total; BMT at age 0.5 to 10 months.</p>	<ul style="list-style-type: none"> • All children with reticular dysgenesis. • Presented with infection in first days of life. • HLA-non -identical HSCT resulted in three of the 10 patients surviving. • Deaths due primarily to graft failure.
<p>Case series*</p>		
<p>Borghans, J.A., Bredius, R.G., Hazenberg, M.D., Roelofs, H., Jol-van der Zijde, E.C., Heidt, J., Otto, S.A., Kuijpers, T.W., Fibbe, W.E., Vossen, J.M., Miedema, F. & van Tol, M.J. 2006, "Early determinants of long-term T-cell reconstitution after hematopoietic stem cell transplantation for severe combined immunodeficiency", <i>Blood</i>, vol. 108, no. 2, pp. 763-769.</p>	<p>192 patients total; 19 children with SCID 1 month to 33 months old at time of BMT (follow-up now 5-32 years post BMT) compared to 173 healthy controls.</p>	<ul style="list-style-type: none"> • Median number of T-cells was lower than in healthy matched controls: 11 SCID patients had normal T-cell counts. • 8 SCID patients who had low t-cell counts at last follow-up also had low counts early (1-4 years after BMT). • Predictors of low T-cell count included NK+ SCID, B- SCID, earlier transplant. • No significant difference in late clinical outcomes found between patients with and without "good" immune reconstitution.
<p>Case-control study*</p>		
<p>Brugnoni, D., Airo, P., Malagoli, A., Cattaneo, R., Pennacchio, M. & Porta, F. 1998, "Rapid regeneration of normally functional naive CD4(+) T-cells after bone marrow transplantation from unrelated donors for combined immunodeficiency", <i>Blood</i>, vol. 92, no. 9, pp. 3484-3486.</p>	<p>8 children treated with BMT from unrelated donors.</p>	<ul style="list-style-type: none"> • Number of activated T-cells decreased in the months after BMT. • Proliferative response to PHA initially decreased and then increased to normal by 18 months post-transplant.
<p>Case series*</p>		
<p>Buckley, R.H., Schiff, S.E., Schiff, R.I., Markert, L., Williams, L.W., Roberts, J.L., Myers, L.A. & Ward, F.E. 1999, "Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency", <i>The New England Journal of Medicine</i>, vol. 340, no. 7, pp. 508-516.</p>	<p>89 children total; 22 less than 3.5 months old at transplant, 67 greater than or equal to 3.5 months at transplant.</p>	<ul style="list-style-type: none"> • 72 (81%) alive 3 months-16.5 years post-transplant, with a median follow up of 5.6 years. • 65 survived greater than 1 year, 38 greater than 5 years and 21 greater than 10 years. • All 12 HLA-identical recipients survived. • Mean number of T/B/NK-cells varies by genotype; all genotypes had normal average in vitro mitogen response after transplant. • Poor B-cell function with 45 kids requiring IVIG. • NK-cell activity low in γc-chain deficiency and JAK3 deficiency, normal in other SCID subtypes.
<p>Case series ^Potential patient overlap of Myers et al. 2002, Buckley et al. 1999</p>		

<p>Cavazzana-Calvo, M., Carlier, F., Le Deist, F., Morillon, E., Taupin, P., Gautier, D., Radford-Weiss, I., Caillat-Zucman, S., Neven, B., Blanche, S., Cheynier, R., Fischer, A. & Hacein-Bey-Abina, S. 2007, "Long-term T-cell reconstitution after hematopoietic stem-cell transplantation in primary T-cell-immunodeficient patients is associated with myeloid chimerism and possibly the primary disease phenotype", <i>Blood</i>, vol. 109, no. 10, pp. 4575-4581.</p>	<p>31 children total; 1-42 months old at HSCT, evaluated 10-27 years later.</p>	<ul style="list-style-type: none"> • 26/31 had T-cell count in normal range for age. • 30/31 had normal mitogen-induced T-cell proliferation. • 18/31 had normal TREC counts. • Presence of NK-cells not correlated with TREC. • Presence of TREC/naïve T-cells associated with significantly higher t-cell counts and better t-cell mitogen proliferation.
<p>Case series*</p>		
<p>Chan, B., Wara, D., Bastian, J., Hershfield, M.S., Bohnsack, J., Azen, C.G., Parkman, R., Weinberg, K. & Kohn, D.B. 2005, "Long-term efficacy of enzyme replacement therapy for adenosine deaminase (ADA)-deficient severe combined immunodeficiency (SCID)", <i>Clinical Immunology (Orlando, Fla.)</i>, vol. 117, no. 2, pp. 133-143.</p>	<p>9 children total; birth to 6.5 years old at ADA deficiency diagnosis, and study done 5-12 years after starting PEG-ADA treatment.</p>	<ul style="list-style-type: none"> • One child died after 9 yrs of PEG-ADA treatment and a failed bone marrow transplant. • Remaining 8 children attended school without protective precautions. • 2 children have disabilities likely due to early infection. • Lymphocyte counts (T, B and NK) and function increased significantly following initiation of PEG-ADA and peaked at 1-3 years after treatment initiation. • Lymphocyte counts and T-cell function, as measured by PHA mitogen stimulation diminished overtime.
<p>Case series</p>		
<p>Dalal, I., Reid, B., Doyle, J., Freedman, M., Calderwood, S., Saunders, F. & Roifman, C.M. 2000, "Matched unrelated bone marrow transplantation for combined immunodeficiency", <i>Bone Marrow Transplantation</i>, vol. 25, no. 6, pp. 613-621.</p>	<p>16 children total, 9 with SCID; all lacked histocompatible siblings or closely matched related donors between 1989 and 1997.</p>	<ul style="list-style-type: none"> • Mean age at diagnosis of SCID was 7.4 months. • Neutrophil engraftment was achieved in all patients at a mean of 15.4 days. • Serum IgM and IgA normalized in all patients within a mean of 3.5 and 6 months, respectively. • 12/16 patients survived. • 2/9 (22%) SCID patients died from GVHD complications.
<p>Case series*</p>		

