Inherited Diseases of Adaptive Immunity

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Faculty Disclosures

Jennifer Puck, MD

For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

Honoraria received from:

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•None

Held common stock in:

•None

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• Baxter

I will not be discussing products that are investigational or not labeled for use under discussion.

Causes of Impaired Host Defenses, from Common to Rare, Worldwide

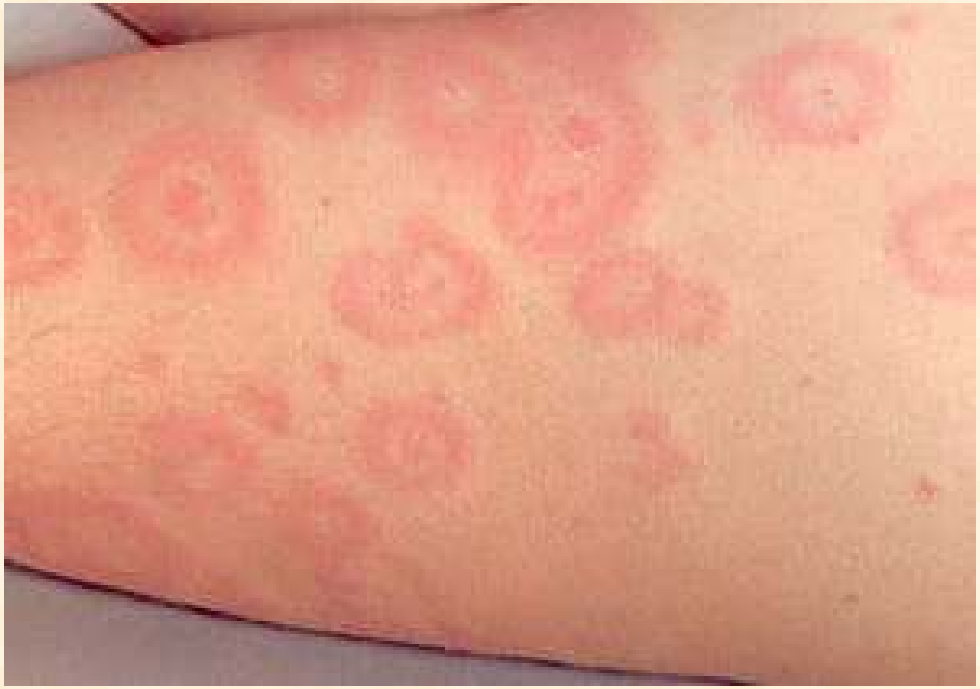
- Environmental
  - Malnutrition
  - Chronic infections: HIV, TB
  - Secondary to drug treatments for cancer, etc
- Genetic
  - Known and unknown factors:
    - Inability to clear invading organisms
      - from respiratory tract (cystic fibrosis)
      - from circulation (sickle cell disease)
  - Defects in immune system genes
    - Primary immunodeficiency disorders

What Are the Barriers to Early Primary Immunodeficiency Diagnosis?

- Immune defects are rare.
- Infections are common in all infants, not just those with immunodeficiency.
- Family history is most often missed, subtle or absent.
- Infants are protected by maternal IgG for their first months of life.
- Both a gene defect and environmental are exposure required for overt disease, so presentation is variable .

Initial Clinical Presentation

- Well and thriving before age 2 1/2, only a few ear infections.
- Recurrent fevers to 39°C (104°F).
- Right lower lobe pneumonia treated with amoxicillin.
- Erythema multiforme rash following amoxicillin.



- Enlarged spleen and liver noted.

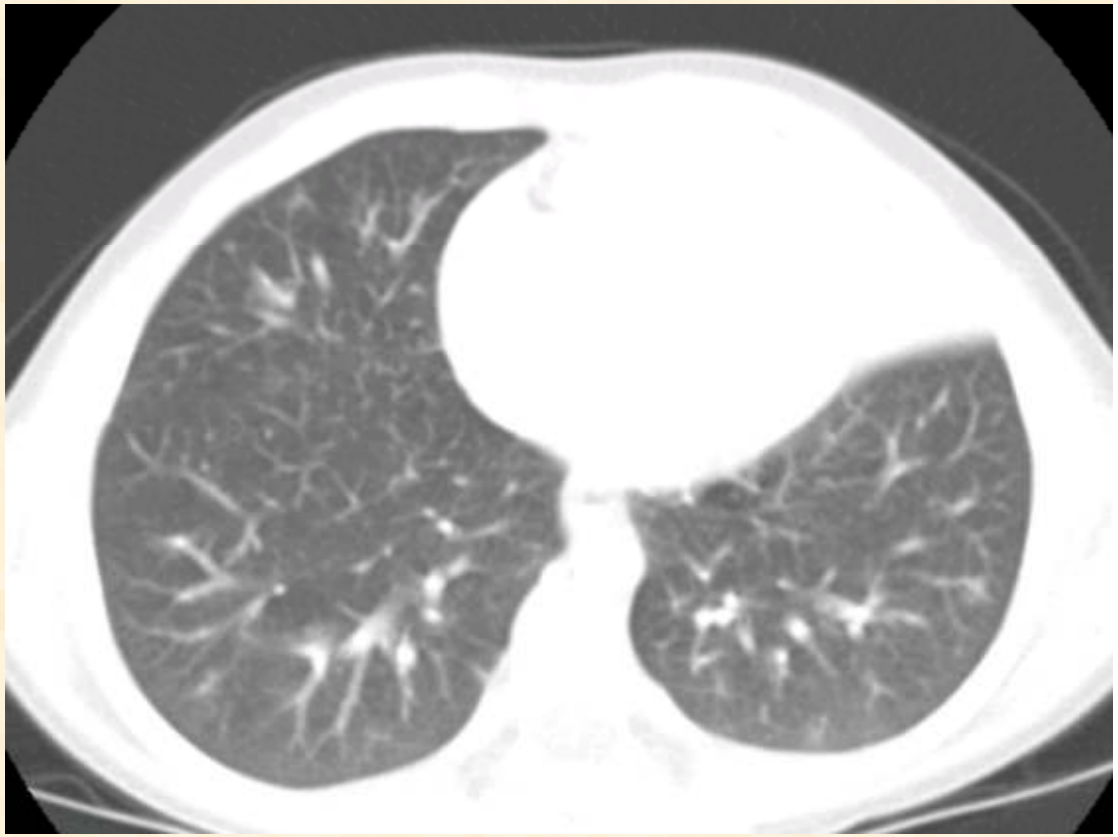
Laboratory Studies

- Normal bone marrow--no malignancy
- Low IgG 98 (normal for age 892 ± 183)
- Absent IgA (normal 71 ± 37)
- Normal IgM 78 (61 ± 19)
- Anti-tetanus antibody undetectable, despite vaccines
- T, B, NK cells present in normal numbers

Diagnosis: Common variable immunodeficiency (CVID)

Treatment and Course

- Intravenous immunoglobulin (IVIG) every 4 weeks
- No penicillin or related antibiotics
- *2 years later, age 4…*
  Growing, feeling well
  CT scan to follow enlarged liver & spleen: pulmonary nodules
  Bronchoscopy negative for bacteria, fungi and mycobacteria. No granulomas.



