

Population Based Newborn Screening for Severe Combined Immunodeficiency (SCID)

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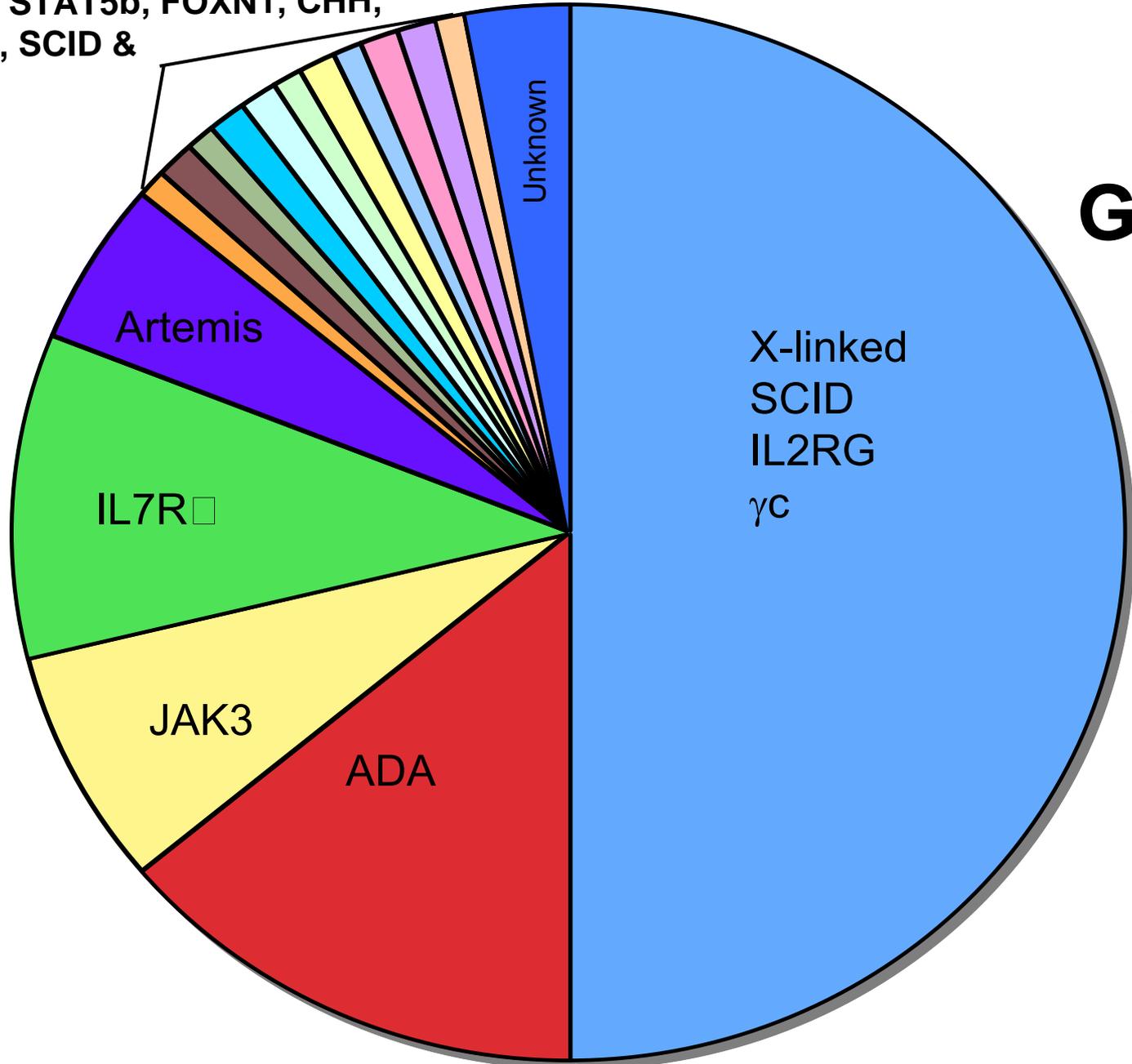
Severe Combined Immunodeficiency--SCID

- Inability to fight infections, few or no T cells; impaired production of specific antibodies.
- Recurrent infections and weight loss from age 2-4 months.
- Infections with attenuated or opportunistic organisms that do not harm healthy infants.
- Early death unless the patient is given a working immune system.
- NOTE: Related disorders, with only a few T cells or non-functional T cells are not as severe as SCID, but still have risks for infection and need to be treated.

SCID Is Treatable by Hematopoietic Cell Transplantation, Enzyme Replacement or Gene Therapy