<p>Dal-Cortivo, L., Ouachee-Chardin, M., Hirsch, I., Blanche, S., Fischer, A., Cavazzana-Calvo, M. & Caillat-Zucman, S. 2004, "Does haplo-identical transplantation in children with primary immunodeficiencies have the potential to exploit donor NK-cell alloreactivity?", <i>Bone Marrow Transplantation</i>, vol. 34, no. 11, pp. 945-947.</p>	<p>38 children total; 25 children with no potential to exert NK-cell alloreactivity compared to 13 with such potential (defined by donor expression of inhibitory killer immunoglobulin-like receptor (KIR)), all receiving haplo-identical transplants.</p>	<ul style="list-style-type: none"> • No difference in the rates of engraftment (64% vs. 61.5%). • Trend towards lower incidence of grade II-IV acute GVHD in the patients with potential NK-cell alloreactivity (37.5% vs. 50%, p=0.68). • One year survival was not significantly different between the two groups (52% vs. 61.5%). 	
<p>Case series*</p>	<p>Diaz de Heredia, C., Ortega, J.J., Diaz, M.A., Olive, T., Badell, I., Gonzalez-Vicent, M. & Sanchez de Toledo, J. 2008, "Unrelated cord blood transplantation for severe combined immunodeficiency and other primary immunodeficiencies", <i>Bone Marrow Transplantation</i>, vol. 41, no. 7, pp. 627-633.</p>	<p>15 children total (11 SCID, 1 Omenn syndrome, 3 non-SCID); 1.6-60.5 months old at diagnosis, and 3-68 months old at transplant.</p>	<ul style="list-style-type: none"> • All patients engrafted. • At one month post-transplant all patients were alive. • 8 patients developed acute GVHD, with one progressing to chronic GVHD. • Complications included 5 viral infections, 4 fungal infections, 3 chronic lung disease, and one case of autoimmune hemolytic anemia.
<p>Case series*</p>	<p>Dror, Y., Gallagher, R., Wara, D.W., Colombe, B.W., Merino, A., Benkerrou, M. & Cowan, M.J. 1993, "Immune reconstitution in severe combined immunodeficiency disease after lectin-treated, T-cell-depleted haplocompatible bone marrow transplantation", <i>Blood</i>, vol. 81, no. 8, pp. 2021-2030.</p>	<p>24 children total; 0.5 to 117 months old at time of BMT.</p>	<ul style="list-style-type: none"> • 24 patients underwent a total of 36 transplants using lectin-treated t-cell depleted haplocompatible BMT. • Durable T-cell engraftment was achieved in 19 patients. • 6/19 required more than one transplant to achieve engraftment. • Pre-transplant conditioning positively affected engraftment, while cell dose, patient's age, and donor and patient sex had no observable effect on engraftment rates.
<p>Case series</p>	<p>Fischer, A., Landais, P., Friedrich, W., Morgan, G., Gerritsen, B., Fasth, A., Porta, F., Griscelli, C., Goldman, S.F. & Levinsky, R. 1990, "European experience of bone-marrow transplantation for severe combined immunodeficiency", <i>Lancet</i>, vol. 336, no. 8719, pp. 850-854.</p>	<p>183 patients total; (HLA-identical BMT: 70; HLA-non-identical BMT: 113), mean age at transplantation 7.3 months, from 15 European centers between 1968 and 1989.</p>	<ul style="list-style-type: none"> • Survival significantly better for HLA-identical (76% survival) than HLA-non-identical transplants (50% survival). • SCID phenotype was not associated with difference in survival. • Lung infection before HSCT and absence of a protective environment significantly affected outcome (multivariate analysis). • A total of 27% had acute GVHD of grade II or higher and 25% developed chronic GVHD. • 97% survival in those treated since 1983.
<p>*A subset of patients in Fischer et al. 1990 are also included in Antoine et al. 2003</p>			

<p>Friedrich, W., Honig, M. & Muller, S.M. 2007, "Long-term follow-up in patients with severe combined immunodeficiency treated by bone marrow transplantation", <i>Immunologic Research</i>, vol. 38, no. 1-3, pp. 165-173.</p>	<p>32 children total; 7 children with SCID with HLA-identical transplant, 25 children with SCID with HLA-haplo-identical transplant, all at least 10 years out from transplant.</p>	<ul style="list-style-type: none"> • Most patients had normal and stable T-cell numbers and functions. • 3 patients' had decreasing T-cell numbers. • 4 patients' had decreasing PHA responses (all in HLA-haplo-identical group and no chemotherapy). • HLA-haplo-identical with no conditioning had lower levels of naïve CD4+ cells and impaired B-cell functioning. 	
<p>Cohort study*</p>	<p>Gennery, A.R., Dickinson, A.M., Brigham, K., Barge, D., Spickett, G.P., Curtis, A., Spencer, V., Jackson, A., Cavanagh, G., Carter, V., Palmer, P., Flood, T.J., Cant, A.J. & Abinun, M. 2001, "CAMPATH-1M T-cell depleted BMT for SCID: long-term follow-up of 19 children treated 1987-98 in a single center", <i>Cytotherapy</i>, vol. 3, no. 3, pp. 221-232.</p>	<p>30 children total; 1987-1998 using CAMPATH-1MT depleted BMT for SCID.</p>	<ul style="list-style-type: none"> • 19/30 (63%) children survived longer than 1 year post-BMT; median follow-up of 5.3 years (range 1.33–12 years); 11/30 (37%) died. • 18/30 showed evidence of successful engraftment (49%). • 17/30 had normal immune function following transplantation. • The overall engraftment rate was 59% (22/37 BMT procedures). • Most deaths attributed to pre-existing infection.
<p>Case series*</p>	<p>Giri, N., Vowels, M., Ziegler, J.B., Ford, D. & Lam-Po-Tang, R. 1994, "HLA- non-identical T-cell-depleted bone marrow transplantation for primary immunodeficiency diseases", <i>Australian and New Zealand Journal of Medicine</i>, vol. 24, no. 1, pp. 26-30.</p>	<p>11 children total; receiving HLA-non-identical BMT between 1985 and 1992, with a median age at time of BMT of 13 months (range: 3 weeks to 77 months).</p>	<ul style="list-style-type: none"> • 9 patients engrafted (8 after first BMT, 1 after second BMT). • 4/9 developed GVHD. • 5 (46%) patients surviving 6-78 months post-BMT.
<p>Case series*</p>	<p>Gomez, L., Le Deist, F., Blanche, S., Cavazzana-Calvo, M., Griscelli, C. & Fischer, A. 1995, "Treatment of Omenn syndrome by bone marrow transplantation", <i>The Journal of Pediatrics</i>, vol. 127, no. 1, pp. 76-81.</p>	<p>9 children total; 0.5-5 months old (mean 2.8) with BMT for Omenn Syndrome between 1981 and 1989.</p>	<ul style="list-style-type: none"> • Engraftment occurred in 4/5 HLA-identical transplants and 3/4 non-identical transplants. • Full chimerism occurred in all but one of the patients that engrafted. • Clinical manifestations of Omenn syndrome disappeared within days of BMT (likely due to pre-treatment with chemo.) • One patient died of CMV 50 days post-transplant, 3 developed interstitial pneumonia. • All survivors except one (who has chronic GVHD) have normal growth rates.
<p>Case series*</p>			

