Diagnosis and Short-Term Follow-up of Cases found by TREC Newborn Screening

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Severe Combined Immunodeficiency, SCID

- Absent T cells; no specific antibody production by B cells.
- Recurrent infections and weight loss from age 2-4 months.
- Serious bacterial, viral, & fungal infections; opportunistic pathogens that do not cause disease in healthy infants.
- Early death unless a working immune system can be established (by allogeneic transplant of hematopoietic stem cells, HSC, or in some cases enzyme replacement or gene therapy).
- Improved outcome with diagnosis at birth (≥92%) or prior to infectious complications (≤75%).

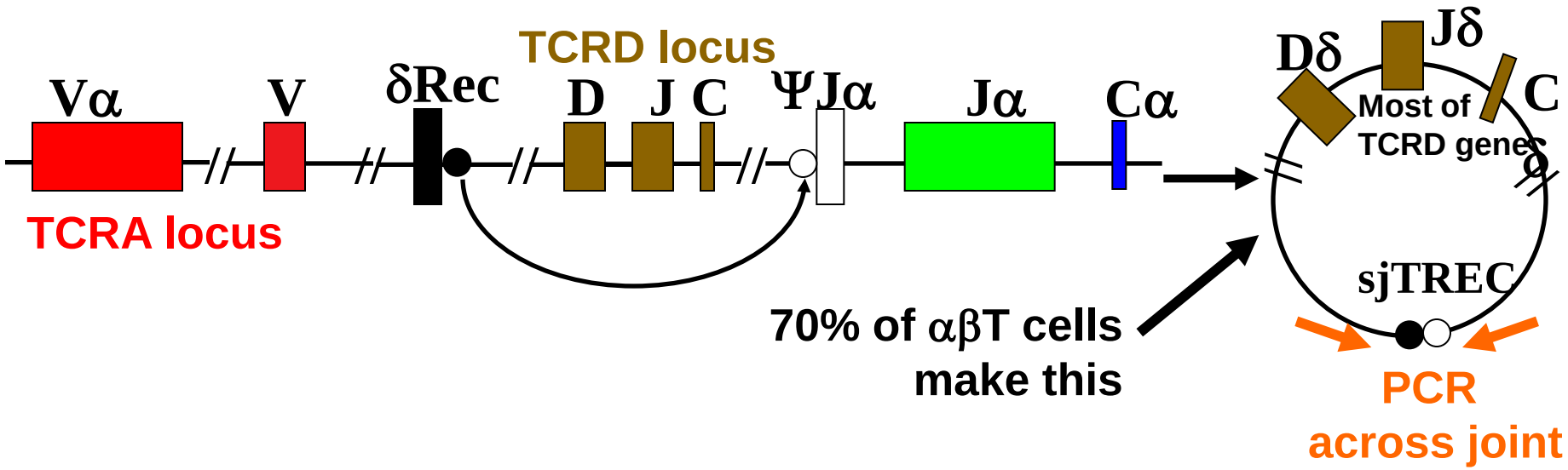
Primary Target: SCID; Many Genes, Distinct T, B, NK profiles

IL2RG (common γ chain, X-linked)		T-	B+	NK-
JAK3 (γ chain associated Janus kinase)	T-	B+	NK-	
IL7R (IL-7 receptor α chain)		T-	B+	NK+
CD45 (membrane tyrosine phosphatase)		T-	B+	NK+
TCRD/E/Z (TCR CD3 δ,ε,ξ chains)		T-	B+	NK+
RAG1/RAG2		T-	B-	NK+
DCLRE1C (Artemis)		T-	B-	NK+
LIG4 (DNA ligase IV)		T-	B-	NK+
PRKDC (DNA PKcs)		T-	B-	NK+
ADA (adenosine deaminase)		T-	B-	NK-
AK2 (reticular dysgenesis, deafness)		T-	B+/-	NK+
TTC7A (multiple bowel atresias)	T-	B+/-	NK+	
RMRP (cartilage hair hypoplasia)		T-	B+/-	NK+
FOXN1 (nude mouse)	T-	B+	NK+	
CORO1A (Coronin-1A, thymic egress)	T-	B+/-	NK+	