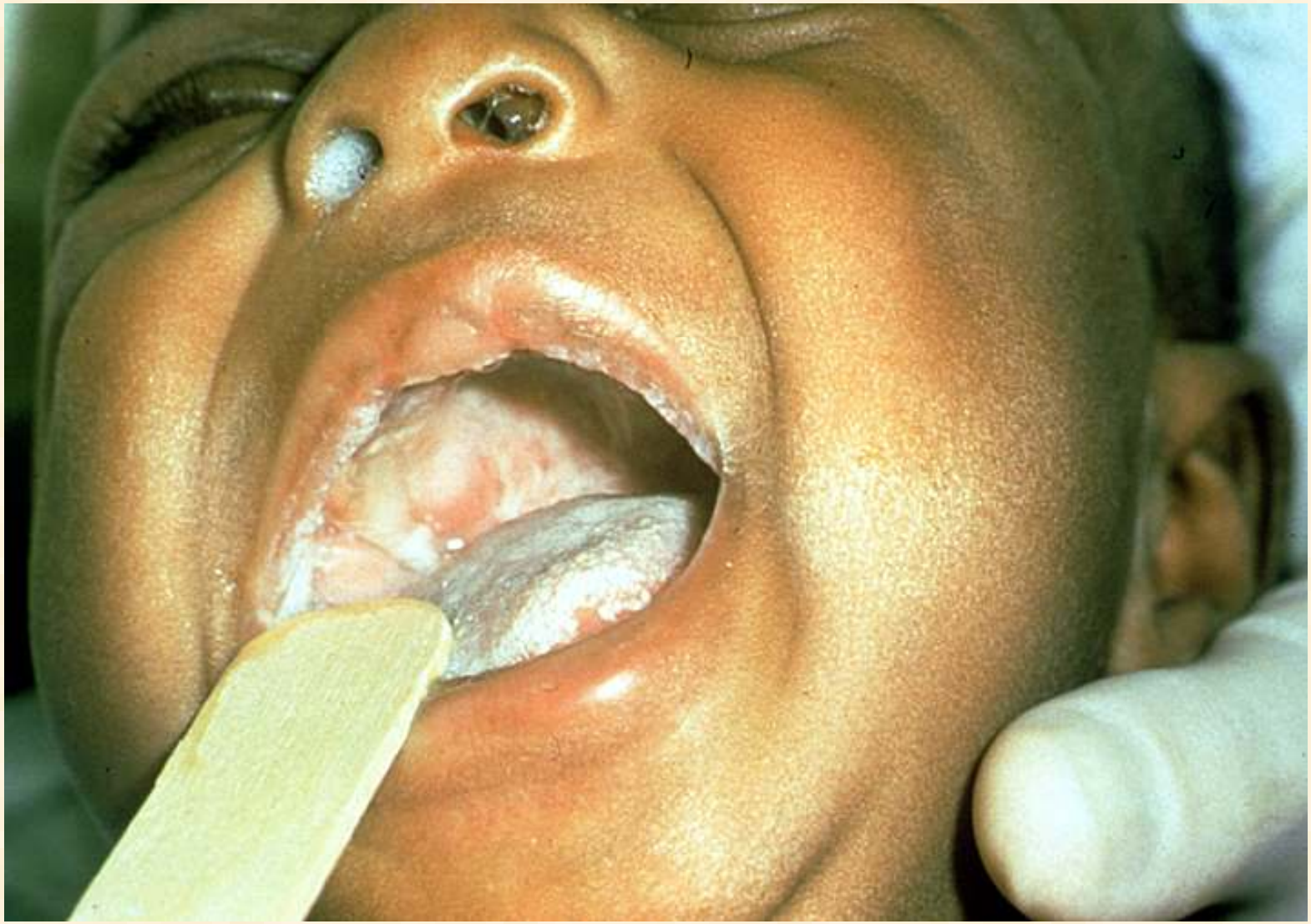
Common Variable Immunodeficiency (CVID)

- Not a single disease. 2 onset peaks, 1-5 & 16-20 years.
- Presentation: sinusitis, pneumonia, bronchiectasis, GI infections, adenopathy/splenomegaly, autoimmunity.
- Delay in diagnosis (average 8 years!!!).
- *Required lab findings*: At least two Ig isotypes low (no IgA in >50%; poor specific antibody responses to challenge.
- *Other features*: other infections, fatigue, arthritis, anemia, inflammatory bowel disease, cancer (lymphoma).
- Underlying cause mostly unknown; 20% have relatives with CVID, absent IgA, autoimmunity. Mutations in ICOS, TACI, BAFF-R, CD19 account for 5-10%.
- Treatment: give IgG; treat infections aggressively & consider prophylactic antibiotics; watch for complications.

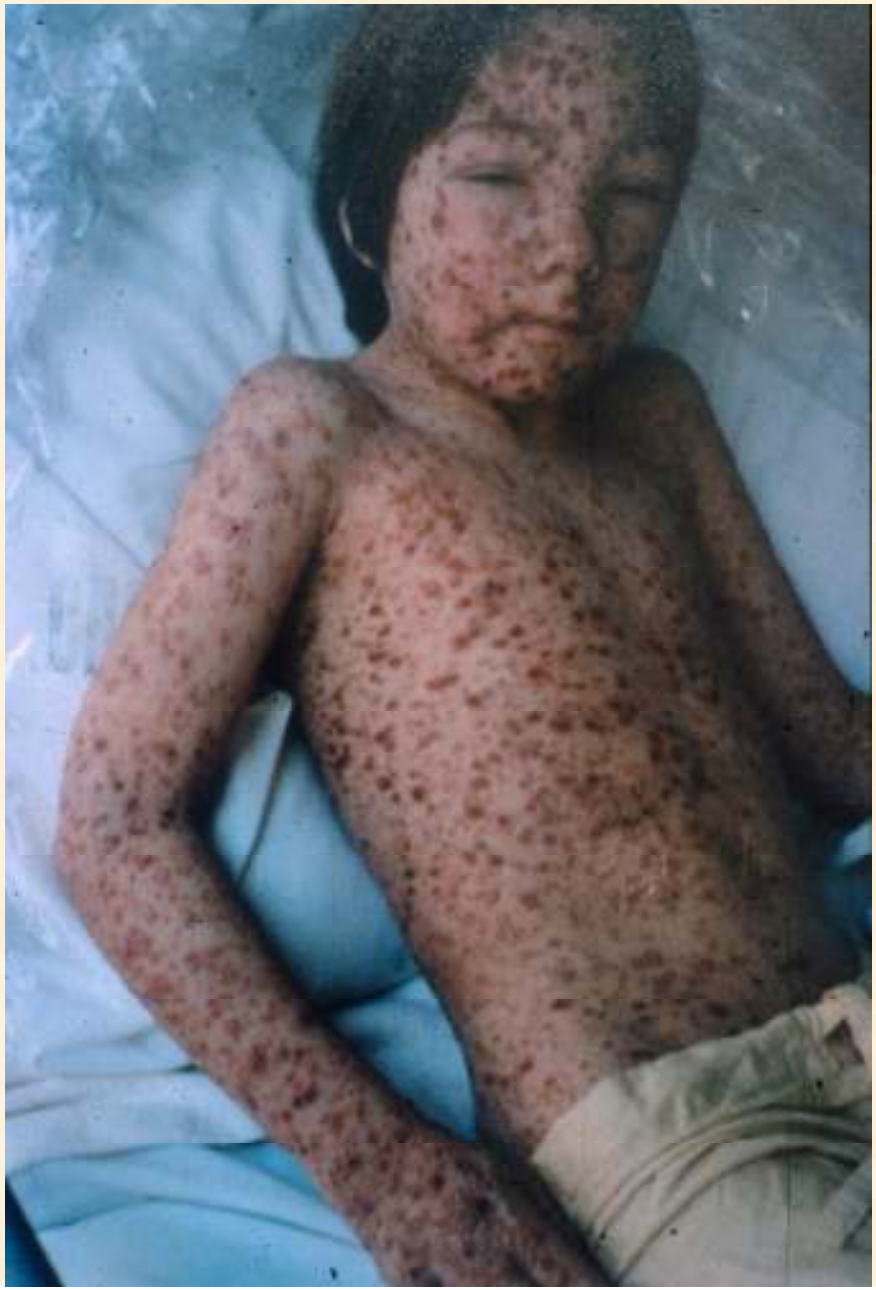
Severe Combined Immunodeficiency--SCID

- Most severe primary immune disorder; no adaptive immunity.
- Recurrent infections and weight loss from age 2-4 months.
- Serious bacterial, viral, & fungal infections; attenuated or opportunistic organisms that do not cause disease in healthy infants.
- Early death unless the patient is given a working immune system.
- Incidence unknown, estimated of 1/50,000 – 1/100,000 births.
- Very low or absent T cells with impaired function; no specific antibodies even if B cells present. NK cells may be present or absent, depending on genotype and other factors.