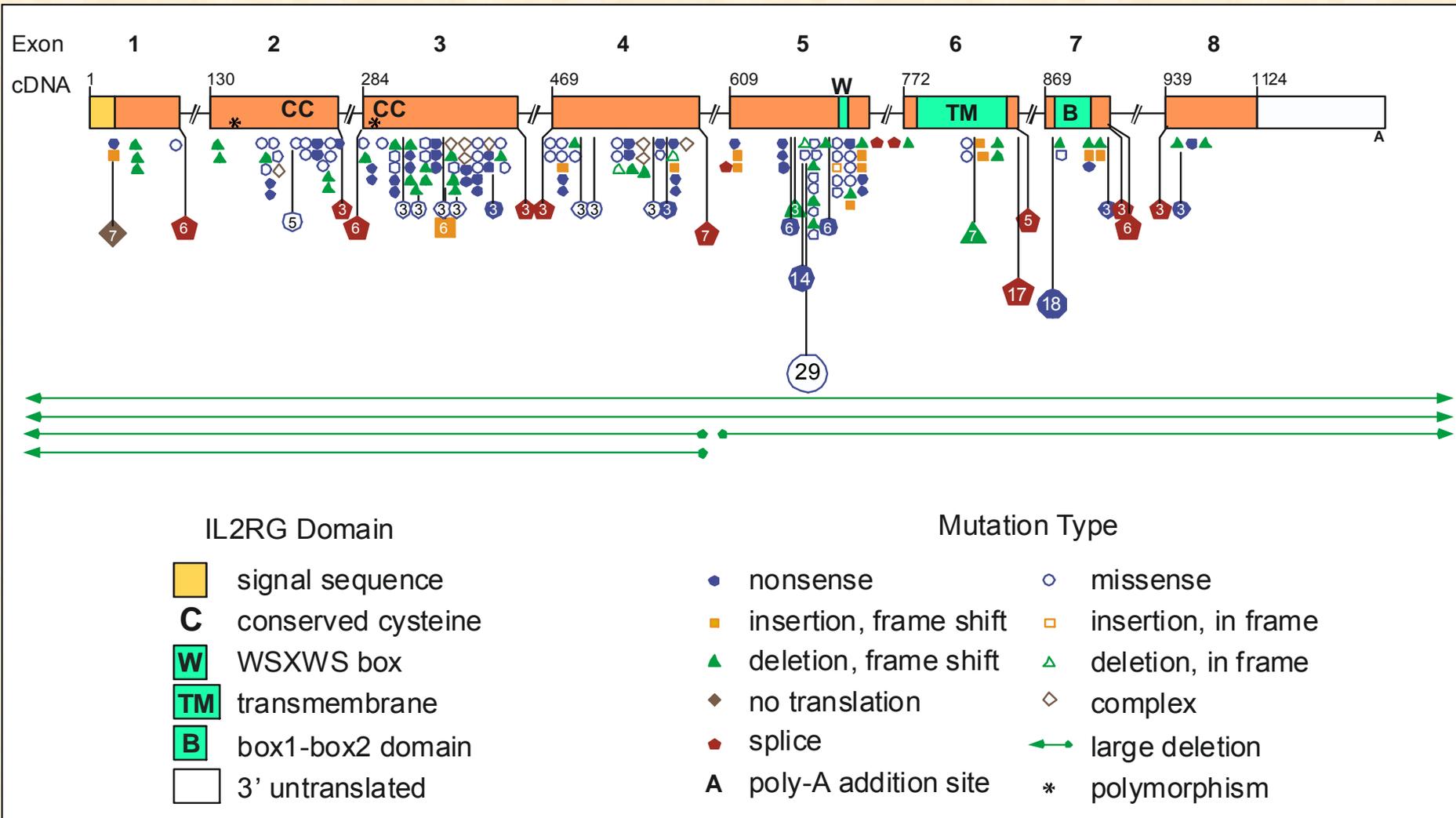
- 1968: first ever successful bone marrow transplant. Recipient was a SCID patient, donor was his healthy, HLA-identical sister
- Best donor is still an HLA-matched sibling
 - other donors: parents (haploidentical T cell depleted bone marrow), HLA matched unrelated cord blood or adult hematopoietic cells
- Adenosine deaminase deficiency, ADA SCID, can be treated by enzyme replacement
- ADA and X-linked SCID can be treated by gene therapy (adding a correct copy of the *ADA* or *IL2RG* gene, respectively, to hematopoietic stem cells ex vivo and re-infusing back into patient)

RAG1/2, CD45, TCR / / , LIG4,
CD45, LCK, STAT5b, FOXP1, CHH,
Coronin-1A, SCID &
GI atresias