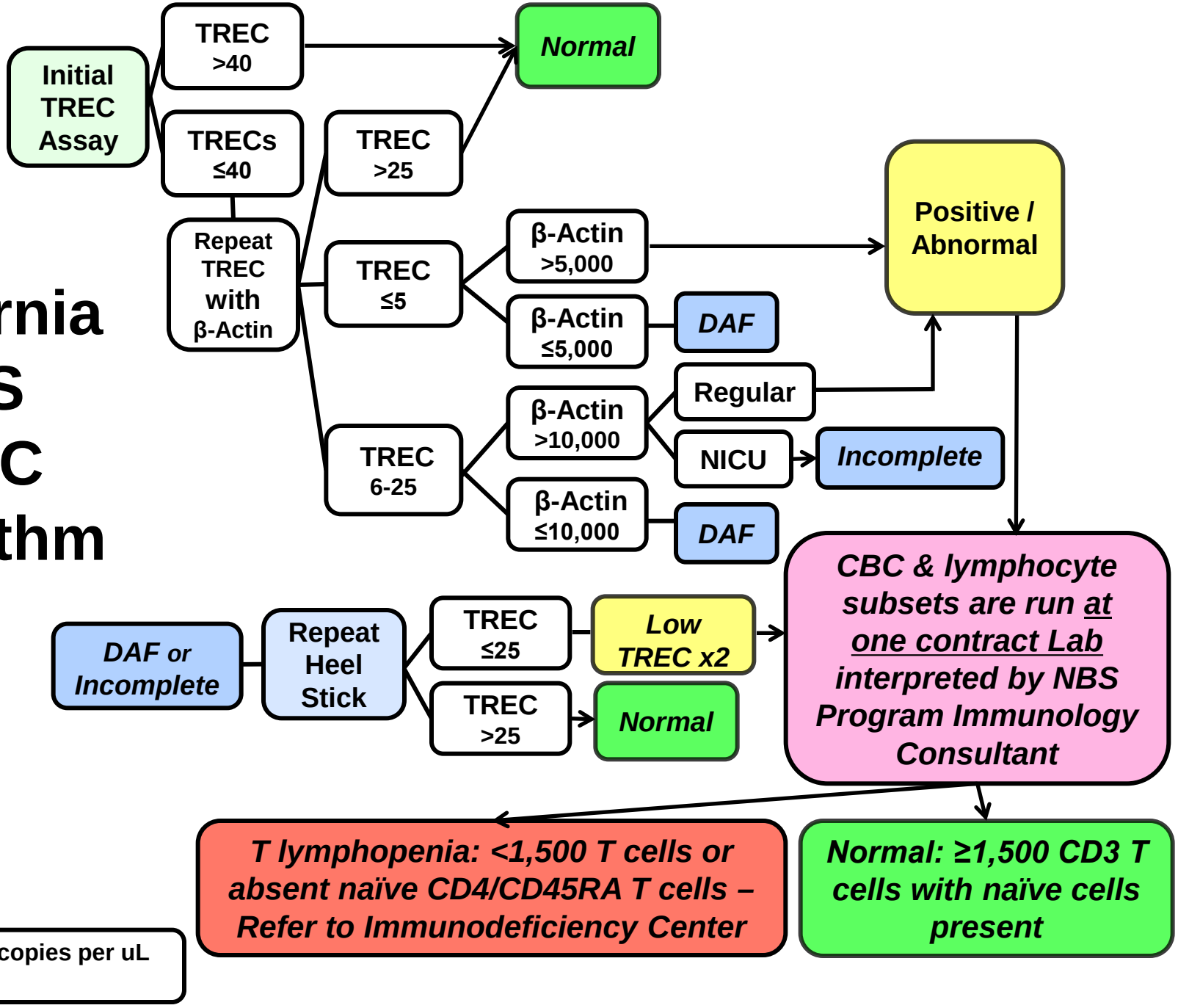
TRECs: Biomarker for Thymic T Cell Production

Thymus produces T cells with a diverse repertoire

- Antigen specificity arises by DNA recombination of T cell receptor genes.
- Excised DNA segments form T Cell Receptor Excision Circles (TRECs) as a byproduct.
- TRECs are stable and are detected by PCR.
- Newborns have the most TRECs; TRECs are diluted as T cells undergo many divisions in the periphery.