<p>Grunebaum, E., Mazzolari, E., Porta, F., Dallera, D., Atkinson, A., Reid, B., Notarangelo, L.D. & Roifman, C.M. 2006, "Bone marrow transplantation for severe combined immune deficiency", <i>JAMA : The Journal of the American Medical Association</i>, vol. 295, no. 5, pp. 508-518.</p>	<p>Compared recipient outcomes between: - related HLA-identical donors (RID, n=13), - HLA-matched unrelated donors (MUD, n= 41) - HLA-mismatched related donors (MMRD, n=40).</p>	<ul style="list-style-type: none"> • Median time to transplant was 1 month for RID, 2 months for MMRD and 4 months for MUD. • Highest survival was RID (92.3%), followed by MUD (80.5%) and MMRD (52.5%). • 0% of RID, 7.3% of MUD and 30% of MMRD had graft failure. • No statistical difference between MUD and MMRD lymphocyte subsets and lymphocyte function. • Patient sex and presence of B-cells has no impact on survival. • No respiratory complications in RID children; respiratory complications occurred in 7.3% of MUD and 35% of MMRD. • GVHD most common following MUD BMT (73.1%) or MMRD BMT (45%).
<p>Cohort study*</p>		
<p>Hacein-Bey-Abina, S., Le Deist, F., Carlier, F., Bouneaud, C., Hue, C., De Villartay, J.P., Thrasher, A.J., Wulfraat, N., Sorensen, R., Dupuis-Girod, S., Fischer, A., Davies, E.G., Kuis, W., Leiva, L. & Cavazzana-Calvo, M. 2002, "Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy", <i>The New England Journal of Medicine</i>, vol. 346, no. 16, pp. 1185-1193.</p>	<p>5 children total; 1-11 months old at time of gene therapy.</p>	<ul style="list-style-type: none"> • After infusion, 4/5 had clinical improvements. • 3/5 patients had normal T-cell values 3 to 4 months post gene therapy. • At last follow up (between 10 and 30 months post gene therapy for each patient), T-cells from 4/5 patients exhibited normal proliferative responses to in vitro simulation with phytohemagglutinin and anti-CD3 antibody. • Serum IgG, IgA, and IgM levels were within age related normal range in 3 patients at 25, 21, and 13 months post gene therapy.
<p>Case series*</p>		
<p>Hacein-Bey-Abina, S., Garrigue, A., Wang, G.P., Soulier, J., Lim, A., Morillon, E., Clappier, E., Caccavelli, L., Delabesse, E., Beldjord, K., Asnafi, V., MacIntyre, E., Dal Cortivo, L., Radford, I., Brousse, N., Sigaux, F., Moshous, D., Hauer, J., Borkhardt, A., Belohradsky, B.H., Wintergerst, U., Velez, M.C., Leiva, L., Sorensen, R., Wulfraat, N., Blanche, S., Bushman, F.D., Fischer, A. & Cavazzana-Calvo, M. 2008, "Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1", <i>The Journal of Clinical Investigation</i>, vol. 118, no. 9, pp. 3132-3142.</p>	<p>4 children total; 1-11 months old at time of gene therapy.</p>	<ul style="list-style-type: none"> • 4 children (of the 9/10 who had successful treatment with gene therapy) developed leukemia between 30 and 68 months after gene therapy. • All cases of leukemia were associated with vector insertion near genes associated with cancer development. • 3/4 children were successfully treated with chemotherapy and regained polyclonal t-cell populations. • The 4th child underwent 2 BMTs and died 60 months after gene therapy, 26 months after leukemia diagnosis.
<p>Case series*</p>		

<p>Haddad, E., Landais, P., Friedrich, W., Gerritsen, B., Cavazzana-Calvo, M., Morgan, G., Bertrand, Y., Fath, A., Porta, F., Cant, A., Espanol, T., Muller, S., Veys, P., Vossen, J. & Fischer, A. 1998, "Long-term immune reconstitution and outcome after HLA-non-identical T-cell-depleted bone marrow transplantation for severe combined immunodeficiency: a European retrospective study of 116 patients", <i>Blood</i>, vol. 91, no. 10, pp. 3646-3653.</p>	<p>193 patients total; from 18 European centers between 1982 and 1993.</p>	<ul style="list-style-type: none"> • 116 alive with evidence of engraftment 5 months after BMT; 24 later died (20%). • T-cell function improved during the 2 years after BMT and continued to be better than B-cell function. • Poor outcomes associated with: absence of T-cell reconstitution, presence of chronic GVHD 6 months after transplant, B- SCID (multivariate analysis). • At last follow up (median, 6 years after transplant), 93% of survivors had normal T-cell function and 68% had normal B-cell function.
<p>Case series*</p>		
<p>Honig, M., Albert, M.H., Schulz, A., Sparber-Sauer, M., Schutz, C., Belohradsky, B., Gungor, T., Rojewski, M.T., Bode, H., Pannicke, U., Lippold, D., Schwarz, K., Debatin, K.M., Hershfield, M.S. & Friedrich, W. 2007, "Patients with adenosine deaminase deficiency surviving after hematopoietic stem cell transplantation are at high risk of CNS complications", <i>Blood</i>, vol. 109, no. 8, pp. 3595-3602.</p>	<p>15 children total; Treated with BMT for ADA deficiency, focus on neurologic symptoms.</p>	<ul style="list-style-type: none"> • 12/15 survived, all with developmental delay. • 6/12 have significant neurocognitive deficits (learning disabilities, gait problems, hearing deficit, and/or hyperactivity).
<p>Case series*</p>		
<p>Horn, B., Viele, M., Mentzer, W., Mogck, N., DeSantes, K. & Cowan, M. 1999, "Autoimmune hemolytic anemia in patients with SCID after T-cell-depleted BM and PBSC transplantation", <i>Bone Marrow Transplantation</i>, vol. 24, no. 9, pp. 1009-1013.</p>	<p>41 patients with SCID; treated with HSCT.</p>	<ul style="list-style-type: none"> • 8/41 (19.5%) developed auto-immune hemolytic anemia (AIHA); one case occurred pre-transplant, others were a median of 8 months post-transplant. • 3 patients died from AIHA complications. • Peripheral blood as source of stem cells was found to be related to increased risk of developing auto-immune hemolytic anemia.
<p>Case-control study</p>		
<p>Kane, L., Gennery, A.R., Crooks, B.N., Flood, T.J., Abinun, M. & Cant, A.J. 2001, "Neonatal bone marrow transplantation for severe combined immunodeficiency", <i>Archives of Disease in Childhood.Fetal and Neonatal Edition</i>, vol. 85, no. 2, pp. F110-3.</p>	<p>13 children total; transplanted between 7 and 68 days old.</p>	<ul style="list-style-type: none"> • All patients alive and well 0.5-11.5 years after transplant (median 3 years). • 2 children developed chronic GvHD chronic. • 3 children required more than one transplant. • All children achieved neutrophil engraftment and normal levels of IgA. • 7 have normal IgG. • 12 have normal IgM. • 10/12 have normal neuro-development; 1/12 has trouble with communication and interactive skills, and 1/12 has motor delay.
<p>Case series*</p>		

