CLSI Guidelines on Newborn Screening for Severe Combined Immunodeficiency (SCID)

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CLSI guidelines

Clinical Laboratory Standards Institute is an international nonprofit organization

Their mission is to develop voluntary consensus standards and guidelines for patient testing

CLSI guidelines

- Uses International Standards Organization (ISO9000) to ensure harmonization of language
- Document development is meant to facilitate the rapid creation of guidelines and their dissemination
- It is an ongoing process and revised editions are expected to be released as the field develops
- The FDA has the authority to use CLSI guidelines for *in vitro* diagnostic testing standards

CLSI guidelines

- Document development committee (DDC) is composed of experts in the field
- Approval of the document is by unanimous vote of the DDC with solicited comments by the CLSI delegates
- Final approval is by the Consensus Committee

Newborn Screening for SCID

2008

Wisconsin begins statewide screening

2009

Massachusetts begins statewide screening

2010

SCID is added to U.S. Recommended Uniform Screening Panel (RUSP)

2010

California and New York begin screening

2011

Connecticut, Colorado begin screening

Guidelines Development

August 2011

CLSI convenes DDC in Atlanta

June 2012

DDC votes to adopt the CLSI draft

Oct-Nov 2012

draft document is open for comments from CLSI Delegates (~1100)

March 2013

draft is finalized and approved by consensus committee

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Appendix A. Immunodeficiency Disorders and T-cell Receptor Excision Circle (TREC) Values in the Newborn Screening Period*

**The term "newborn screening period" refers to the recommended timeframe during which dried blood spots are collected for initial screening, typically 24-72 hours after birth.*

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- **** TREC values have been reported to fall below the expected range in only a subset of affected newborns with these disorders, or insufficient data is available.***

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Appendix A. Immunodeficiency Disorders and T cell Receptor Excision Circle (TREC) Values in the Newborn Screening Period*

A1. Primary Immunodeficiency Disorders Typically Associated with TREC Values Below the Expected Range in the Newborn Screening Period

DISORDERS	AFFECTED GENES
Severe combined immunodeficiency (Typical SCID)	*ADA*[1] *CD3D* (encodes CD3 delta) *CD3E* (encodes CD3 epsilon) *CD3Z* (encodes CD3 zeta) *DCLRE1C* (encodes Artemis) *IL2RG* (except p.R222C mutation) *IL7RA* *JAK3* *PTPRC* (encodes CD45) *PRKDC* (encodes DNA-PKcs) *RAG1* *RAG2* [Others]
Reticular Dysgenesis	*AK2*
Coronin-1A deficiency	*CORO1A*
Thymic Aplasia (Complete DiGeorge Syndrome)	22q11.2 deletion [Others]

[1] Amorphic (null) mutations resulting in a complete enzyme deficiency

**** The term "newborn screening period" refers to the recommended timeframe during which dried blood spots are collected for initial screening, typically 24-72 hours after birth.***

A2. Primary Immunodeficiency Disorders Variably Associated* with TREC Values Below the Expected Range in the Newborn Screening Period

DISORDERS	AFFECTED GENES
Leaky SCID/Omenn syndrome	Hypomorphic Mutations in: *ADA* *DCLRE1C* *PTPRC* *IL2RG* *IL7RA* *JAK3* *LIG4* (DNA ligase IV) *RAG1* *RAG2*
Cartilage hair hypoplasia	*RMRP*
Cobalamin and folate metabolism deficiencies	*MTHFD1, MTR, SLC46A1*
Variant SCID	[Others]
Syndromes with T cell impairment a. DiGeorge syndrome/22q11.2 deletion syndrome b. Cernunnos-XLF deficiency c. CHARGE[1] syndrome d. Jacobsen syndrome e. Small GTP binding protein Rac2 defect[3] f. Dedicator of cytokinesis 8 deficiency g. Ataxia telangiectasia h. VACTERL[2] association i. Barth syndrome[3] j. Thrombocytopenia-absent radius (TAR) syndrome[3] k. Down syndrome/Trisomy 21 l. Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome[3]	 a. 22q11.2 deletion, *TBX1*, 10p deletion b. *NHEJ1* c. *CHD7* d. 11q deletion e. *RAC2* f. *DOCK8* g. *ATM* h. multiple defects i. *TAZ* j. *RBM8A* (1q21.1 deletion) k. Chr 21 trisomy l. *TP63*

* TREC values have been reported to fall below the expected range in only a subset of affected newborns with these disorders, or insufficient data is available.