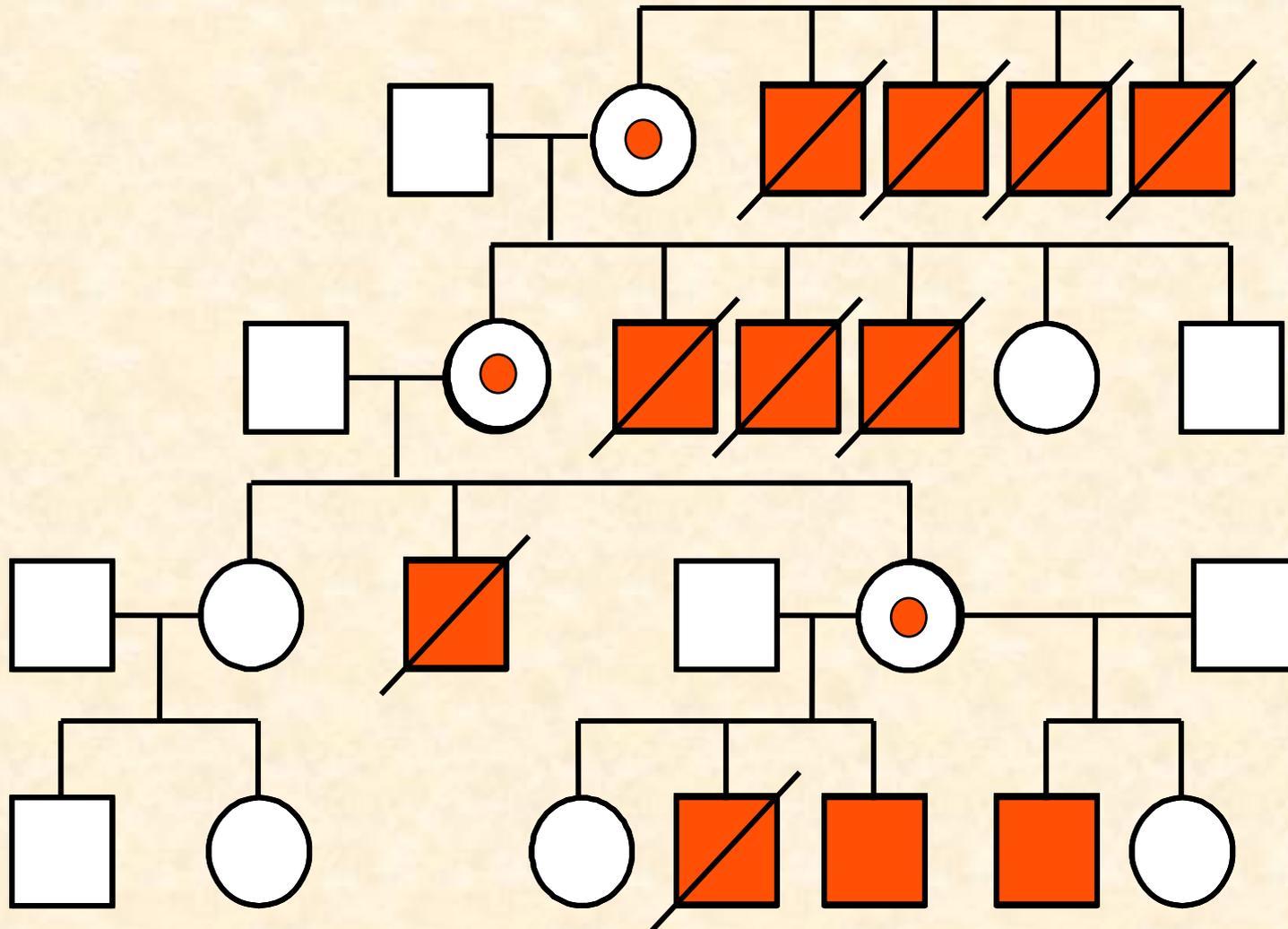


**>19
Genes
for
SCID
in
2010**

Many Mutations: 205 *IL2RG* Mutations in 351 XSCID Families (62% Puck lab)

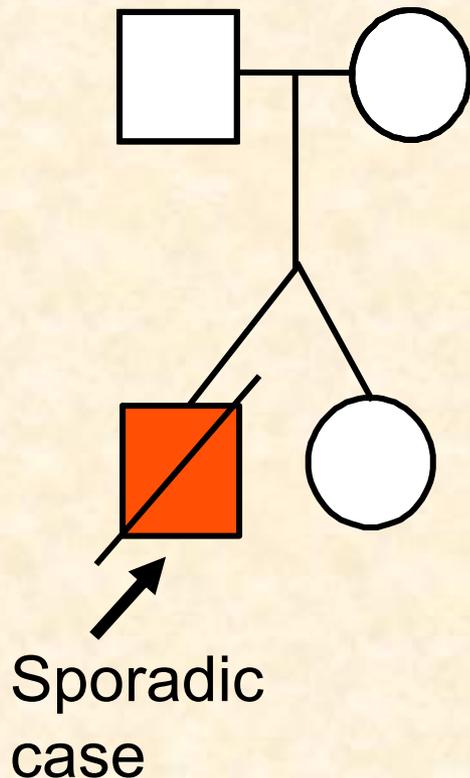


X-Linked Inheritance of SCID



Most SCID Is Sporadic.

<20% Diagnosed at Birth Because of an Affected Relative



Twin had *E. coli* sepsis, pneumonia, CMV.

Low lymphocyte count not recognized as SCID.

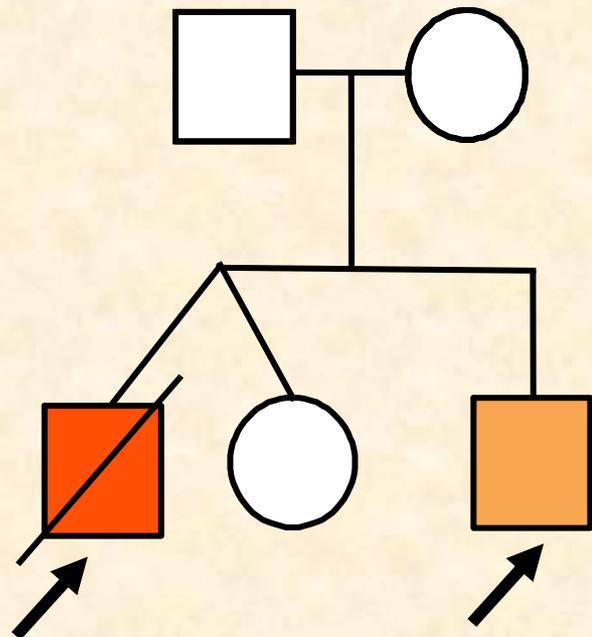
Died at 3.5 months, diagnosis made after death.

Most SCID Is Sporadic.

<20% Diagnosed at Birth Because of an Affected Relative

Twin had *E. coli* sepsis, pneumonia, CMV.
Low lymphocyte count not recognized as SCID.
Died at 3.5 months, diagnosis made after death.

Subsequent brother had SCID diagnosed at birth.
Received early bone marrow transplant from matched sister and is now healthy.