California NBS TREC Algorithm



TREC and Actin copies per uL of blood

Classification of infants with low T cells

Category	Definition of Condition[a]
Typical SCID	<300 autologous T cells/μL, <10% of normal proliferation to PHA,[b] frequently with maternal T cell engraftment and defect(s) in a known SCID gene
Leaky SCID	300-1,499 autologous T cells/μL, reduced proliferation to PHA, no maternal engraftment, generally with incomplete defect(s) in a known SCID gene
Omenn syndrome	Similar to leaky SCID, but also with oligoclonal T cells, erythroderma, hepatosplenomegaly, eosinophilia, and elevated serum IgE
Syndrome with low T cells	Recognized genetic syndrome that includes low T cells within its spectrum of clinical findings
Secondary low T cells	Congenital malformation or disease process without intrinsic immunodeficiency that results in low circulating T cells
Preterm birth alone	Preterm infants with low T cells early in life that become normal over time
Idiopathic T cell lymphopenia	Persistently low T cells (300-1,499 /μL), functional T and/or B cell impairment, no defect in a typical SCID gene; etiology and clinical course undetermined[c]

[a]Definitions of R4S and Primary Immunodeficiency Treatment Consortium (PIDTC).
[b]PHA, phytohemagglutinin.
[c]When/if etiology for low T cells discovered, the individual is moved to the appropriate category.

Severe Combined Immunodeficiency, SCID

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SCID with Newborn Screening

- Absent T cells; no specific antibody production by B cells.
- ~~Recurrent infections and weight loss from age 2-4 months.~~
- ~~Serious bacterial, viral, & fungal infections; opportunistic pathogens that do not cause disease in healthy infants.~~
- ~~Early death unless a~~ working immune system can be established.
- Incidence 1/55,000 births in CA, similar in 11 programs (Kwan et al, JAMA 2014).
- Typical SCID: <300/uL autologous T cells, <10% of normal PHA proliferation; no specific antibodies.
- Leaky SCID: 300-1500 T cells, functional impairment, no maternal engraftment.