Thrush (Candida oral infection) in Severe Combined Immunodeficiency--SCID



Later Diagnosis, Variant SCID or CID

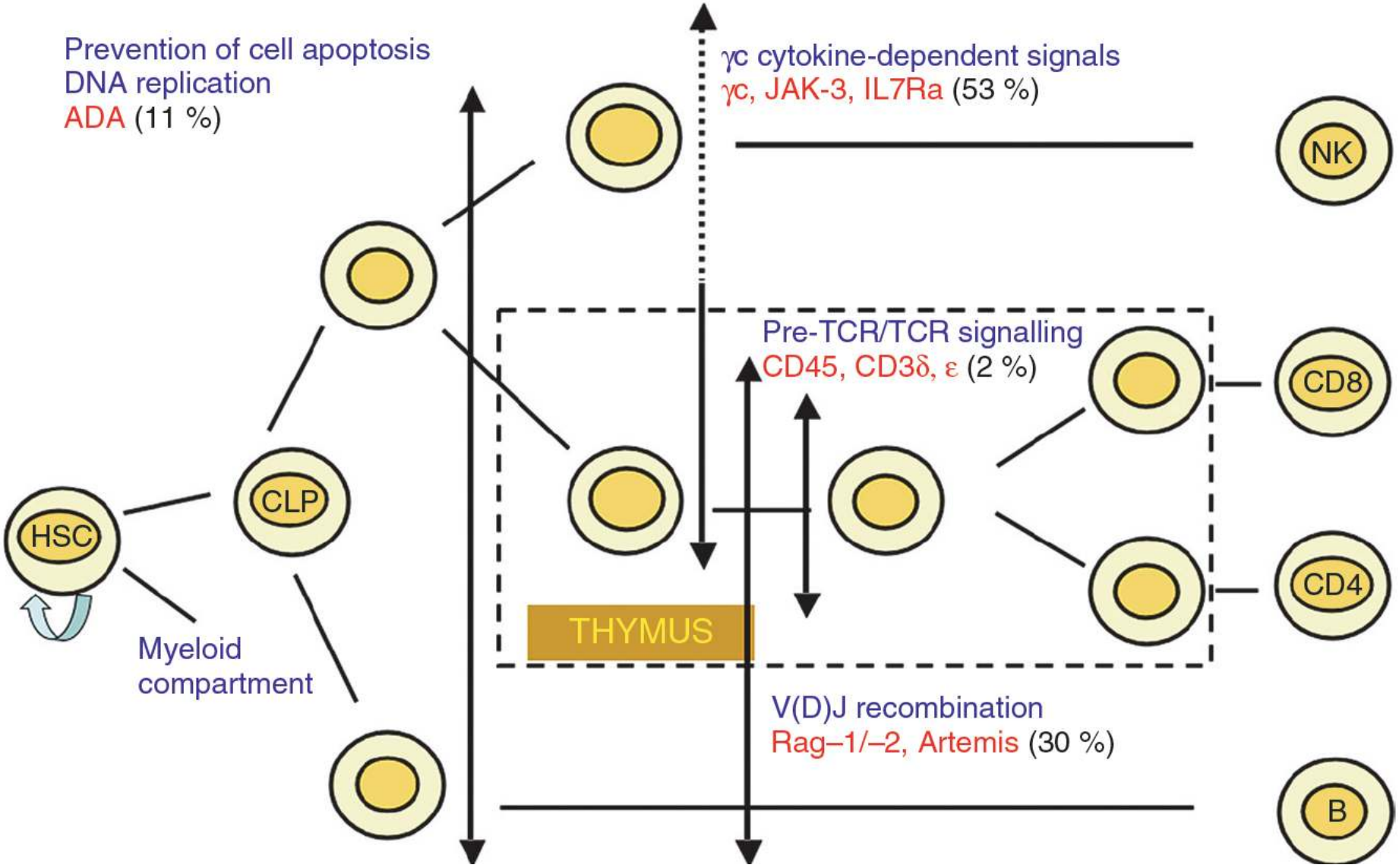


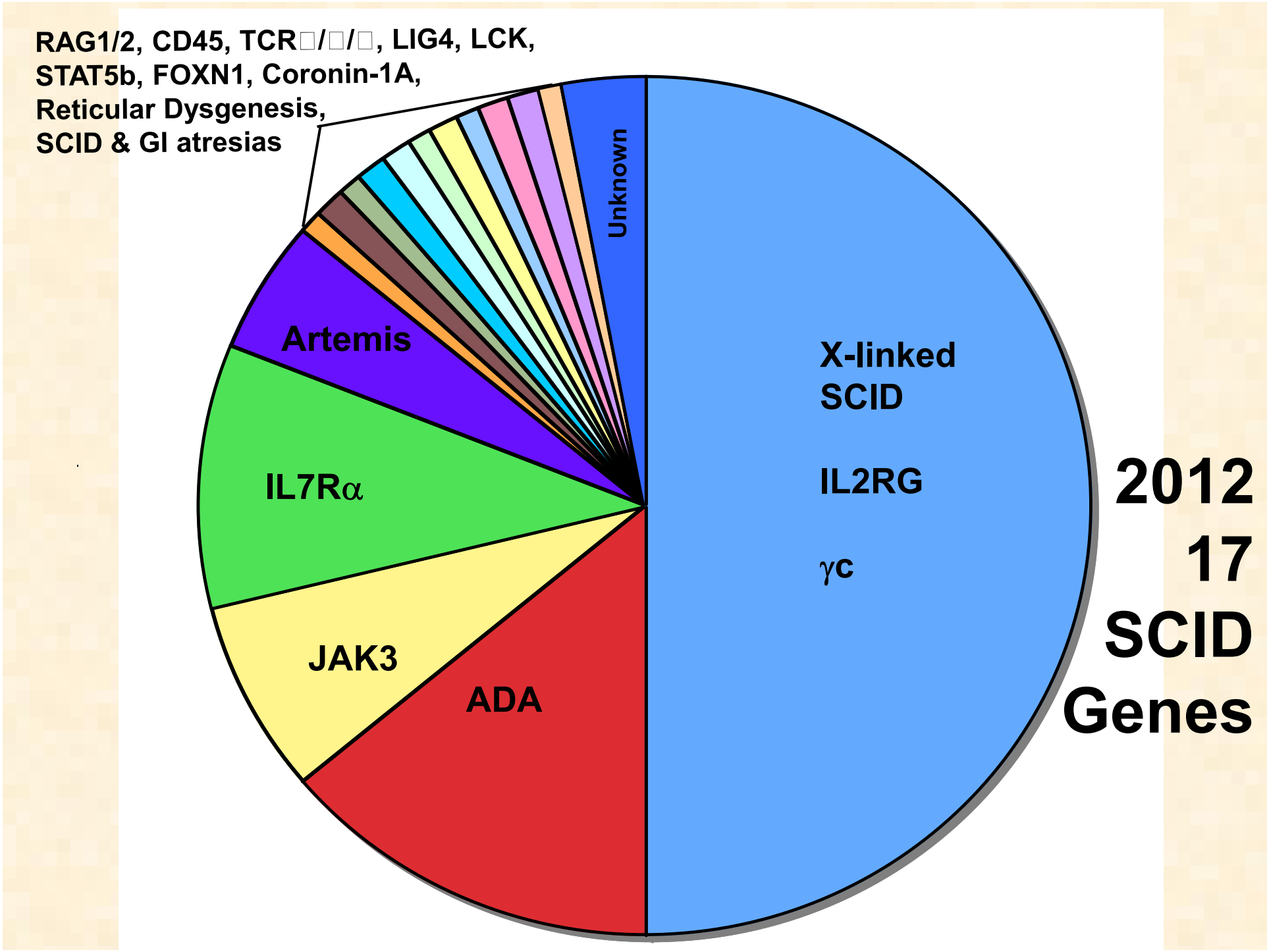
Severe varicella: pneumonia and hemorrhagic blisters.