A3. Primary Combined Immunodeficiency Disorders Unlikely to be Associated with TREC Values Below the Expected Range in the Newborn Screening

DISORDERS	AFFECTED GENES
a. Adenosine deaminase deficiency (Partial)	a. *ADA*[1]
b. CD3γ deficiency	b. *CD3G*
c. CD8 deficiency	c. *CD8A*
d. Common gamma-chain deficiency	d. *IL2RG p.R222C mutation*
e. IKAROS family zinc finger 1 deficiency	e. *IKZF1*
f. IL2-inducible T-cell kinase deficiency	f. *ITK*
g. Lymphocyte-specific protein tyrosine kinase deficiency	g. *LCK*
h. Magnesium transporter 1 deficiency	h. *MAGT1*
i. MHC class I deficiency (Bare Lymphocyte Syndrome I)	i. *TAP1, TAP2, TAPBP*
j. MHC class II deficiency (Bare Lymphocyte Syndrome II)	j. *CIITA,RFX5,RFXAP RFXANK*
k. Macrophage stimulating 1 protein deficiency	k. *MST1*
l. Calcium channelopathies	l. *ORAI1, STIM1*
m. Purine nucleoside phosphorylase deficiency	m. *PNP*
n. ras homolog family member H deficiency	n. *RHOH*
o. STAT5b transcription factor deficiency	o. *STAT5B*
p. TCR-alpha deficiency	p. *TRAC*
r. Uncoordinated protein119 deficiency	r. *UNC119*
s. zeta-chain (TCR) associated protein kinase deficiency	s. *ZAP70*

[1] Hypomorphic mutations that result in only a partial enzyme deficiency

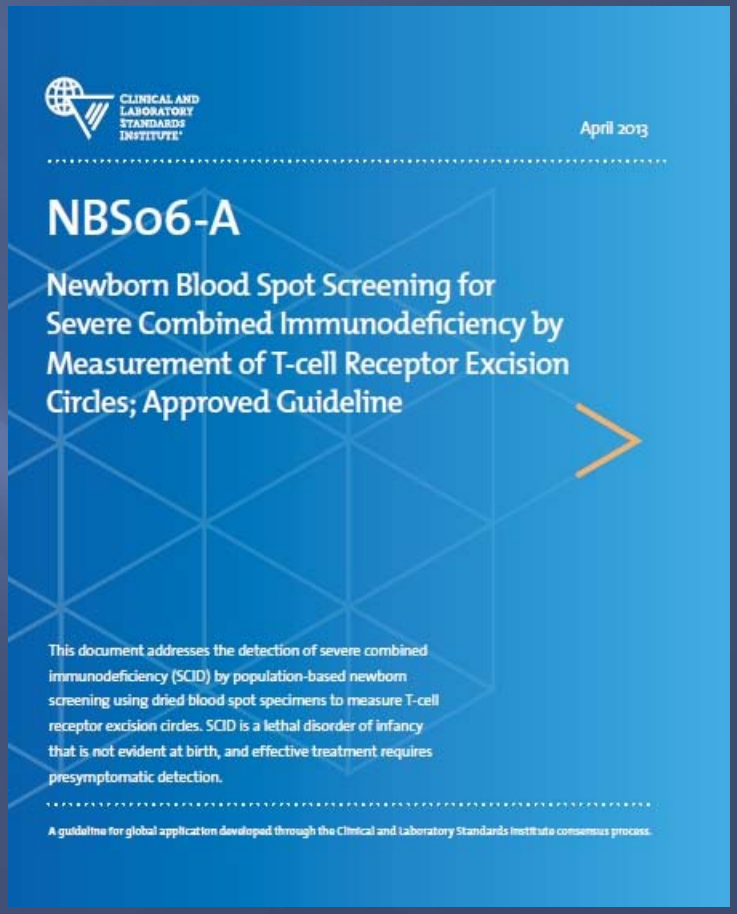
A4. Secondary Disorders Variably Associated* with TREC Values Below the Expected Range in the Newborn Screening Period

Prematurity
Secondary T-cell lymphopenia other than prematurity alone Intestinal lymphangiectasia Anasarca Gastroschisis Third-spacing Gastrointestinal atresia Cardiac surgery ± thymectomy Congenital heart defects Neonatal leukemia Chylothorax Chyloperitoneum Hypoplastic left heart syndrome Multiple congenital anomalies / not otherwise specified (NOS) Degenerative neuromuscular disease/NOS Presumed metabolic disorders/NOS "Unmarkable" lymphocytes/NOS

* TREC values have been reported to fall below the expected range in only a subset of affected newborns with these disorders, or insufficient data is available.

Conclusions

- CLSI guidelines on Newborn Blood Spot Screening for SCID are now available
- An ongoing review process will initiate updates of this document at regular intervals



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