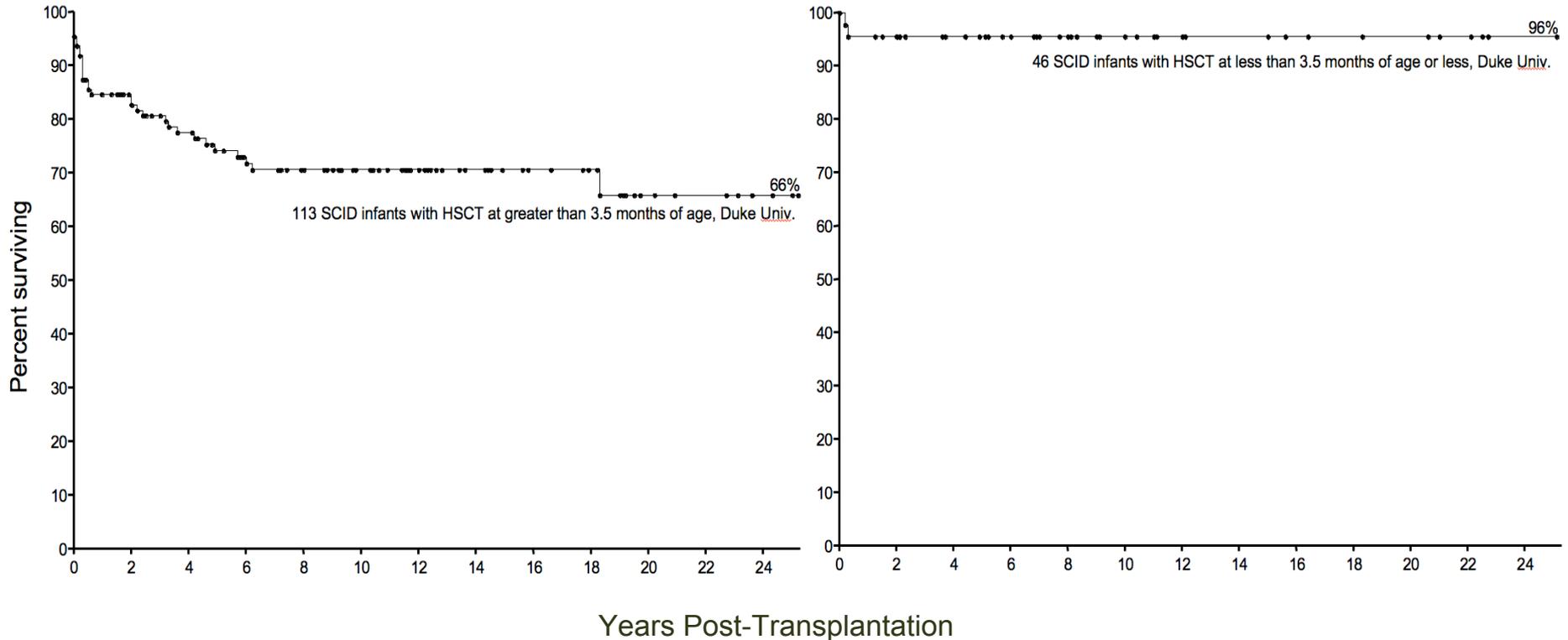
Sporadic case

Suspected, tested at birth

Justifications for Newborn Screening

<u>Screening Criteria</u>	<u>How SCID Meets the Criteria</u>
Disease is serious	Fatal in first year of life if untreated
Disease is not detected by exam	Newborns with SCID appear healthy
Incidence supports screening PKU = 1/10,000; Galactosemia = 1/60,000 Biotinidase Deficiency = 1/80,000	Estimated 1/50,000-100,000. 1/2,000 in Navajo. 8-12 per year in CA
Well-established confirmative testing	Blood T-cell counts (mutation testing)
Effective treatment exists	Transplant matched healthy blood-forming cells, enzyme/gene therapy
Earlier treatment is better	Best survival and outcomes when treated before infections occur
Diagnosis & treatment are available	Specialized transplant centers, PIDTC Rare Disease Network
Screening is cost-effective	TREC test. WI, MA, NB and Navajo now screening. CA, others to start.

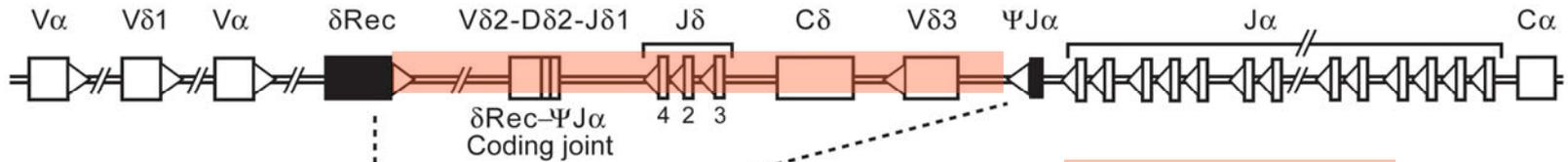
SCID Patients Treated Early Have Better Survival



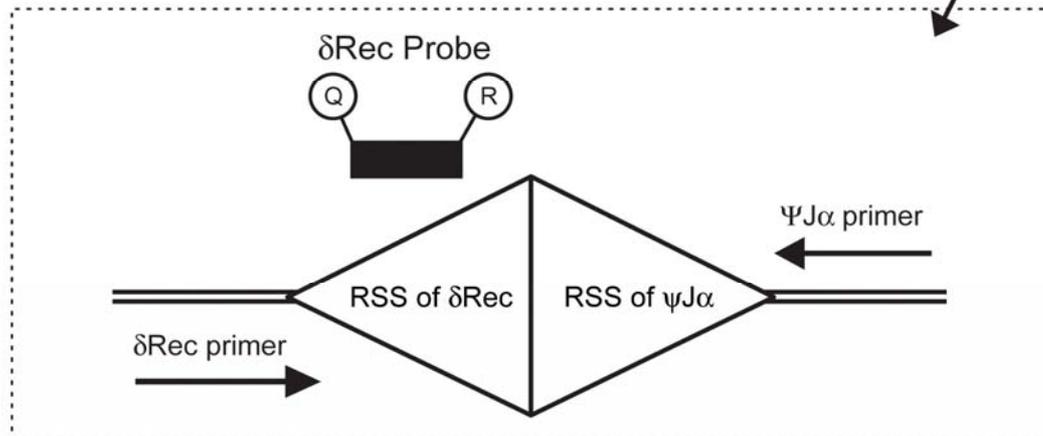
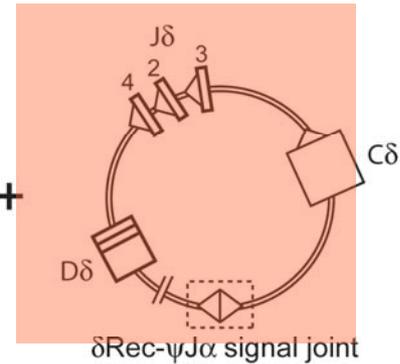
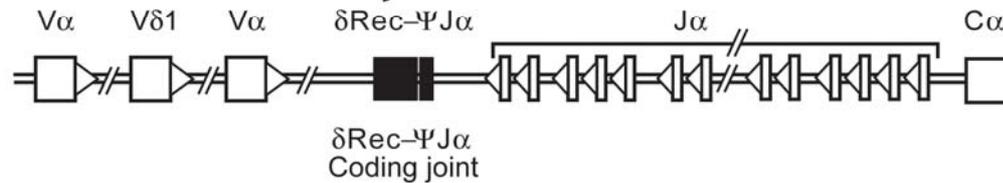
Duke BMT older vs. younger than 3.5 months (R. Buckley)