<p>Kline, R.M., Stiehm, E.R. & Cowan, M.J. 1996, "Bone marrow 'boosts' following T-cell-depleted haplo-identical bone marrow transplantation", <i>Bone Marrow Transplantation</i>, vol. 17, no. 4, pp. 543-548.</p>	<p>9 patients total; 8 with SCID and 1 aplastic anemia.</p>	<ul style="list-style-type: none"> • Bone marrow "boost" increased absolute lymphocyte counts in 5/9, also increased mean CD3, CD4 and CD8 counts and improved mean T-cell function. • The 2 patients who did not show complete recovery after "boost" were on chronic steroid therapy. • 8/9 patients are alive and well 0.8 to 6.2 years (median 2.9) years after "boost".
<p>Case series</p>		
<p>Knutsen, A.P. & Wall, D.A. 2000, "Umbilical cord blood transplantation in severe T-cell immunodeficiency disorders: two-year experience", <i>Journal of Clinical Immunology</i>, vol. 20, no. 6, pp. 466-476.</p>	<p>8 children with SCID; 2 weeks to 8 years old.</p>	<ul style="list-style-type: none"> • Transplanted using umbilical cord blood derived stem cells. • Neutrophil recovery time was the same as that reported in BMT. • Platelet recovery was delayed compared to BMT. • 6/8 children alive and well 18 to 24 months after transplant. • All patients had 100% chimerism.
<p>Case series</p>		
<p>Laffort, C., Le Deist, F., Favre, M., Caillat-Zucman, S., Radford-Weiss, I., Debre, M., Fraitag, S., Blanche, S., Cavazzana-Calvo, M., de Saint Basile, G., de Villartay, J.P., Giliani, S., Orth, G., Casanova, J.L., Bodemer, C. & Fischer, A. 2004, "Severe cutaneous papillomavirus disease after haemopoietic stem-cell transplantation in patients with severe combined immune deficiency caused by common gamma cytokine receptor subunit or JAK-3 deficiency", <i>Lancet</i>, vol. 363, no. 9426, pp. 2051-2054.</p>	<p>41 patients total; at least 10 years after HSCT for SCID.</p>	<ul style="list-style-type: none"> • 9/41 developed extensive chronic human papilloma virus. • 4 had lesions typical of a rare genodermatosis. • All with human papilloma virus had γc/Adenylate kinase- 3 (AK-3) deficiency, though only 9/18 with γc/JAK3 developed human papilloma virus.
<p>Case-control study*</p>		
<p>Mazzolari, E., Forino, C., Guerci, S., Imberti, L., Lanfranchi, A., Porta, F. & Notarangelo, L.D. 2007, "Long-term immune reconstitution and clinical outcome after stem cell transplantation for severe T-cell immunodeficiency", <i>The Journal of Allergy and Clinical Immunology</i>, vol. 120, no. 4, pp. 892-899.</p>	<p>58 children total; treated with HSCT (in-utero to 34 months old at time of transplant).</p>	<ul style="list-style-type: none"> • 42/58 (72.4%) survived at least 5 years (median follow-up of 132 months). • 85% produced antibodies to tetanus toxoid or hepatitis B vaccines. • 26/28 immunized with Measles, Mumps and Rubella vaccine had evidence of anti-measles antibodies. • Most children had height (77.5%) and weight (82.5%) in the normal range. • At last follow-up, 24/40 required no treatment, 6 required IVIG and/or antibiotics; 5 are on thyroid replacement; 3 receive anti-epileptics; 1 treated for portal hypertension.
<p>Case series*</p>		

<p>Myers, L.A., Patel, D.D., Puck, J.M. & Buckley, R.H. 2002, "Hematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival", <i>Blood</i>, vol. 99, no. 3, pp. 872-878.</p>	<p>21 children total; transplanted prior to 28 days of life (early treatment) and 96 children transplanted at a median age of 190 days (range: of 45-516 days) (late treatment).</p>	<ul style="list-style-type: none"> • 20/21 (95%) early treatment children survived. • 71/96 (74%) late treatment children survived. • Mean time to significant T-cell function in all early treatment was 33 days and to normal T-cell function was 103 days. • Mean TREC value peaked earlier post-transplant for early treatment recipients but the 2 groups were indistinguishable by 5 years. • Early transplantation did not have an affect on B-cell function.
<p>Cohort study* ^Potential patient overlap of Myers et al. 2002, Buckley et al. 1999</p>		
<p>O'Marcaigh, A.S., DeSantes, K., Hu, D., Pabst, H., Horn, B., Li, L. & Cowan, M.J. 2001, "Bone marrow transplantation for T-B- severe combined immunodeficiency disease in Athabaskan-speaking native Americans", <i>Bone Marrow Transplantation</i>, vol. 27, no. 7, pp. 703-709.</p>	<p>18 children total; Birth to 3 months of age at diagnosis; mean age of 17.5 months at first transplant.</p>	<ul style="list-style-type: none"> • 12/18 developed oral/genital ulcers associated with SCIDA. • 16/18 children were well enough for transplant. • 15/16 achieved engraftment. • 11/16 developed normal T-cell function.
<p>Case series</p>		
<p>Patel, D.D., Gooding, M.E., Parrott, R.E., Curtis, K.M., Haynes, B.F. & Buckley, R.H. 2000, "Thymic function after hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency", <i>The New England Journal of Medicine</i>, vol. 342, no. 18, pp. 1325-1332.</p>	<p>173 total patients; 83 SCID with a mean age of transplant of 0.5 ±0.4 years; 90 healthy controls from less than 1 to 79 years old.</p>	<ul style="list-style-type: none"> • Non-thymus-dependent cells predominated in the first 100 days after transplant. • 140-180 days after transplant thymus-dependent cells predominated. • After transplant thymus-dependent cells peaked at approximately one year but then diminished over the next 14. • Controls showed a decline in thymus-dependent cells from birth to 79 years old.
<p>Case series</p>		
<p>Rao, K., Amrolia, P.J., Jones, A., Cale, C.M., Naik, P., King, D., Davies, G.E., Gaspar, H.B. & Veys, P.A. 2005, "Improved survival after unrelated donor bone marrow transplantation in children with primary immunodeficiency using a reduced-intensity conditioning regimen", <i>Blood</i>, vol. 105, no. 2, pp. 879-885.</p>	<p>52 children with primary immunodeficiency; 33 children receiving reduced intensity pre-transplant chemotherapy; 19 receiving myeloablation.</p>	<ul style="list-style-type: none"> • All children in both groups had primary engraftment. • Reduced intensity group: 32/33 were alive at one month and 31/33 alive at one year • Myeloablation group: 14/19 were alive at one month and 11/19 alive at one year. • At one year: all in the myeloablative group had normal B-cell function, 5 of reduced intensity group still required IVIG. • GVHD incidence not different between groups but limited chronic GVHD was more common in myeloablation group. • Quality of life, measured by Lansky score, was similar between the groups (97 vs. 94).
<p>Cohort study* ^Potential patient overlap of Amrolia et al. 2000, Rao et al. 2005, and Veys, Rao & Amrolia 2005</p>		

