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# NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY (SCID)

Routine screening of all newborns for harmful or potentially lethal conditions (e.g., genetic, endocrine, hemoglobin, metabolic disorders) began in the United States in the 1960s. Since that time, "universal newborn screening has become a well-established, state-based, public health system involving education, screening, diagnostic follow-up, treatment and management, and system monitoring and evaluation".[1] Beginning May 1, 2014, Severe Combined Immunodeficiency (SCID) was added to the panel of disorders for which all Oregon newborns are screened. The Oregon State Public Health Laboratory (OSPHL) screens dried blood samples collected at birth for 29 core conditions (designated by the U.S. Department of Health and Human Serivces (DHHS) as the national standard), and 25 secondary conditions. SCID is the most recent addition to the "core list." This *CD Summary*, adapted from a publication by Dr. Jennifer Puck, focuses on the basics of SCID screening.[2]

## EVIDENCE FOR ADDING SCID TO CORE PANEL

SCID includes more than 10 genetic disorders characterized by profound defects in both cellular immunity and specific antibody production; it is estimated to occur in one of every 50,000–100,000 babies. All SCID infants have absent or extremely low production of naïve T cells from their thymus. The combined defects of T and B cells, plus absent natural killer (NK) cells in some forms of SCID, severely compromise an infant's ability to resist infections. Thus, SCID has long been clinically identified in infants without HIV infection who present with *Pneumocystis jiroveci* pneumonia, other bacterial, fungal and viral infections, and failure to thrive, which can be caused by persistent enteric infection.

The rationale for SCID newborn screening, outlined in Table 1, centers on the fact that SCID is potentially treatable but infrequently recognized prior to the onset of devastating infections. SCID infants do not survive unless provided with functional immunity, which can be achieved by hematopoietic cell transplantation (HCT) from a healthy donor.[3]

**Table 1. Rationale for newborn screening for SCID**

| | |
|---|---|
| Importance of early identification | • Establish diagnosis and institute immediate lifesaving treatment.<br>• Avoid inefficient, costly, dangerous 'diagnostic Odyssey.'<br>• Provide families with genetic diagnosis and advice on reproductive risks.<br>• Learn incidence and true spectrum of SCID.<br>• Educate providers and public about SCID.<br>• Permit multicenter collaborative trials to determine optimal treatments. |
| Barriers to early diagnosis without screening | • SCID and related conditions are rare.<br>• Infections are common in all infants, not just those with SCID.<br>• >80% of cases are sporadic, with no family history.<br>• Family history can be missed, or nonspecific.<br>• SCID infants are protected by maternal IgG during the first months of life.<br>• Because both a gene defect and environmental exposures are required for overt diseases, presentation is variable. |



Infants with SCID are healthy at birth and initially protected by passive transfer of maternal antibodies, but typically develop severe and opportunistic infections by 4–7 months of age. Repeated observations have shown superior outcomes in SCID infants diagnosed and treated at younger ages.[4–9]

Upon the recommendation of the Advisory Committee on Heritable Disorders in Newborns and Children, the DHHS added SCID to the national Recommended Uniform Screening Panel for all U.S. infants in May 2010.

## THE TREC TEST

A breakthrough in population-based newborn screening for SCID was the development of a screening test that could be performed on the dried blood spot samples already collected for routine newborn screening. Results are based on the detection of T-cell receptor ex cision circles (TRECs). Late in maturation, 70% of thymocytes that will ultimately express αβ-T cell receptors form a circular DNA TREC from the excised TCRδ gene that lies within the TCRα genetic locus.*[10] The circles are stable but do not increase following cell division and, therefore, become diluted as T cells proliferate. A quantitative polymerase chain reaction (PCR) across the joint of the circular DNA provides the TREC copy number, a marker of newly-formed, antigenically-naïve thymic emigrant T cells.

Normal newborns have TREC numbers equal to ~10% of their total T-cell numbers, whereas older children and adults have progressively lower ratios of TRECs to T cells, reflecting peripheral T-cell expansion.[10] Infants with SCID, sampled both at diagnosis and from neonatal dried blood spots, have very low or undetectable TRECs.[11,12] The TREC test was first adapted to statewide newborn screening in Wisconsin;[13] 24 states now offer SCID screening for all newborns.

## CONDITIONS DETECTED BY NEWBORN SCREENING

SCID newborn screening programs have successfully identified a range of typical SCID and other conditions

*as if you didn't know...

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that would not otherwise have been identified before the onset of serious infections (Table 2). In addition, severely affected patients with variant forms of SCID such as cartilage-hair hypoplasia could be expected to have abnormal TREC results because their T cells can be nearly absent. CHARGE syndrome, Down syndrome and DiGeorge syndrome, the latter usually with chromosome 22 deletion,[12] can present with life-threatening infections in infancy due to T-cell deficiency, and have been identified by neonatal TREC screening.[14–16]

## FOLLOW-UP OF ABNORMAL TREC RESULTS

Newborns with abnormally low TREC results will be referred to our consultants, Drs. Eneida Nemecek and Evan Shereck, pediatric bone marrow transplant specialists at Oregon Health & Science University. They will contact primary providers immediately upon notification to provide recommendations for further evaluation, diagnosis and treatment. The goal is to get infants with positive screens evaluated as soon as possible.

## FOR MORE INFORMATION

- OSPHL's Newborn Screening Program *https://public.health.oregon.gov/LaboratoryServices/NewbornScreening/Pages/index.aspx*
- The American College of Medical Genetics: *www.acmg.net/staticcontent/act/scid.pdf*

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**Table 2. Conditions detected by low or absent TRECs**

| | |
|---|---|
| Typical SCID | Due to mutations in IL2RG,* IL7R,* JAK3,* ADA,* RAG1,* RAG2,* DCLRE1C (Artemis),* LIG4,** CD3 receptor chains, STAT5, PNP, Coronin-1A, and—as yet—unknown genes |
| Leaky SCID | Due to incomplete (hypomorphic) mutation in a typical SCID gene |
| Variant SCID | With no known gene defect and persistence of 300–1500 T cells/μL that have impaired function |
| Syndromes with variably affected cellular immunity that can be severe | Complete DiGeorge syndrome,* Partial DiGeorge syndrome with low T lymphocytes,* CHARGE syndrome,* Jacobsen syndrome,* Trisomy 21,* RAC2 dominant interfering mutation,* DOCK8 deficient hyper-IgE syndrome,** Cartilage hair hypoplasia |
| Secondary T lymphocytopenia | Cardiac surgery with thymectomy,* Neonatal leukemia,* Gastroschesis,* Third spacing,* Extreme prematurity (resolves to normal with time),* HIV* |

*observed to have low or absent TRECs upon newborn screening in one or more cases to date in U.S. pilot programs or published reports.
**observed to have low or absent TRECs in one or more cases after diagnosis.