T Cell Receptor Excision Circles (TRECs)

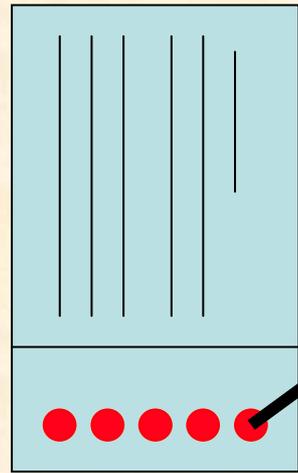
V δ 2-D δ 2 Rearrangement
TCRA/D locus



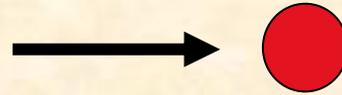
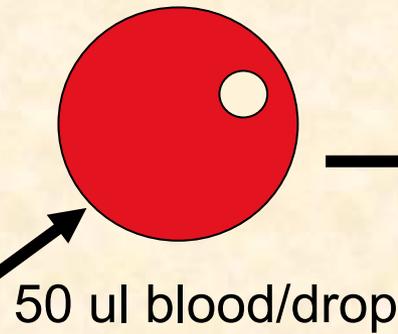
δ Rec- Ψ J α Rearrangement
TCRD deletion



TREC Dried Blood Spot Assay

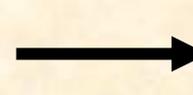


Guthrie Card



3 mm hole
punched from
blood spot

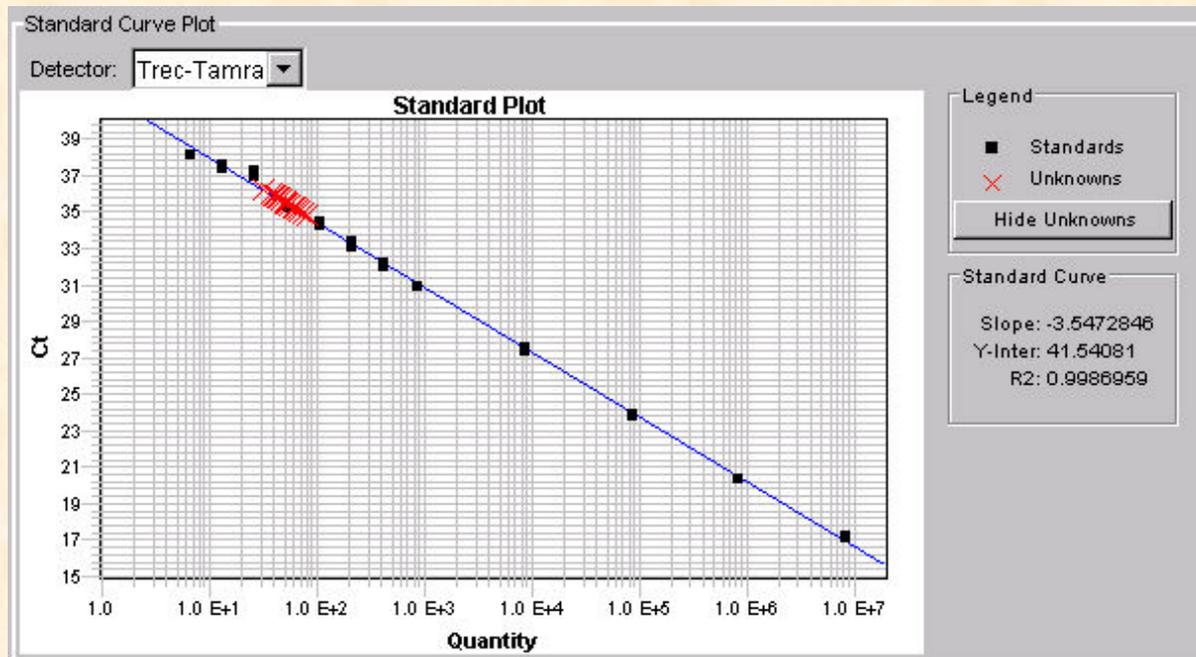
~3 ul blood



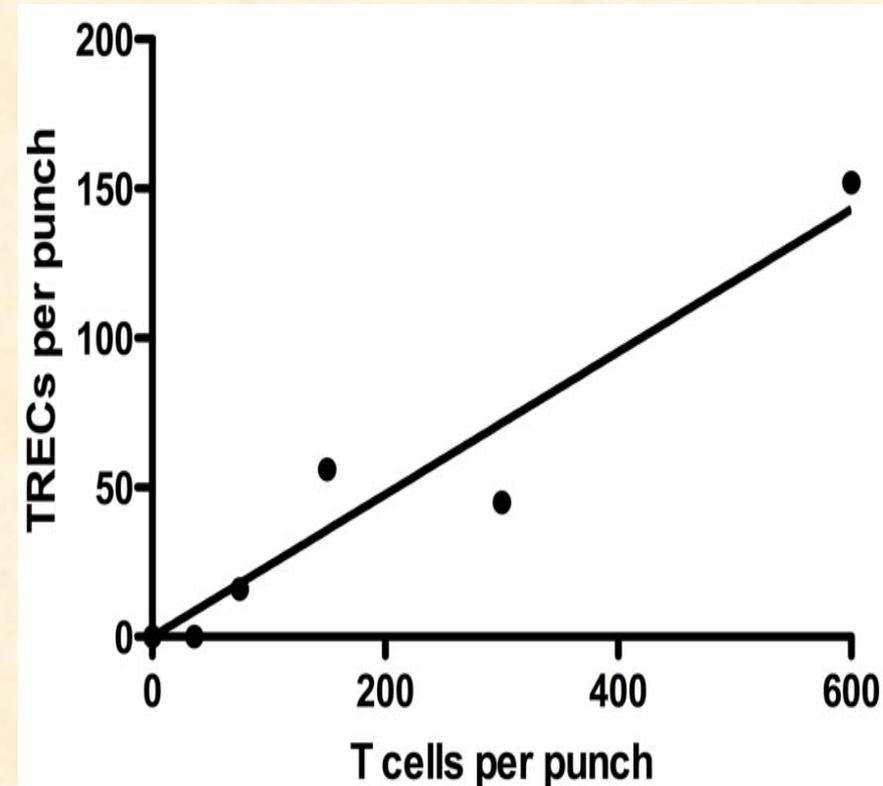
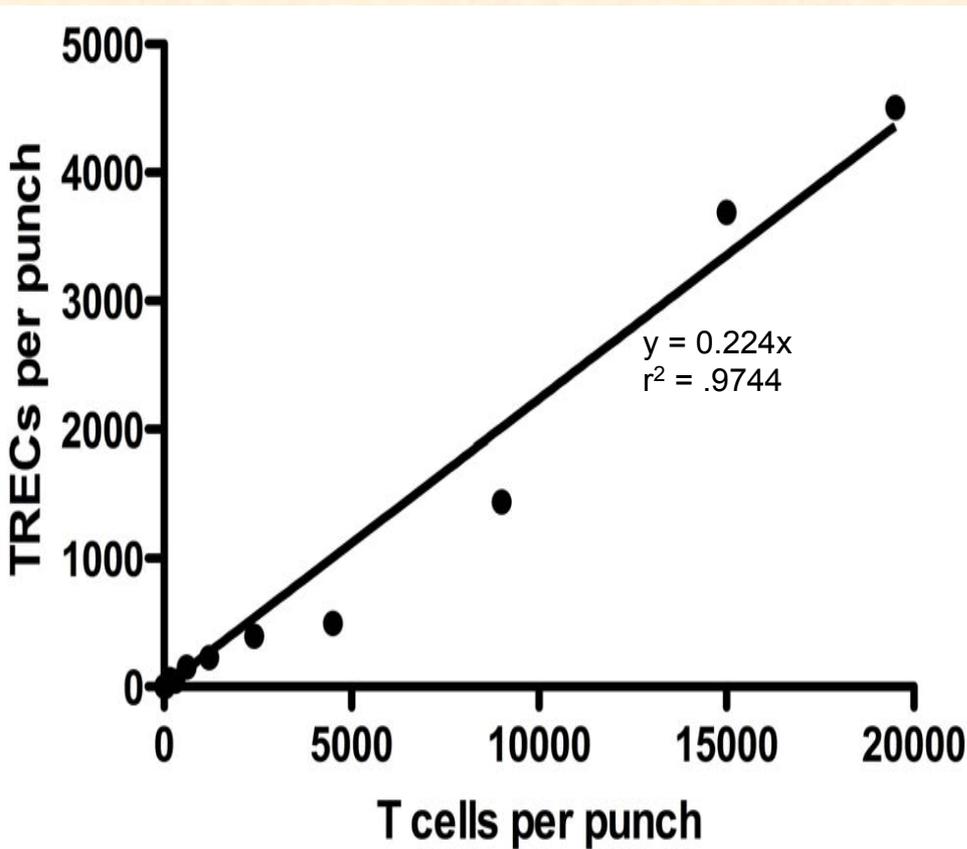
Extract DNA