4 Years of California SCID Newborn Screening (8/2010-8/2014)

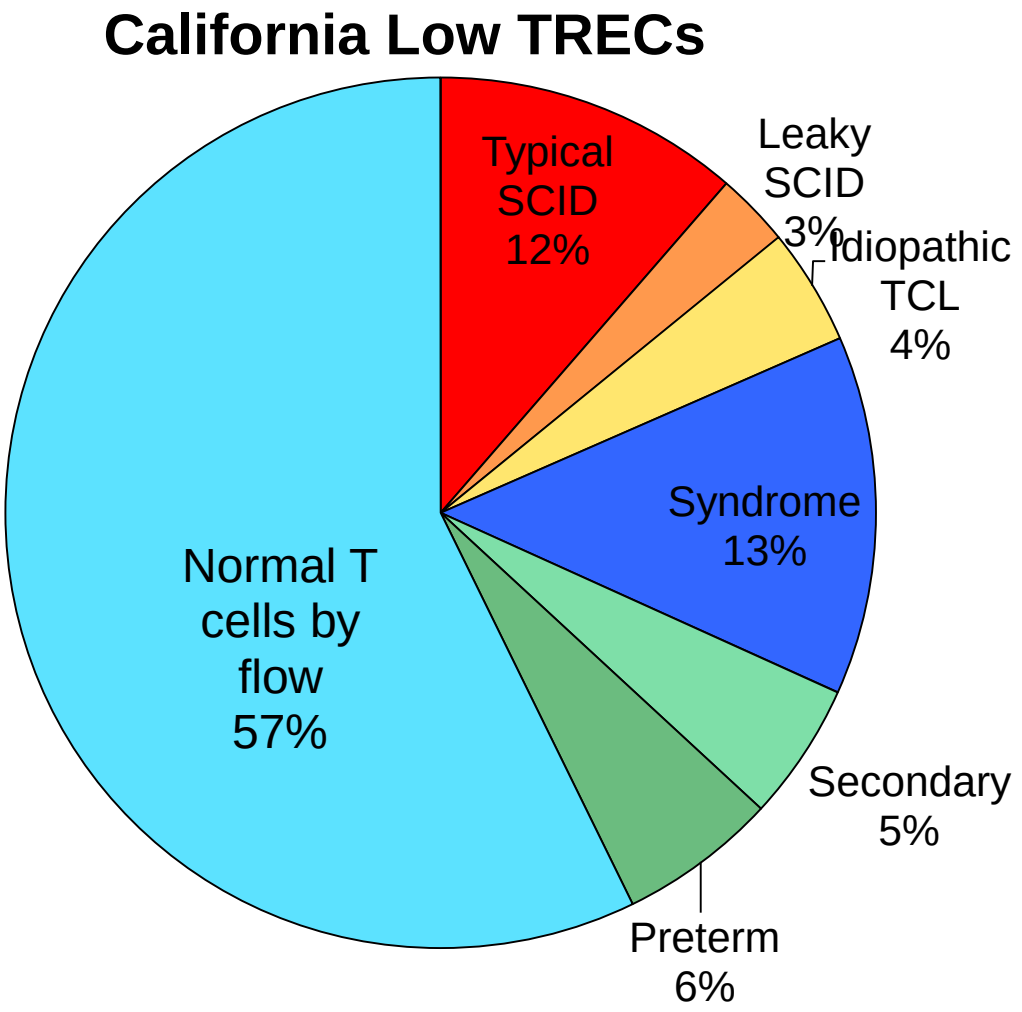
1,980,133 infants screened

1.3 infants per 10,000 (255) required flow cytometry

109/255 had fewer than 1500 T cells/uL (43%)

1/55,000 had SCID (Typical and Leaky)