Human SCID Leads the Way to Immunology Discoveries and Medical Treatments

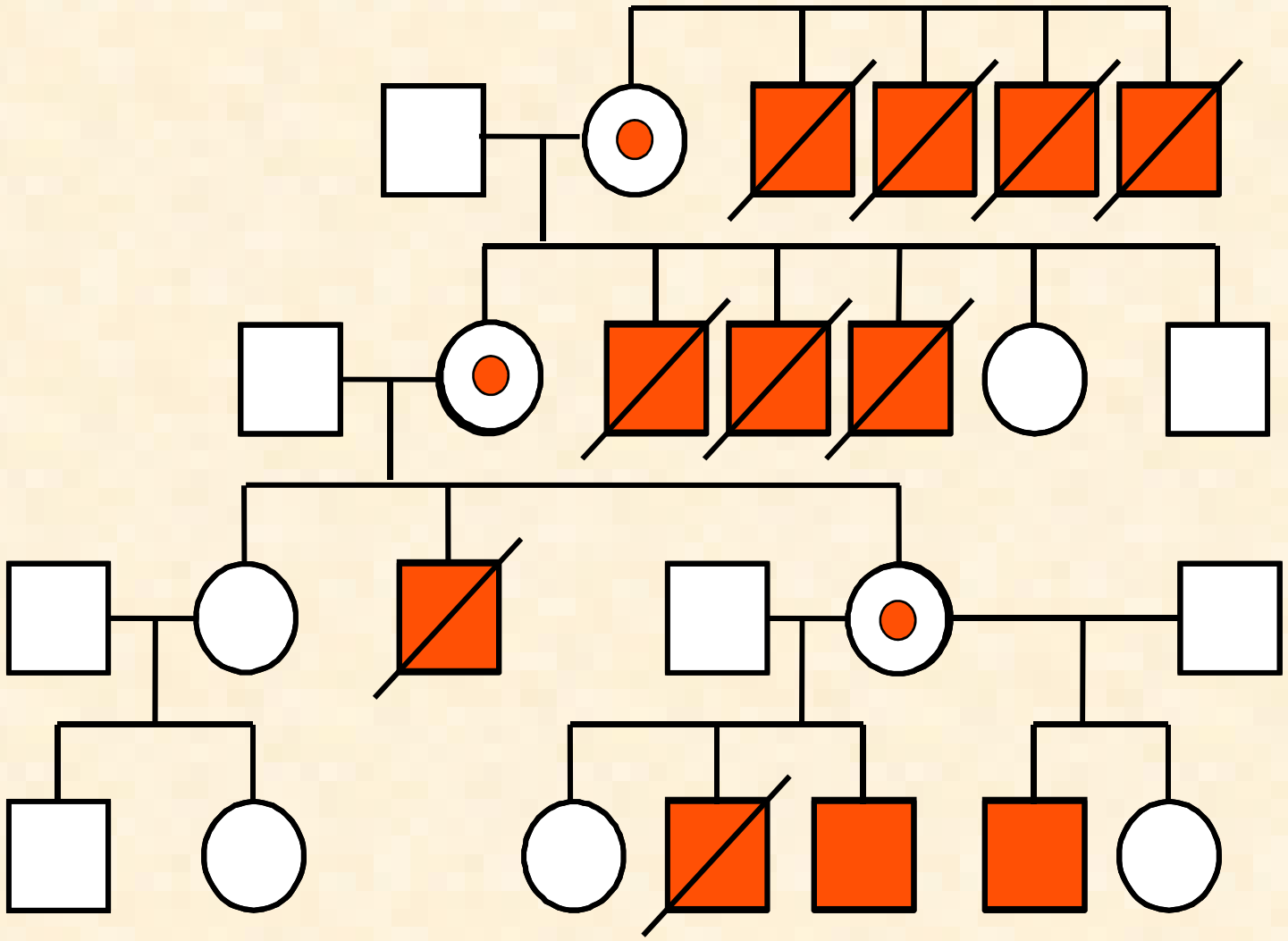
- 1950's: "Swiss type agammaglobulinemia" (Walter Hitzig) and distinct roles of T and B cells (Robert Good).
- 1968: first successful human transplant. Recipient had SCID, donor was his healthy, HLA-identical sister.
- 1970's - 2000's:Transplant breakthroughs: hematopoietic cell transplant (HCT) beyond HLA-matched sibling—parent (haploidentical T cell depleted) or unrelated HLA matched adult or cord blood.
- 1990's: Enzyme replacement with PEG-ADA for Adenosine deaminase deficient SCID.
- 2000's: Gene therapy: X-linked and ADA SCID treatment by adding a correct copy of the *IL2RG* or *ADA* gene to autologous ex vivo; then re-infusing back into patient.

Known Typical SCID Defects

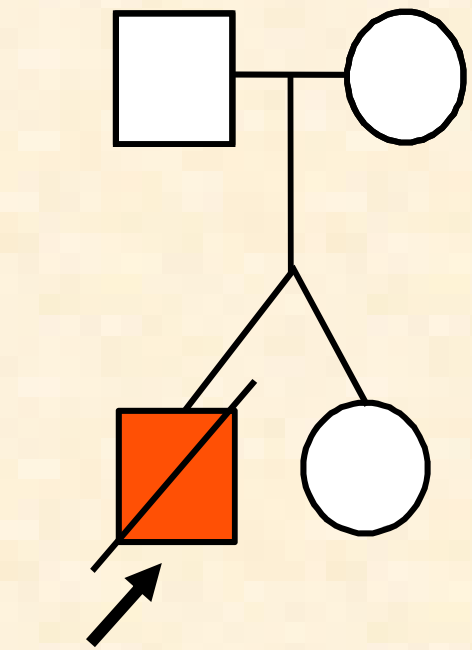



RAG1/2, CD45, TCR□/□/□, LIG4, LCK,
STAT5b, FOXN1, Coronin-1A,
Reticular Dysgenesis,
SCID & GI atresias
Unknown
Artemis
IL7Rα
JAK3
ADA
X-linked SCID
IL2RG
γc
2012
17
SCID
Genes

X-Linked Inheritance of SCID



Most SCID Is Sporadic

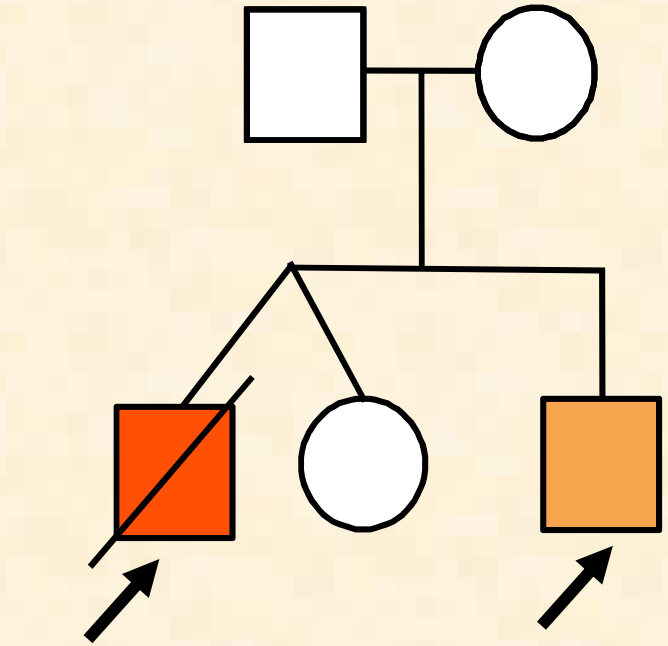


Baby boy, twin, in NICU had *E. coli* sepsis, pneumonia, then disseminated CMV.