<p>Roberts, J.L., Lengi, A., Brown, S.M., Chen, M., Zhou, Y.J., O'Shea, J.J. & Buckley, R.H. 2004, "Janus kinase 3 (JAK3) deficiency: clinical, immunologic, and molecular analyses of 10 patients and outcomes of stem cell transplantation", <i>Blood</i>, vol. 103, no. 6, pp. 2009-2018.</p>	<p>170 total patients; 10 with JAK3 deficiency and 160 with other types of SCID.</p>	<ul style="list-style-type: none"> • All patients had abnormal B-cell JAK3 dependent interleukin-2 induced signal transducer and activator of transcription 5 (STAT5) phosphorylation. • 9/10 patients with JAK3 deficiency were alive and well 4 to 18 years after stem cell transplant.
<p>Case series</p>		
<p>Rogers, M.H., Lwin, R., Fairbanks, L., Gerritsen, B. & Gaspar, H.B. 2001, "Cognitive and behavioral abnormalities in adenosine deaminase deficient severe combined immunodeficiency", <i>The Journal of Pediatrics</i>, vol. 139, no. 1, pp. 44-50.</p>	<p>22 children total; 1-51 months old at HSCT; 0.9-18 years old at follow-up; 11 children with ADA deficiency, 11 other SCID types.</p>	<ul style="list-style-type: none"> • No significant difference in full-scale IQ between groups; children with ADA deficiency 2 standard deviations below mean. • Significant behavioral differences in children with ADA deficiency: more hyperactivity, higher scores for dysfunction in social, emotional and behavioral domains. • Abnormal behavior more evident in older children. • Children with ADA deficiency group with no abnormal motor function on gross neurological evaluation.
<p>Cohort study*</p>		
<p>Schmidt, M., Hacein-Bey-Abina, S., Wissler, M., Carlier, F., Lim, A., Prinz, C., Glimm, H., Andre-Schmutz, I., Hue, C., Garrigue, A., Le Deist, F., Lagresle, C., Fischer, A., Cavazzana-Calvo, M. & von Kalle, C. 2005, "Clonal evidence for the transduction of CD34+ cells with lymphomyeloid differentiation potential and self-renewal capacity in the SCID-X1 gene therapy trial", <i>Blood</i>, vol. 105, no. 7, pp. 2699-2706.</p>	<p>10 patients treated for SCID with gene therapy.</p>	<ul style="list-style-type: none"> • In 9/10 patients who developed normal T-cell counts after treatment, they were indistinguishable from those of age-matched controls. • 7/9 maintained polyclonal lymphocyte population up to 5 years after treatment, and 2/9 developed monoclonal lymphoproliferation 2.5 years post transplant. • Circulating naïve T-cells were similar to that of age-matched controls.
<p>Case series*</p>		
<p>Slatter, M.A., Brigham, K., Dickinson, A.M., Harvey, H.L., Barge, D., Jackson, A., Bown, N., Flood, T.J., Cant, A.J., Abinun, M. & Gennery, A.R. 2008, "Long-term immune reconstitution after anti-CD52-treated or anti-CD34-treated hematopoietic stem cell transplantation for severe T-lymphocyte immunodeficiency", <i>The Journal of Allergy and Clinical Immunology</i>, vol. 121, no. 2, pp. 361-367.</p>	<p>36 children total; 2 months to 2 years old, treated with BMT with depletion of T-cells from a non-identical donor and followed for 1-19 years.</p>	<ul style="list-style-type: none"> • No significant survival difference between children receiving transplants depleted of T-cells using anti-CD52 or anti-CD34 antibodies. • 5 patients in the anti-CD52 group and 2 in anti-CD34 group developed GVHD.
<p>Cohort study*</p>		

<p>Smogorzewska, E.M., Brooks, J., Annett, G., Kapoor, N., Crooks, G.M., Kohn, D.B., Parkman, R. & Weinberg, K.I. 2000, "T-cell depleted haplo-identical bone marrow transplantation for the treatment of children with severe combined immunodeficiency", <i>Archivum Immunologiae et Therapiae Experimentalis</i>, vol. 48, no. 2, pp. 111-118.</p>	<p>48 children total; 11 children treated with histocompatible transplants from a sibling; 37 children treated with T-cell depleted haplo-identical parental bone marrow between 1984 and 1997.</p>	<ul style="list-style-type: none"> • 100% survival in histocompatible group. • 46% survival in haplo-identical group. • Mean age at transplant of children who survived: 7.5 months. • Mean age at transplant of children who died: 11.4 months. • All surviving children recovered T-cell function. • Recovery slower for children receiving haplo-identical transplants.
<p>Cohort study</p>		
<p>Stephan, J.L., Vlekova, V., Le Deist, F., Blanche, S., Donadieu, J., De Saint-Basile, G., Durandy, A., Griscelli, C. & Fischer, A. 1993, "Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 patients", <i>The Journal of Pediatrics</i>, vol. 123, no. 4, pp. 564-572.</p>	<p>117 patients total; treated for SCID between 1970 and 1992; 85 children were treated with BMT.</p>	<ul style="list-style-type: none"> • Estimated SCID incidence: 1/ 100-150,000. • HLA-identical transplant from a related donor 21/25 (84% survived). • Pheno-identical transplant (HLA-genotypically haplo-identical) from related donor 2/5 (40% survived). • HLA- haplo-identical transplant without T-cell depletion 0/5 (0% survived). • T-cell depleted haplo-identical transplant 28/50 (56% survived). • 22 children did not receive any type of transplant and died. • 10 received fetal liver transplant, 9 died post transplant.
<p>Case series* ^Potential patient overlap with Stephan et al. 1993 and Wijnaendts et al. 1989</p>		
<p>Touraine, J.L., Plotnicky, H., Roncarolo, M.G., Bacchetta, R. & Gebuhrer, L. 2007, "Immunological lessons learnt from patients transplanted with fully mismatched stem cells", <i>Immunologic Research</i>, vol. 38, no. 1-3, pp. 201-209.</p>	<p>19 patients total; 17 infants and 2 fetuses.</p>	<ul style="list-style-type: none"> • Stem cells from fetal liver were used for transplants. • 14/19 had evidence of engraftment and immunological reconstitution. • In the 3 patients for whom information was available, there was normal antibody responses several years after transplant.
<p>Case series*</p>		
<p>van Leeuwen, J.E., van Tol, M.J., Joosten, A.M., Schellekens, P.T., van den Bergh, R.L., Waaijer, J.L., Oudeman-Gruber, N.J., van der Weijden-Ragas, C.P., Roos, M.T. & Gerritsen, E.J. 1994, "Relationship between patterns of engraftment in peripheral blood and immune reconstitution after allogeneic bone marrow transplantation for (severe) combined immunodeficiency", <i>Blood</i>, vol. 84, no. 11, pp. 3936-3947.</p>	<p>31 patients total; 1-94 months old at BMT.</p>	<ul style="list-style-type: none"> • HLA-identical related 6/10 (60% survived) • HLA- haplo-identical related: 9/19 (47% survived). • HLA-matched unrelated: 0/2 (0% survived). • Major causes of death were graft and respiratory failure. • All who died of respiratory failure had a lung infection prior to transplant. • All children with sustained engraftment had evidence of humoral immunity.
<p>Case series*</p>		