Measure
TRECs by
PCR

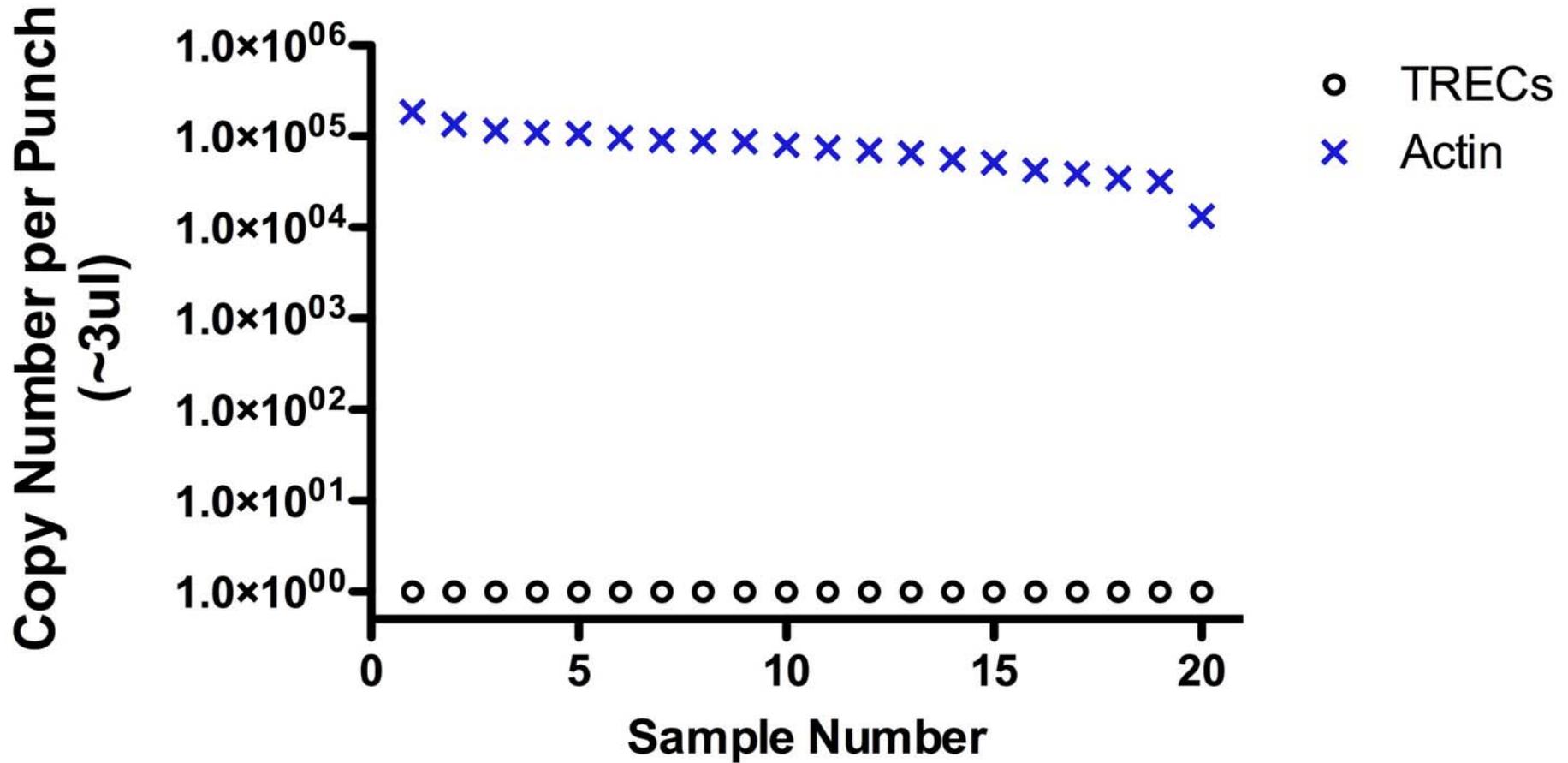


TRECs correspond to T cell number

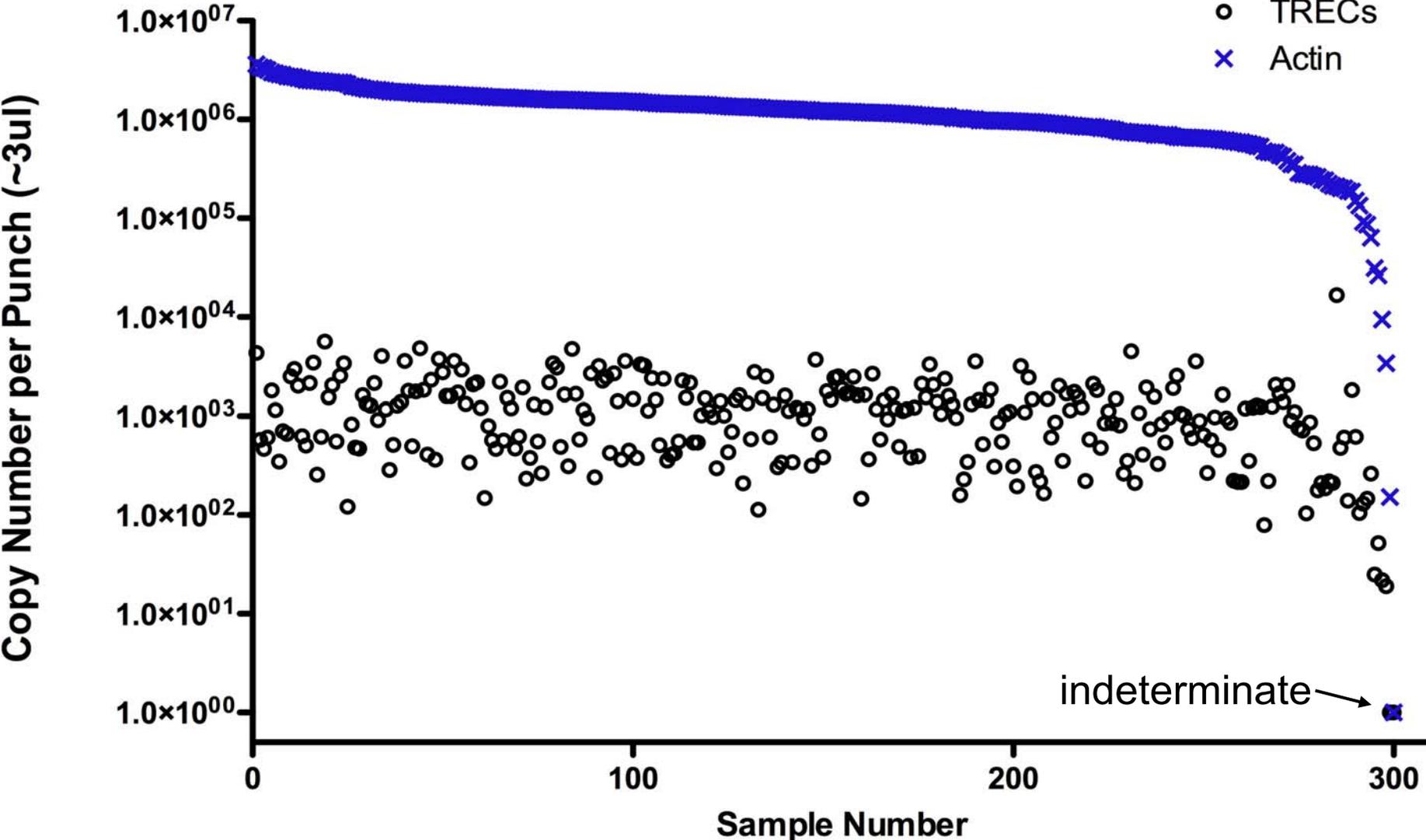


Graded numbers of T cells added back to T-depleted blood.
T cells per 3-mm punch, corresponds to 3 ul of blood.

SCID Actual Guthrie Card



Anonymous Newborn Guthrie Cards



Nomination of SCID/T Cell Defects

for inclusion in the uniform NBS panel:

Secretary of Health and Human Services' Advisory
Committee on Heritable Disorders in Newborns and
Children

Originally considered 2009

Follow-up January 21, 2010

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Jeffrey Modell Foundation

Immune Deficiency Foundation

Jack Routes, Medical College of Wisconsin

Anne Comeau, University of Massachusetts

Bob Vogt, Center for Disease Control and Prevention

2009 Evidence Review: SCID Fulfills Requirements for Consideration, but ...

“The major weakness of the nomination is whether there are sufficient population-based data to evaluate the clinical validity of the TREC-based screening test.”