Low lymphocyte count not recognized as SCID.

Died at 3.5 months, diagnosis of SCID made after death.

<20% of SCID Cases Diagnosed at Birth Because of an Affected Relative



Sporadic case

Suspected, tested at birth

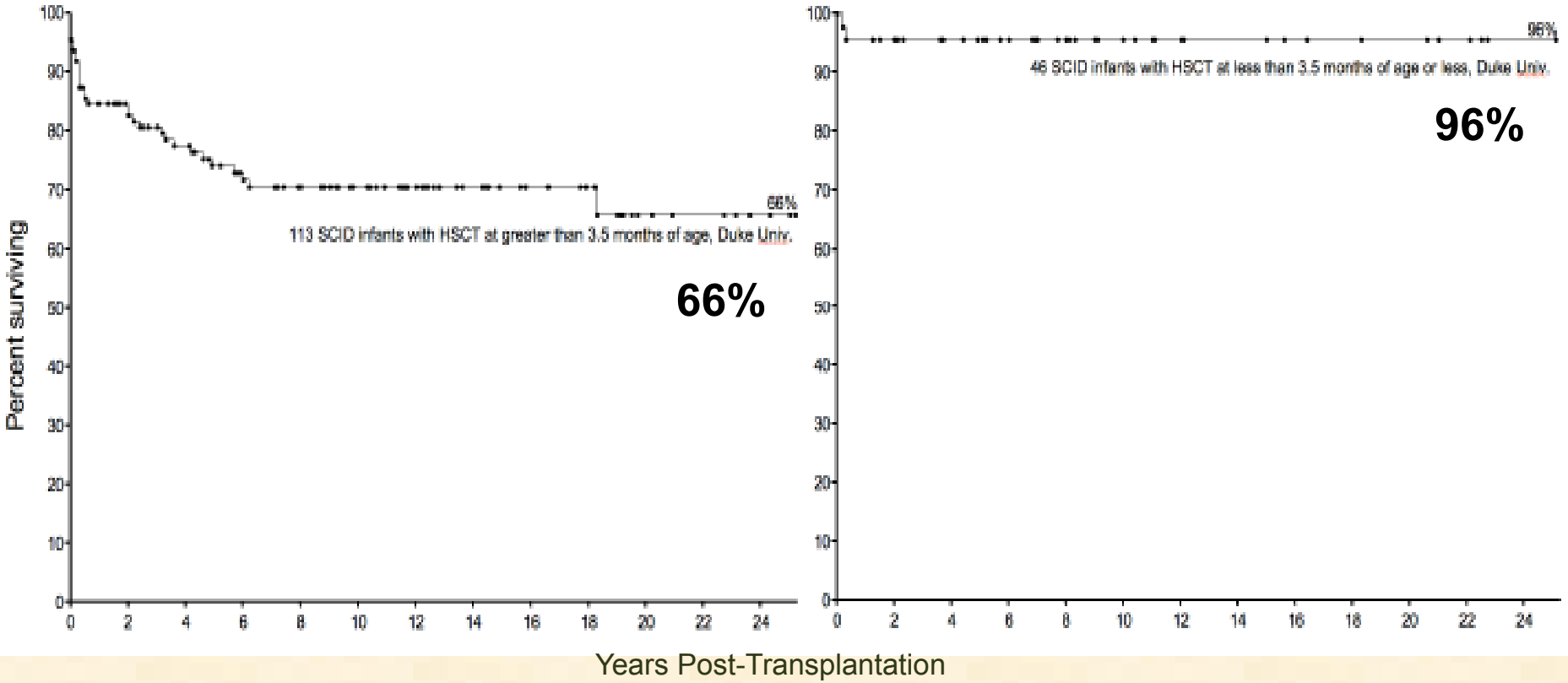
Subsequent brother had SCID diagnosed at birth by absent T and B lymphocytes.
Received early bone marrow transplant from HLA matched sister and is now healthy.

Justifications for Newborn Screening

Screening Criteria	How SCID Meets the Criteria
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/year in California
Well-established confirmative testing	Lymphocyte subsets by flow cytometry
Effective treatment exists	Transplant allogeneic 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, CA, NY, LA, CO, CT, MI (others planning to start)