<p>Veys, P., Rao, K. & Amrolia, P. 2005, "Stem cell transplantation for congenital immunodeficiencies using reduced-intensity conditioning", <i>Bone Marrow Transplantation</i>, vol. 35 Suppl 1, pp. S45-7.</p>	<p>81 children total; 0.1-17.6 years old, with congenital immunodeficiencies, 20 with SCID.</p>	<ul style="list-style-type: none"> • All subjects treated with HSCT with reduced-intensity conditioning. • Survival rate 84% (68/81) with survival difference between SCID and non-SCID. • Increase in reactivation of EBV compared to conventional BMT procedures. • HSCT with reduced-intensity conditioning appeared to be well tolerated.
<p>Case series* ^Potential patient overlap of Amrolia et al. 2000, Rao et al. 2005, and Veys, Rao & Amrolia 2005</p>		
<p>Vossen, J.M., van Leeuwen, J.E., van Tol, M.J., Joosten, A.M., van den Berg, H., Gerritsen, E.J., Haraldsson, A. & Khan, P.M. 1993, "Chimerism and immune reconstitution following allogeneic bone marrow transplantation for severe combined immunodeficiency disease", <i>Immunodeficiency</i>, vol. 4, no. 1-4, pp. 311-313.</p>	<p>14 children evaluated; 1-23 years after BMT.</p>	<ul style="list-style-type: none"> • All children who survived greater than 1 year had some donor T-cell engraftment. • Cellular immunity was quantitatively low but mostly qualitatively normal.
<p>Case series*</p>		
<p>Waruiru, C., Slatter, M.A., Taylor, C., Ramesh, V., Flood, T.J., Abinun, M., Cant, A.J. & Gennery, A.R. 2007, "Outcome of hematopoietic stem cell transplantation in severe combined immune deficiency with central nervous system viral infection", <i>The Pediatric Infectious Disease Journal</i>, vol. 26, no. 2, pp. 129-133.</p>	<p>8 patients total; median age of 3 months old (range: 6 weeks to 7 years), 7 are children with SCID treated with HSCT.</p>	<ul style="list-style-type: none"> • All children with central nervous system viral infections prior to HSCT. • Neurologic manifestations of infection were present in 4 patients before HSCT. • Magnetic resonance image abnormalities ranged from cerebral atrophy to multifocal diffuse mass lesions. • Of 6 patients who had an electroencephalographic examination, most showed slow wave activity. • Only 3 children remain alive. • 5/8 children died in first 200 days after HSCT from neurologic sequelae or disseminated infection.
<p>Case series*</p>		
<p>Wijnaendts, L., Le Deist, F., Griscelli, C. & Fischer, A. 1989, "Development of immunologic functions after bone marrow transplantation in 33 patients with severe combined immunodeficiency", <i>Blood</i>, vol. 74, no. 6, pp. 2212-2219.</p>	<p>33 children treated with HST between 1972 and 1987 surviving a minimum of 6 months: 18 HLA-identical transplants and 15 HLA-non-identical transplants.</p>	<ul style="list-style-type: none"> • Development of immune function occurred faster in patients with HLA-identical transplants. • Development of T- and B-cell function occurred faster when chemotherapy preceded BMT. • Poor B-cell function was observed more frequently when chemotherapy was not used.

* Study conducted outside the United States

Economic evaluation

(alphabetical by last name of first author)

Author(s) , Year, Title of Paper
& Study Design

Population

Significant Findings

McGhee, S.A., Stiehm, E.R. & McCabe, E.R. 2005, "Potential costs and benefits of newborn screening for severe combined immunodeficiency", *The Journal of Pediatrics*, vol. 147, no. 5, pp. 603-608.

N/A

- At a threshold of \$100,000/QALY there is 86% likelihood of screening being cost-effective; this would be true with 61.2% false-neg rate, 3.2% false-positive rate; test cost of about \$15, incidence of 1:125,00 and treatment costs of \$1.35 million.
- Assuming base case scenario, the cost to identify and treat each case would be \$485,000; implementation of screening would cost \$23,920,000 and save 760 life-years per year of screening.

Economic Evaluation (from Drummond)

XI. Appendix B- Conflict of interest form

MGH Center for Child and Adolescent Health Policy



MassGeneral Hospital
for Children[™]

**BACKGROUND INFORMATION
AND
CONFIDENTIAL CONFLICT OF INTEREST DISCLOSURE
*For Newborn Screening Evidence Working Group Reviews***

NAME: _____ TELEPHONE: _____

ADDRESS: _____

EMAIL ADDRESS: _____

CURRENT EMPLOYER: _____

ROLE: Staff member _____ Proposer _____ Consultant _____
Company representative _____ Principal investigator _____
Parent group _____ State health department _____
Other (specify) _____

(Please make all that apply.)

There are two parts to this form, Part I Background Information, and Part II Confidential Conflict of Interest Disclosure. Complete both parts, **sign** and **date** this form on the last page, and return the form to the responsible staff member for the ***MGH Center for Child and Adolescent Health Policy Newborn Screening Evidence Working Group*** program. **Retain a copy for your records.**

PART I BACKGROUND INFORMATION

INSTRUCTIONS

Please provide the information requested below regarding **relevant** organizational affiliations, government service, public statements and positions, research support, and additional information (if any). Information is "relevant" if it is related to -- and might reasonably be of interest to others concerning -- your knowledge, experience, and personal perspectives regarding the subject matter and issues to be addressed by the evidence team efforts in general or for a specific screening proposal. If some or all of the requested information is contained in your curriculum vitae, you may if you prefer simply attach your CV to this form, supplemented by additional responses or comments below as necessary.

- I. **ORGANIZATIONAL AFFILIATIONS.** Report your relevant business relationships (as an employee, owner, officer, director, consultant, etc.) and your relevant remunerated or volunteer non-business relationships (e.g., professional organizations, trade associations, public interest or civic groups, etc.).
- II. **GOVERNMENT SERVICE.** Report your relevant service (full-time or part-time) with federal, state, or local government in the United States (including elected or appointed positions, employment, advisory board memberships, military service, etc.).
- III. **RESEARCH SUPPORT.** Report relevant information regarding both public and private sources of research support (other than your present employer), including sources of funding, equipment, facilities, etc.
- IV. **PUBLICATIONS.** Please list all publications related to the evidence topic or the work of the Evidence Working Group. Please separate peer-reviewed from other publications.
- V. **PUBLIC STATEMENTS AND POSITIONS.** List your relevant articles, testimony, speeches, etc., by date, title, and publication (if any) in which they appeared, or provide relevant representative examples if numerous. Provide a brief description of relevant positions of any organizations or groups with which you are closely identified or associated.
- VI. **ADDITIONAL INFORMATION.** If there are relevant aspects of your background or present circumstances not addressed above that might reasonably be construed by others as affecting your judgment in matters within the specified evidence reviews and therefore might constitute an actual or potential source of bias, please describe them briefly.