Gaps identified

1. Prospective identification of “real” SCID cases.
2. Willingness and capacity of states to implement newborn screening for SCID.
3. Test reproducibility, false positive rate of <math><0.1\%</math>.
4. Standardization; laboratory proficiency testing.
5. Resources to appropriately address costs.

2010 Reconsideration: There is a Public Health Interest for Infants with Low TRECs

1. Avoid potential harm from an otherwise beneficial public health program, i.e. do not give live vaccines until patient is evaluated by a qualified expert in immunology who finds that it would be safe;
2. Assure that infants with low TRECs are evaluated by an expert without delay;
3. Track ultimate outcomes to measure effectiveness of screening, diagnosis and management.

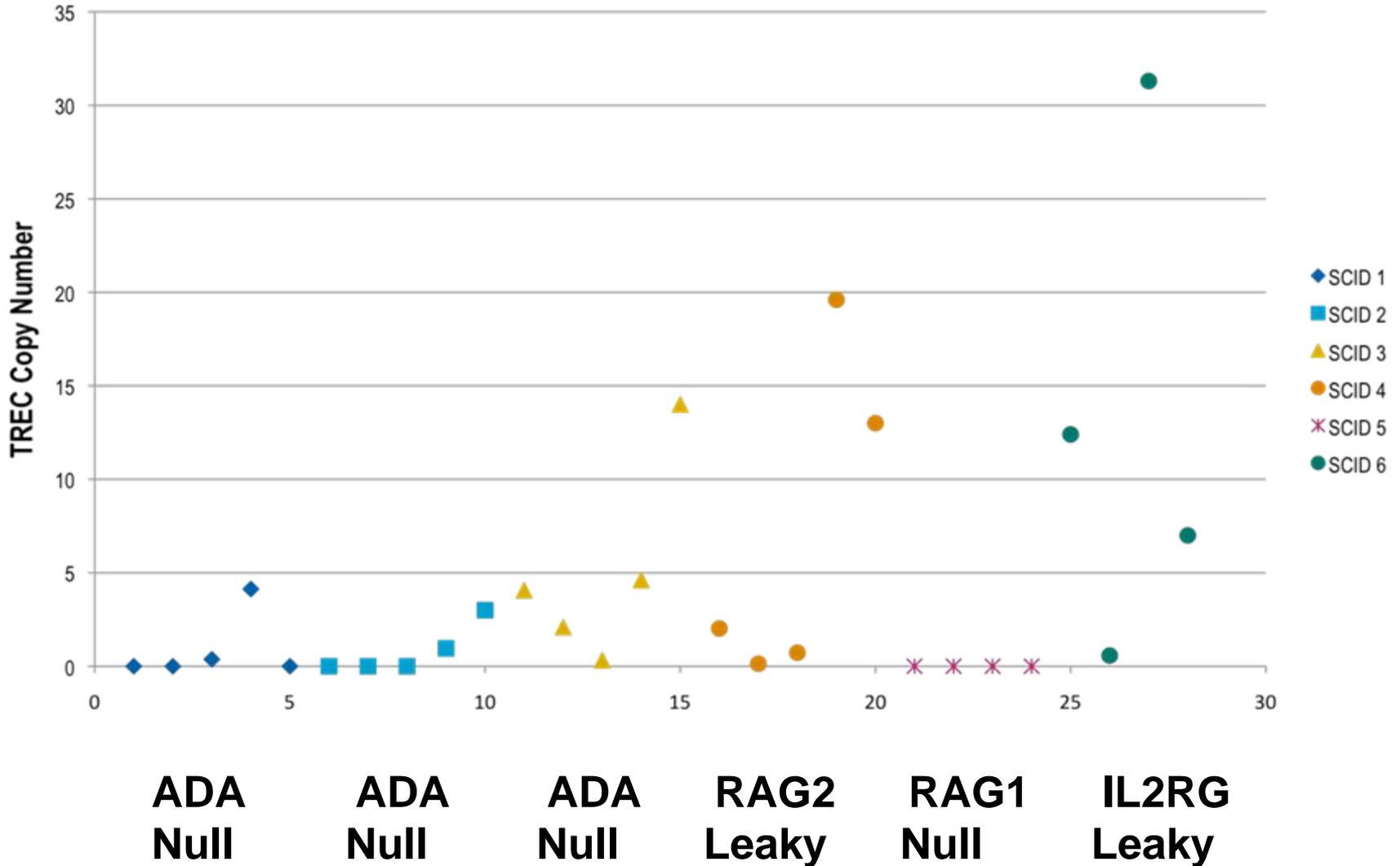
January, 2010: Committee unanimously recommends adding SCID to uniform newborn screening panel.

May, 2010: U. S. Sec. of Health Kathleen Sibelius endorses SCID screening and outcome tracking.

TREC Test at CDPH by PE

- Extract DNA from 1 punch. Run Q-PCR assay for TRECs.
- >60 TRECs/punch: not consistent with SCID. Done
- Undetectable or ≤ 60 TRECs (0.5%): new punch for DNA; lab runs TRECs and actin genomic control.
- Low TRECs and low actin: DNA amplification failure. Request 2nd DBS; heelstick, no heparin.
- Actin PCR positive, ≤ 60 TRECs: consistent with SCID. Request venous blood sample for T cells.
- Second DBS DNA amplification failure or consistent with SCID. Request venous blood sample for T cell analysis by flow cytometry.

Repeat Testing of 6 CA SCID Samples



Thanks to Many Collaborators

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Kee Chan, Joie Davis

SCID Families

Immunologists and Geneticists

Support

Jeffrey Modell Foundation

USIDNet

UCSF CTSI

NIH RO3

NNSGC

CDC