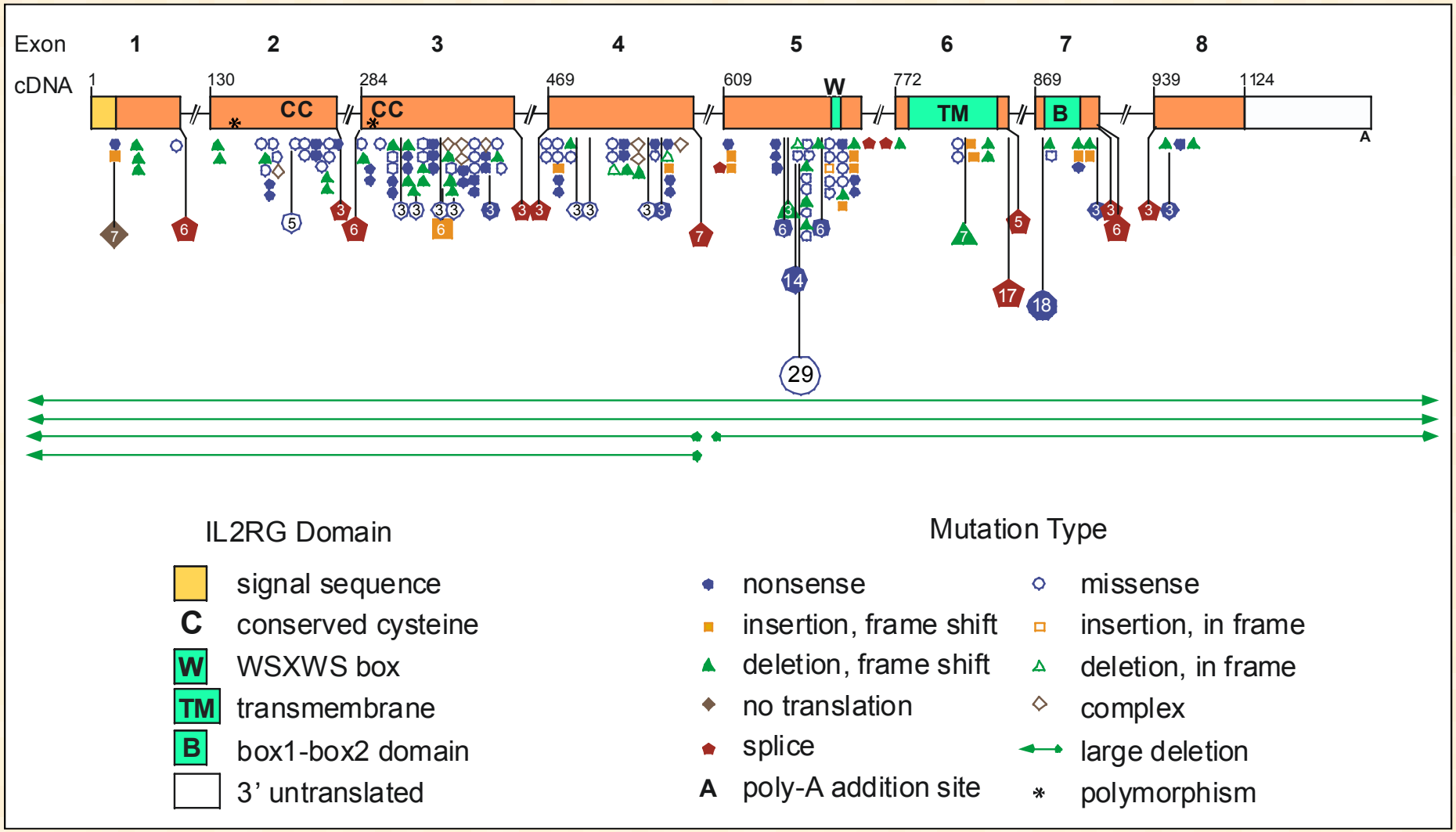
SCID Is Treatable

SCID Patients Treated Early Have Better Survival



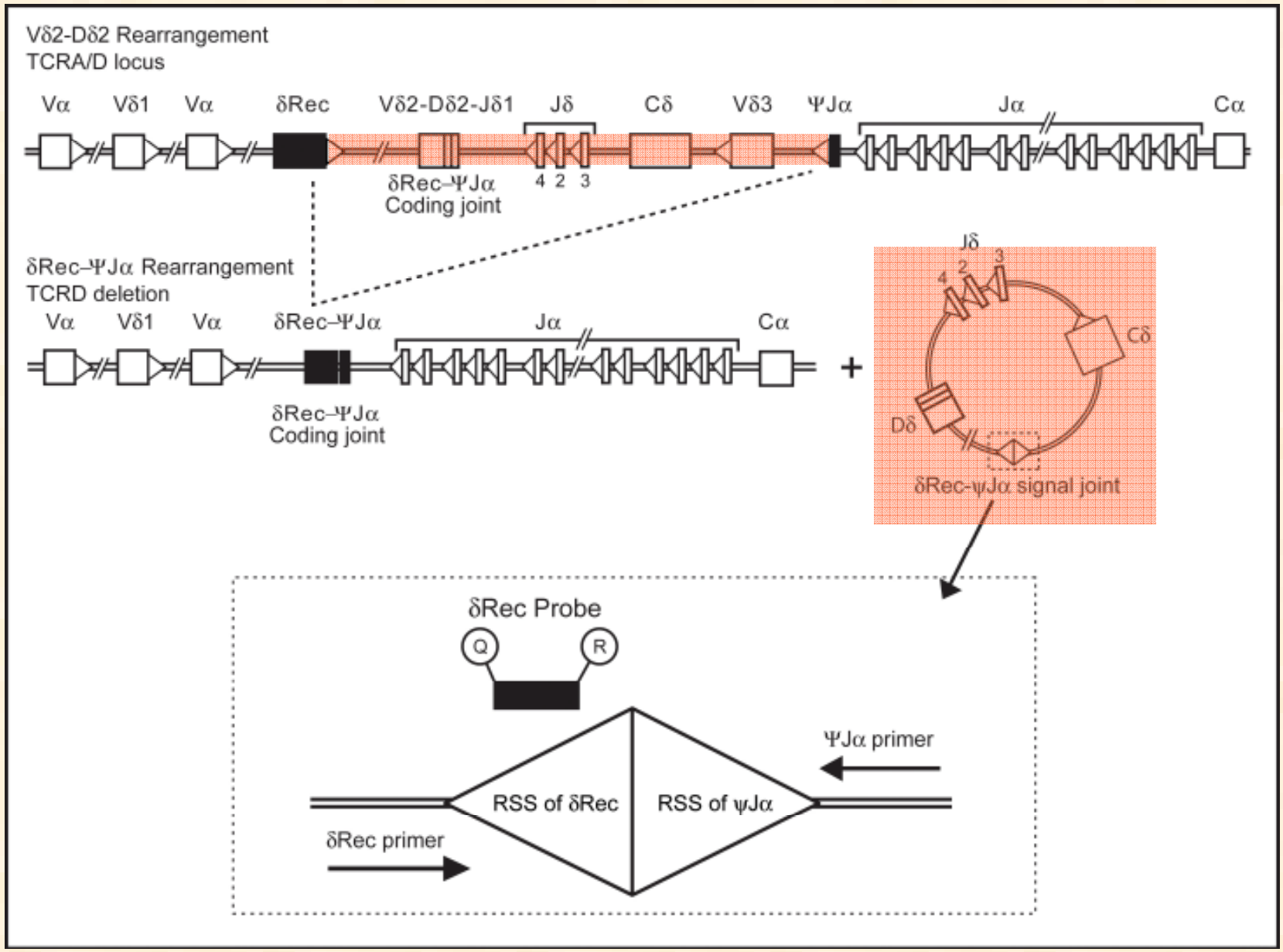
Duke University's largest single institution series of SCID transplants (Dr. R. Buckley); survival for patients treated when older vs. younger than 3.5 months.

205 *IL2RG* Mutations in 351 Unrelated Families with XSCID (62% Puck lab)

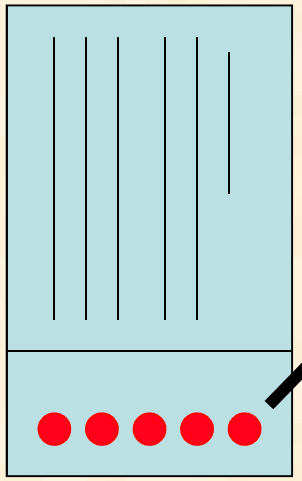


IL2RGbase, J. Puck

T Cell Receptor Excision Circles (TRECs)