PART II CONFIDENTIAL CONFLICT OF INTEREST DISCLOSURE

INSTRUCTIONS

It is essential that the work of the Evidence Working Group and its advisors used in the development of reports for the Advisory Committee on Heritable Disorders and Genetic Diseases of Newborns and Children (ACHDGDNC) not be compromised by any significant conflict of interest. For this purpose, **the term "conflict of interest" means any financial or other interest which conflicts with the service of the individual because it (1) could significantly impair the individual's objectivity or (2) could create an unfair competitive advantage for any person or organization.** Except for those situations in which the working group determines that a conflict of interest is unavoidable and promptly and publicly discloses the conflict of interest, no individual can be participate in the development of evidence reports if the individual has a conflict of interest that is relevant to the functions to be performed.

The term "conflict of interest" means something more than individual bias. There must be an *interest*, ordinarily financial, that could be directly affected by the work of the committee.

Conflict of interest requirements are *objective* and *prophylactic*. They are not an assessment of one's actual behavior or character, one's ability to act objectively despite the conflicting interest, or one's relative insensitivity to particular dollar amounts of specific assets because of one's personal wealth. Conflict of interest requirements are objective standards designed to eliminate certain specific, potentially compromising situations from arising, and thereby to protect the individual, the other members of the working group and its advisors, the ACHDGDNC, and the public interest. The individual, the committee, and the institution should not be placed in a situation where others could reasonably question, and perhaps discount or dismiss, the work of the group simply because of the existence of conflicting interests.

The term "conflict of interest" applies only to *current interests*. It does not apply to past interests that have expired, no longer exist, and cannot reasonably affect current behavior. Nor does it apply to possible interests that may arise in the future but do not currently exist, because such future interests are inherently speculative and uncertain. For example, a pending formal or informal application for a particular job is a current interest, but the mere possibility that one might apply for such a job in the future is not a current interest.

The term "conflict of interest" applies not only to the personal interests of the individual but also to the *interests of others* with whom the individual has substantial common financial interests if these interests are relevant to the functions to be performed. Thus, in assessing an individual's potential conflicts of interest, consideration must be given not only to the interests of the individual but also to the interests of the individual's spouse/partner and minor children, the individual's employer, the individual's business partners, and others with whom the individual has substantial common financial interests. Consideration must also be given to the interests of those for whom one is acting in a fiduciary or similar capacity (e.g., being an officer or director of a corporation, whether profit or nonprofit, or serving as a trustee).

Much of the work of the Evidence Working Group involves scientific and technical studies and assistance for the ACHDGDNC. Related activities may include, for example: assessing prevalence, testing, and treatment data; defining research needs, priorities, opportunities and agendas; addressing questions of human health promotion and assessment; and assessing the state of scientific or technical knowledge on particular genetic diseases. Such activities frequently address scientific and technical issues that are sufficiently broad in scope that they do not implicate specific financial interests or conflict of interest concerns.

However, where such activities address more specific issues having significant financial implications -- e.g., judging the quality of the evidence related to a specific disease or disorder, making recommendations to agencies regarding specific research needs, etc. -- careful consideration must be given to possible conflict of interest issues with respect to the role of staff, consultants, and advisors who will be used by the Evidence Working Group in the development of reports to be provided to the ACHDGDNC.

The overriding objective of the conflict of interest inquiry in each case is to identify whether there are interests -- primarily financial in nature -- that conflict with the service of the individual because they could impair the individual's objectivity or could create an unfair competitive advantage for any person or organization. The fundamental question in each case is does the individual, or others with whom the individual has substantial common financial interests, have identifiable interests that could be directly affected by the outcome of the Evidence Working Group activities?

The application of these concepts to specific scientific and technical studies and assistance projects must necessarily be addressed in each case on the basis of the particular facts and circumstances involved. The questions set forth below are designed to elicit information from you concerning possible conflicts of interest that are relevant to the functions to be performed by the Evidence Working Group and your relationship to the group.

1. FINANCIAL INTERESTS. (a) Taking into account stocks, bonds, and other financial instruments and investments including partnerships (but excluding broadly diversified mutual funds and any investment or financial interests valued at less than \$10,000), do you or, to the best of your knowledge others with whom you have substantial common financial interests, have financial investments that could be affected, either directly or by a direct effect on the business enterprise or activities underlying the investments, by the outcome of the Evidence Working Group and its reports to the ACHDGDNC?

(b) Taking into account real estate and other tangible property interests, as well as intellectual property (patents, copyrights, etc.) interests, do you or, to the best of your knowledge others with whom you have substantial common financial interests, have property interests that could be directly affected by the outcome of the Evidence Working Group and its reports to the ACHDGDNC?

(c) Could your employment or self-employment (or the employment or self-employment of your spouse/partner), or the financial interests of your employer or clients (or the financial interests of

your spouse's employer or clients) be directly affected by the outcome of the Evidence Working Group and its reports to the ACHDGDNC?

(d) Taking into account research funding and other research support (e.g., equipment, facilities, industry partnerships, research assistants and other research personnel, etc.), could your current research funding and support (or that of your close research colleagues and collaborators) be directly affected by the outcome of the Evidence Working Group and its reports to the ACHDGDNC?

(e) Could your service create a specific financial or commercial competitive advantage for you or others with whom you have substantial common financial interests?

If the answer to all of the above questions under FINANCIAL INTERESTS is either "no" or "not applicable," check here _____ (NO).

If the answer to any of the above questions under FINANCIAL INTERESTS is "yes," check here ____ (YES), and briefly describe the circumstances on the last page of this form.

2. OTHER INTERESTS. (a) Is the central purpose of the project for which this disclosure form is being prepared a critical review and evaluation of your own work or that of your employer?

(b) Do you have any existing professional obligations (e.g., as an officer of a scientific or engineering society) that effectively require you to publicly defend a previously established position on an issue that is relevant to the functions to be performed by the Evidence Working Group?

(c) To the best of your knowledge, will your participation in this committee activity enable you to obtain access to a competitor's or potential competitor's confidential proprietary information?

(d) If you are or have ever been a U.S. Government employee (either civilian or military), to the best of your knowledge are there any federal conflict of interest restrictions that may be applicable to your service in connection with this committee activity?

If the answer to all of the above questions under OTHER INTERESTS is either "no" or "not applicable," check here _____ (NO).

If the answer to any of the above questions under OTHER INTERESTS is "yes," check here ____ (YES), and briefly describe the circumstances on the last page of this form.

EXPLANATION OF "YES" RESPONSES:

During your period of service in connection with the activity for which this form is being completed, any changes in the information reported, or any new information, which needs to be reported, should be reported promptly by written or electronic communication to the responsible staff member.