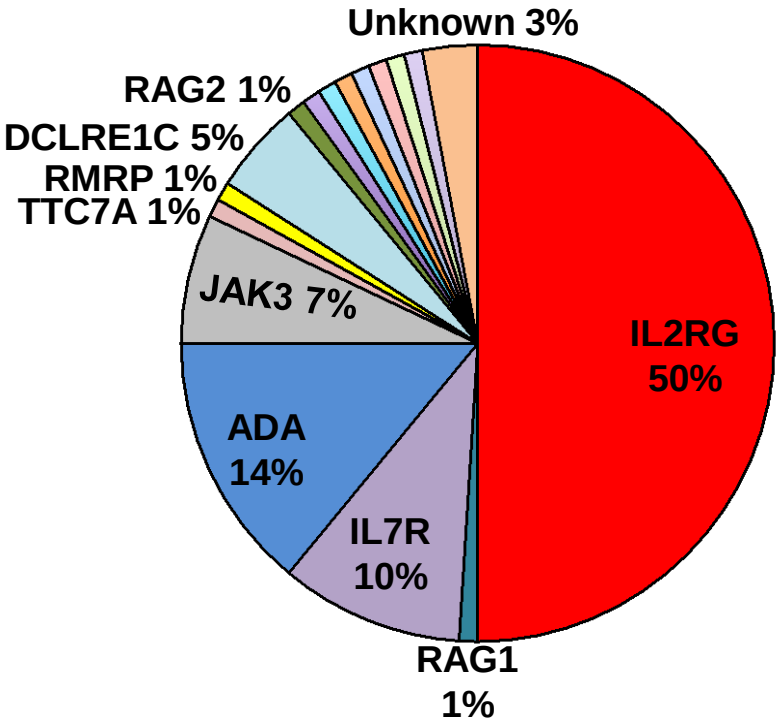
1/180,000 idiopathic TCL



Genotypes of Typical and Leaky SCID

Reports from Transplant Centers, no Screening

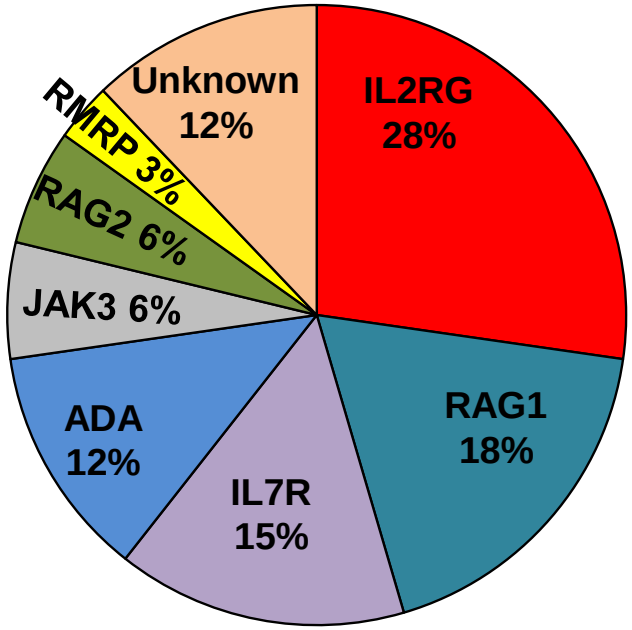
Duke University, European centers (estimates)



Overall Survival ~74% or lower

California, with TREC Screening

4 years, ~2 million infants



Overall Survival 95%

California Treatment/Outcome for SCID/Leaky/OS

Treatment	**Survival**
24 HCT	**94%**
3 PEG-ADA	**1 died of CMV**
4 gene therapy (*ADA*, *IL2RG*)	**1 died of busulfan toxicity**
1 left USA	
2 awaiting treatment	

Non-SCID Conditions Detected (Secondary Targets of TREC Screening)