TREC Assay on Dried Blood Spots



Guthrie Card

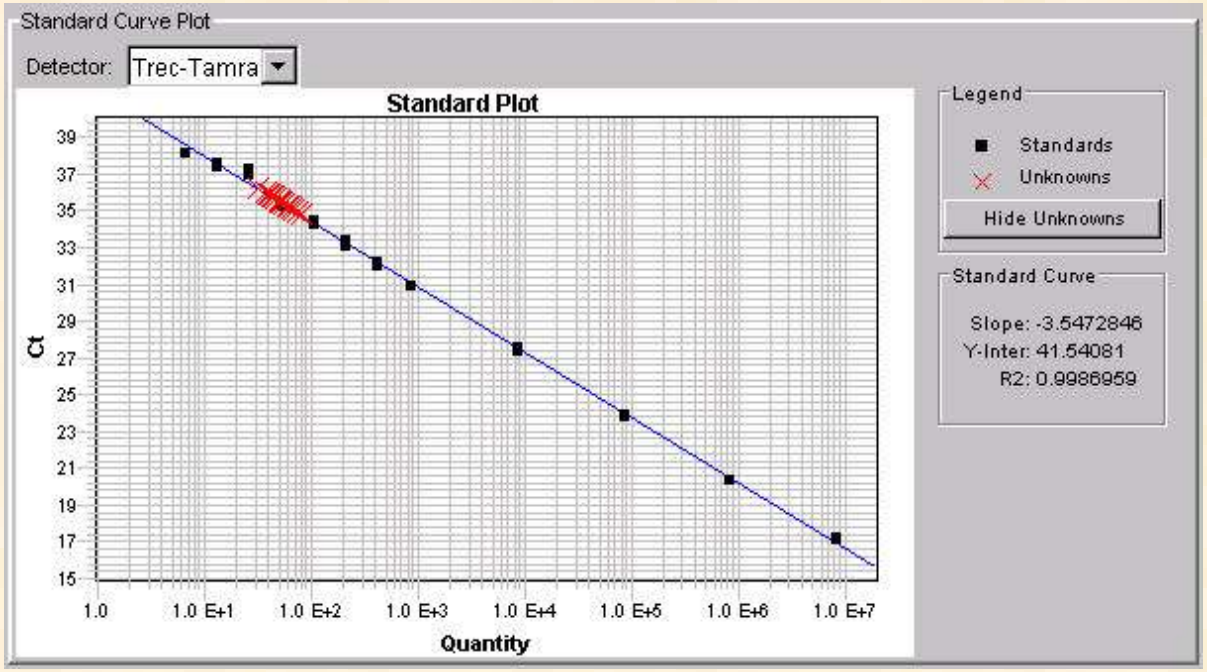
50 ul blood/drop

3 mm hole punched from blood spot

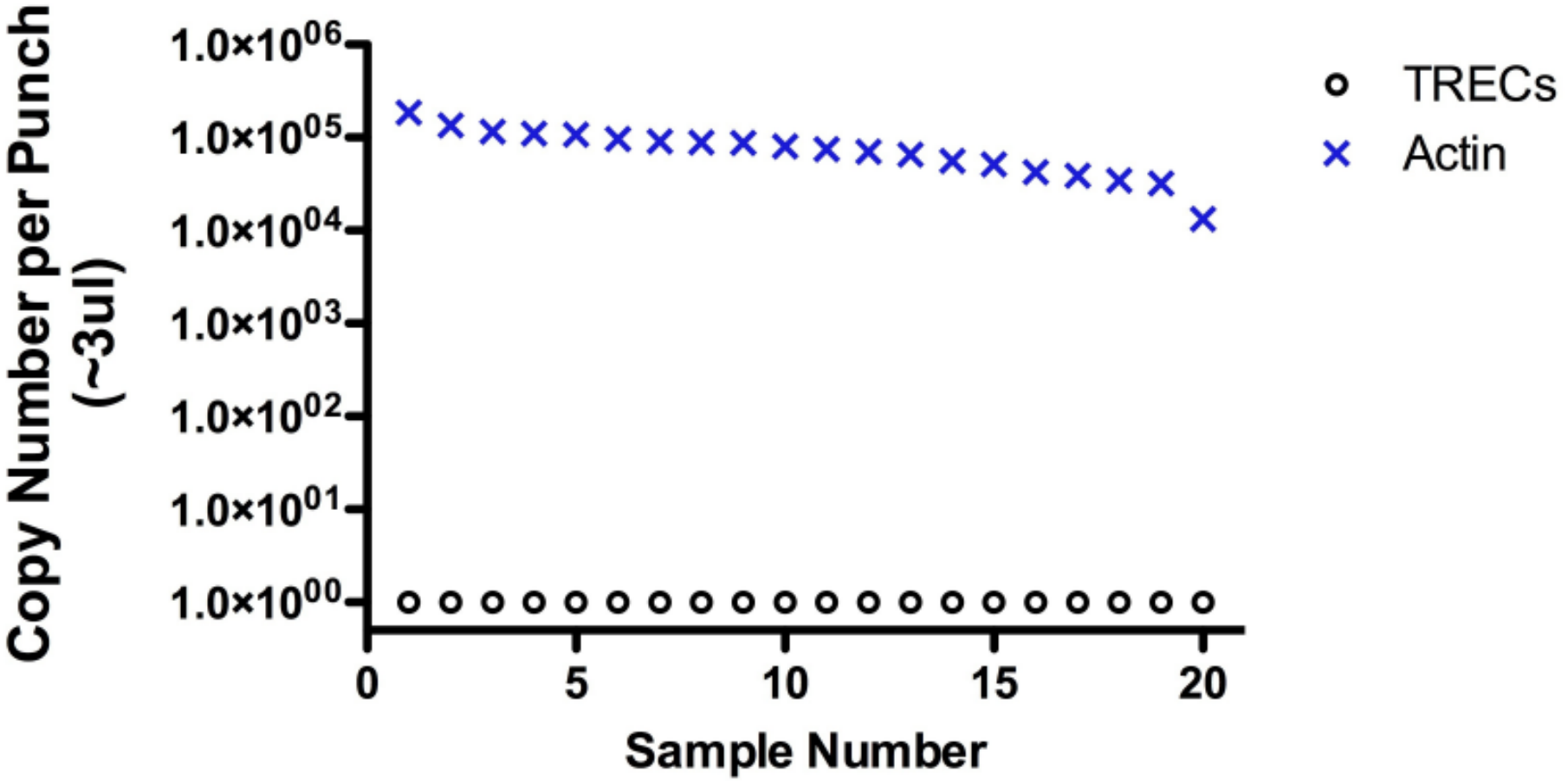
~3 ul blood

Extract DNA

Measure TRECs by PCR



TRECs in Stored Residual Blood Spots from SCID Newborns



DHHS Secretary's Advisory Committee 2010: Public Health Interest Favors Identifying Infants with Low TRECs.

1. Assure that infants with low TRECs are evaluated by an expert and treated without delay.
2. Avoid potential harm from an otherwise beneficial public health program, **live attenuated rotavirus vaccination**.
3. Track outcomes to measure effectiveness of screening, diagnosis and management.

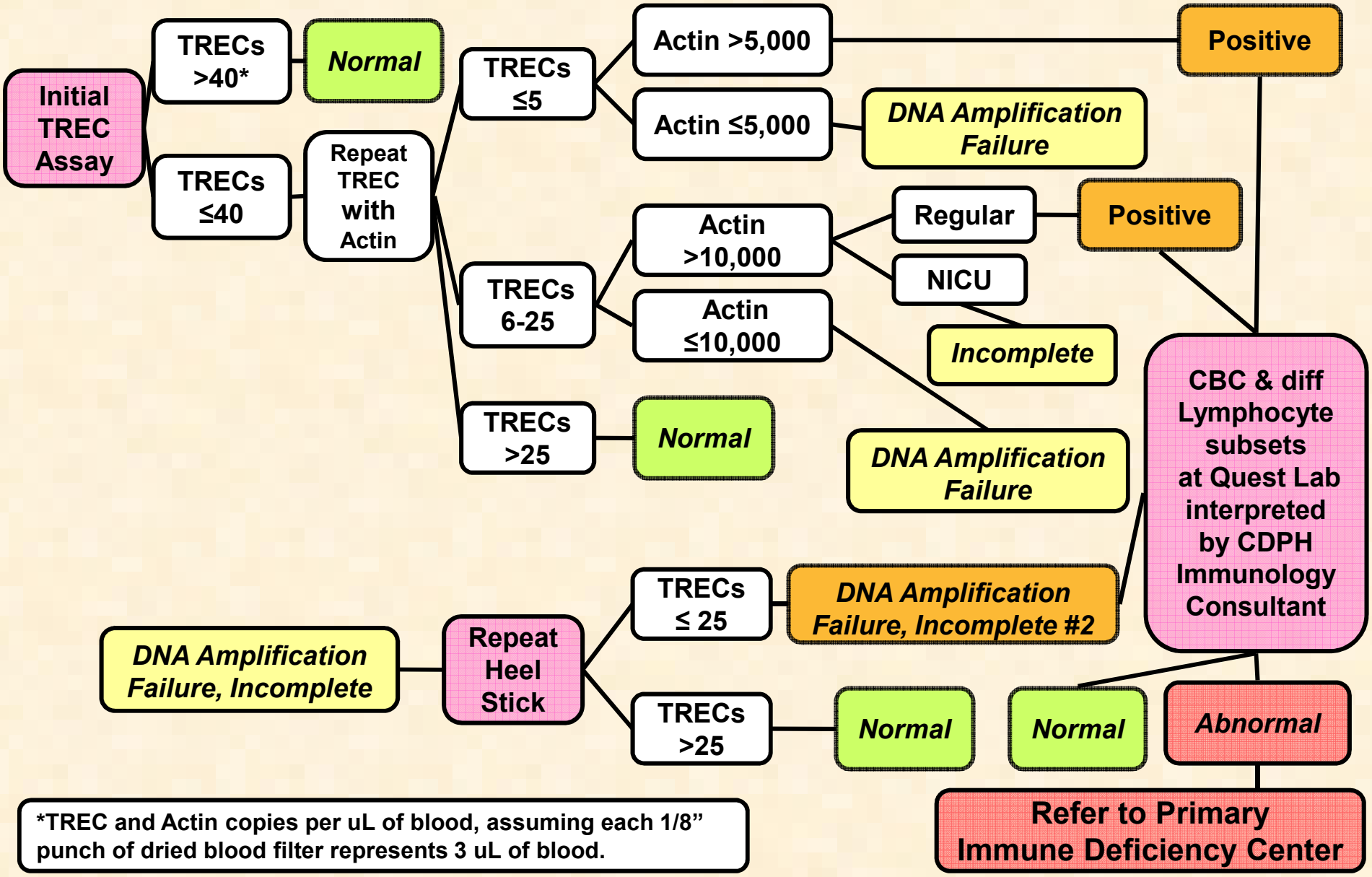
First programs 2008, 2009: Wisconsin, Massachusetts, Navajo