YOUR SIGNATURE

DATE

Reviewed by: _____
PRINCIPAL INVESTIGATOR

DATE

XII. Appendix C- Letter and questions sent to SCID experts

Dear (name of specialist),

You have been identified as a key subject matter expert in the field of Severe Combined Immunodeficiency (SCID). As such, we are requesting input from you concerning the viability and efficacy of newborn screening for this condition.

As you likely know, the Secretary of the Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) has the responsibility to make evidence-based recommendations regarding newborn screening. The Committee has recently been given the task of evaluating evidence for heritable diseases that have been formally nominated for neonatal screening. The advisory committee has in turn asked an Evidence Review Workgroup, based in the MGH Center for Child and Adolescent Health Policy, to develop systematic reviews of evidence to help the committee in its deliberations.

We are currently in the process of conducting a review of Severe Combined Immunodeficiency (SCID) and are writing to request your help with this process. Specifically, we would like to know if you are available to share your experience and expertise regarding the current state of SCID screening, diagnosis, and treatment. Participating in this project would involve answering a short set of questions which ask about your clinical experience with SCID (see attachment). After providing responses to these inquiries, we will likely want to contact you by phone, so that we may clarify some of your answers or seek more information about certain topics.

Our goal in contacting you is to have access to the most recent and up to date information available regarding SCID. In all of its activities, the Evidence Review Group has maintained sensitivity to issues of conflict of interest and the importance of limiting bias in the development of evidence. Should you agree to discuss your work with us, we will discuss with you at that time our approach to confidentiality, transparency, conflict of interest, and our requirements for public reporting.

If you are willing to help in this crucial review process, please return your answers to the attached questions by Friday August 29th, along with a signed copy of the attached conflict of interest form. Additionally, in case we need clarification regarding your responses, please send us a list of times between September 2nd and September 12th when you would be available to discuss you answers over the phone. You may send all of these materials to Project Manager Alix Knapp by email (aaknapp@partners.org) or confidential fax (617-726-1886).

We appreciate your unique insight into this condition. We thank you in advance for participation and look forward to hearing from you.

Sincerely,

Marsha Fearing Browning, M.D., M.P.H., MMSc.
Medical Genetics, MassGeneral Hospital for Children

James M Perrin, M.D.
Professor of Pediatrics, Harvard Medical School
Director, Division of General Pediatrics
Director, MGH Center for Child & Adolescent Health Policy
Associate Chair for Research, MassGeneral Hospital for Children

Key Questions:

A. Diagnosis

1. Do you have any data regarding the distribution of the different phenotypes/genotypes of SCID?
2. At the time of diagnostic evaluation, what processes are used to determine genotype?
3. Describe the most effective process to phenotype patients and issues that may confound the diagnosis:

B. Treatment

1. If you are currently involved in the treatment of patients with SCID, what is your treatment protocol for SCID in patients either diagnosed clinically or through newborn screening?
2. What are the major challenges to treating SCID?
3. What unique outcomes data for the treatment of SCID can you provide?
4. From your perspective, how many treatment centers in the U.S. exist that can provide appropriate treatment for SCID?
5. What estimates (insight?) do you have regarding the cost of treatment for SCID or ways of measuring those costs?

C. Screening

If you currently participate in a newborn screening protocol for SCID and/or you participate in a "clinical laboratory" screening program for SCID please answer the following:

Describe your screening protocol, including:

1. Describe your screening protocol, including:

- a. What is your first tier test (e.g., fluorometry, PCR, etc)?
 - b. What, if anything is your second tier test (i.e., testing on the same screening sample if the first tier test is abnormal)?
 - c. What subsequent testing do you perform on a new sample from an individual with an abnormal first tier/second tier test (i.e., third tier testing)?
2. What are the advantages and disadvantages of your screening protocol?
- a. If your screening protocol has been implemented, please describe your experience, including:
 - b. When screening began
 - c. The number of children who have been screened
 - d. The total number of children that had a positive screening test that required a diagnostic evaluation
 - e. The number of cases identified. If possible, please characterize the immune phenotype or genotype of these cases. How many were SCID? How many were other types of immunodeficiencies?
 - f. The cost of screening. Because costs can be determined so many different ways, please outline what is included in your calculation.

D. Additional Comments:

Please submit any additional comments that may contribute towards implementation of newborn screening for this disease.

XIII. Appendix D- Letter and questions sent to SCID advocacy groups

Dear Name of Advocacy Group,

As you likely know, the Secretary of the Health and Human Services Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC) is responsible for making evidence-based recommendations regarding what tests to include in newborn screening. The Committee has the responsibility to evaluate evidence for heritable diseases that have been formally nominated for neonatal screening. The advisory committee asked an Evidence Review Workgroup, based in the MGH Center for Child and Adolescent Health Policy, to develop systematic reviews of evidence to help the committee in its deliberations. As a parent of a child with a genetic disorder, I am working as a member of the Evidence Review Workgroup to gather views and evidence from parents and advocacy groups.

We are currently conducting a review of Severe Combined Immunodeficiency (SCID) and are writing to request your help with this endeavor. Specifically, we would like to know if you are available to share your experience and expertise as a parent regarding the current state of SCID screening, diagnosis, and treatment. Participating in this project would involve answering a short set of questions about your experience with SCID. After providing responses to these inquiries, you may also be contacted by phone, so that we may clarify some of your answers or seek more information about certain topics.

Our goal in contacting you is to have access to the most recent and up to date information available regarding SCID. In all of its activities, the Evidence Review Group has maintained sensitivity to issues of conflict of interest and the importance of limiting bias in the development of evidence. Should you agree to discuss your experience with us, we will discuss with you at that time our approach to confidentiality and transparency.

If you can help in this review process, please return your answers to the questions we have provided by Friday, December 19th, along with a signed copy of the attached conflict of interest form. Additionally, in case we need clarification regarding your responses, please send us a list of times between January 6th and 9th, 2009, when you would be available to discuss your answers over the phone. You may send all of these materials to Project Manager Alixandra Knapp by email (aaknapp@partners.org) or fax (617-726-1886).

Thank you very much for your time. We look forward to hearing from you.

Sincerely,

Denise Queally
Consumer Perspective
Evidence Review Group

James M. Perrin, MD
Professor of Pediatrics

Key Questions:

Please answer the following questions based on your experiences with families of children with SCID.

I. Screening

- What do you know about screening children for SCID? Do you have information about how effective it is?
- Do you or your group recommend particular screening approaches? If so, which, and why?

II. Diagnosis

- Can you provide any information regarding the distribution or rates of the different physical or clinical characteristics of SCID?
- What information can you provide about the relationship between any gene findings (especially, by screening in infancy) and the child's clinical course?
- Are there benefits to early identification and diagnosis of SCID? If so, what are they?

III. Treatment

- How effective is treatment for SCID? What is done and how well does it work?
- How many treatment centers exist in the United States, and how do you learn of them?
- What are your experiences with any potential harms, physical or non-physical, associated with treatment?

IV. Other Information

- Is there anything else about SCID that you would like to share with us?