Multisystem syndromes with variable T cell deficiency

57% DiGeorge/chromosome 22q11.2 deletion

15% Trisomy 21

3% Ataxia telangiectasia

2% CHARGE syndrome

Many others…

Trisomy 18, Jacobsen, CLOVES, Fryns, Nijmegen breakage syndrome

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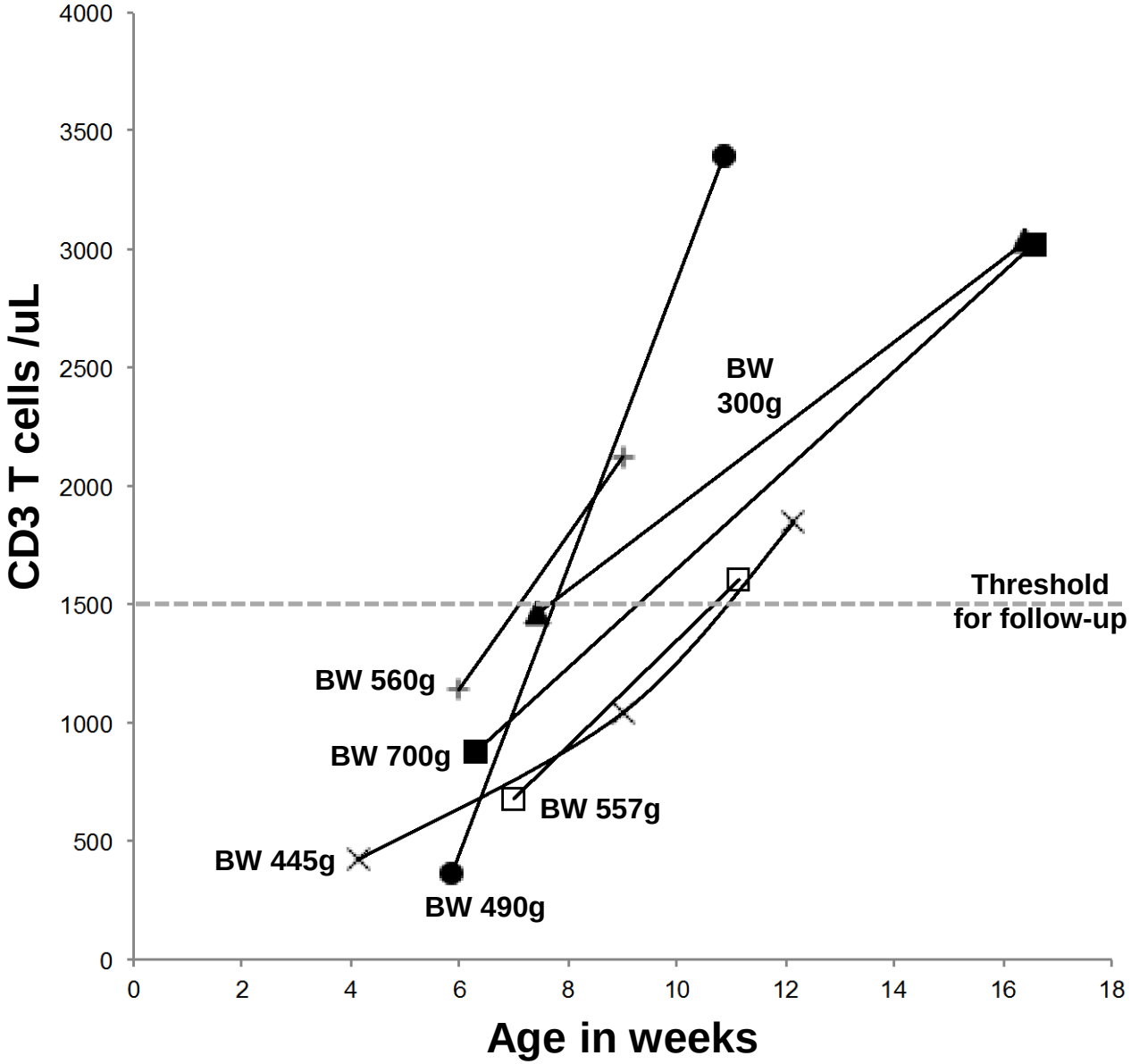
- 2% CHARGE syndrome

Secondary T lymphopenia

- 25% Congenital cardiac anomalies
- 38% Other (multiple) congenital anomalies
- 13% Vascular leakage, third spacing, hydrops
- 3% Neonatal leukemia

Extreme preterm birth—T cells become normal over time

Preterm Low Birthweight Infants with Low TRECs and T Lymphopenia



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Extreme preterm birth—T cells become normal over time

"Variant SCID" or Idiopathic T lymphopenia—few naïve T cells, no maternal engraftment, impaired T cell or antibody responses, no known gene defect

Variant SCID or Idiopathic T Lymphopenia

- **Persistent low but not absent T cells and TRECs, low naïve CD45RA T cells, no maternal engraftment.**
- **No known SCID gene mutation.**
- **Impaired T cell and/or antibody responses.**
- **When an etiology is found, case is moved to the appropriate category.**

Conclusions

1. SCID, the primary target of TREC NBS, is a treatable serious, genetic immune deficiency affecting around 1/50,000 births.
2. NBS permits optimal treatment and best outcomes.
3. Non-SCID secondary targets of NBS may benefit from early identification
4. Tracking incidence, pursuing gene diagnosis and learning outcomes of TREC screen positive cases will be informative for public health programs and immunologists.

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Immune Deficiency Foundation

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Center for Disease Control and Prevention

DHHS Maternal and Child Health Bureau, NBSTRN