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

May, 2010: Sec. of Health Kathleen Sibelius endorses SCID screening.

August, 2010: CA TREC screening begins. NY, LA, CO, CT, MI, Navajo Nation follow.

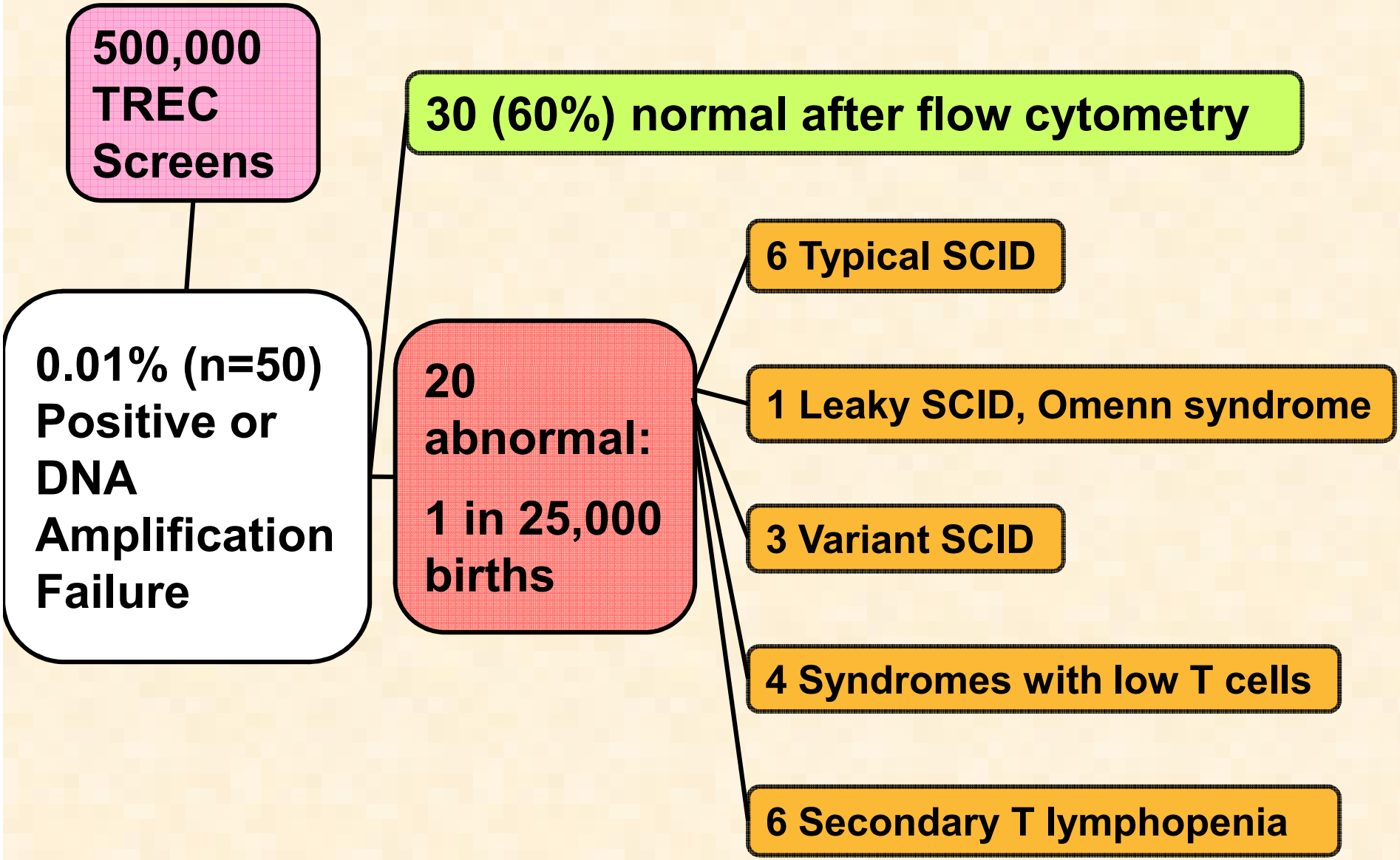
CALIFORNIA SCID NEWBORN SCREENING
TREC Test and Follow Up [Puck, Church and Lorey, 1/2012]



*TREC and Actin copies per uL of blood, assuming each 1/8" punch of dried blood filter represents 3 uL of blood.

THIS MAY ALL SEEM VERY CONFUSING, BUT NEWBORNS WITH SCID HAVE HAD **0-5 TRECS**!

California TREC Screening Results, First Year



Typical and Leaky SCID/Omenn

- **6 Typical SCID:** <300 autologous T cells/uL (may have maternal cells), PHA proliferation <10% of control. Normal newborns have 2500-5500 T cells/uL.

  No recurrent gene or mutation, all but one with at least 1 Hispanic parent

  2 IL-7 receptor alpha chain

  2 RAG1

  2 X-linked, IL-2 receptor gamma (1 familial, 1 new)

- **1 Omenn syndrome:** 300-1500 T cells/uL, no maternal cells, PHA proliferation 10-30% of control.

  (Erythroderma, eosinophilia, oligoclonal T cells, hypomorphic mutation in known SCID gene)

  RAG2


GRANDMA'S
biggest joy

Syndromes with Variable T Cell Defects That Can Be Severe

- **1 Complete DiGeorge syndrome with thymic aplasia (ch22q11.2 deletion):** Diagnose by copy number array, CGH
- **2 Partial DiGeorge syndrome with low T cells**
- **1 Trisomy 21**

CHARGE syndrome

Cartilage hair hypoplasia

Jacobsen syndrome

RAC2 dominant interfering mutation

DOCK8 deficient hyper-IgE syndrome

Others…

Secondary T Lymphopenia

- 2 Gastroschesis
- 1 Gastrointestinal atresia
- 3 Extreme prematurity

Congenital heart disease surgery with thymectomy

Neonatal leukemia

Vascular leakage, chylothorax, third spacing

Prenatal HIV infection

Variant SCID

- **300 – 1,500 autologous T cells/uL (normal 2500-5500/uL). [Typical SCID can have >300 T cells if maternal engraftment is present.]**
- **No known SCID gene mutation.**
- **Impairment in T cell and/or antibody responses.**

Conclusions

1. Primary immune disorders are caused by a wide range of rare, but treatable gene defects. Secondary immune disorders confer a risk of serious infections.
2. Early diagnosis permits optimal treatment and better outcome.
3. Newborn screening has clinical validity, having made possible pre-symptomatic diagnosis of SCID and related conditions, and offers opportunities for learning spectrum of T cell disorders and arriving at best treatments.
4. High index of suspicion is still needed for conditions not picked up by screening.

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