Diagnosis of SCID
and
Disorders with Insufficient T cells

Jennifer Puck, MD

Jennifer.Puck@ucsf.edu

Department of Pediatrics
University of California San Francisco
and Benioff Children's Hospital
San Francisco, California

Severe Combined Immunodeficiency, SCID—Primary Target of TREC Screen

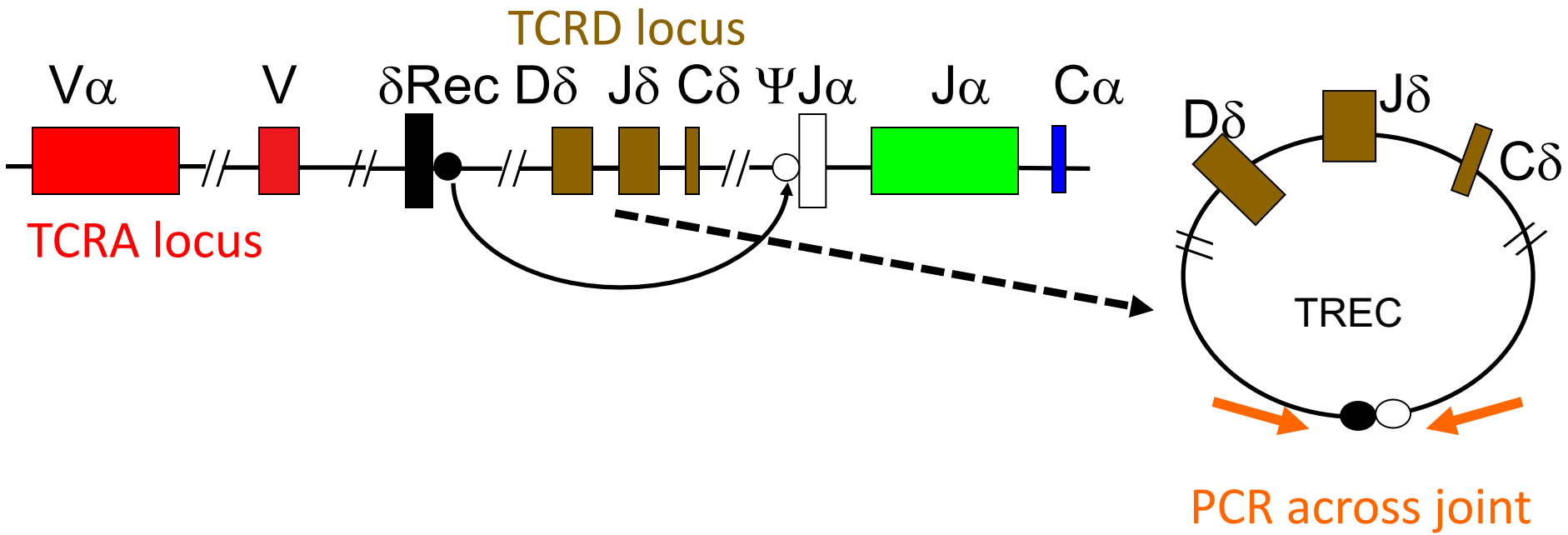
- Rare; many genes.
- Healthy at birth, but recurrent, severe infections, failure to thrive if not recognized.
- **Absent or low T cells.**
- **Absent or non-functional B cells.**
- High early mortality, mostly due to severe viral infections—CMV, adenovirus.
- Can be cured by bone marrow transplant from a healthy matched donor (first in 1968), or increasingly gene therapy, or for ADA-SCID, enzyme injections.

David Vetter (1971-1984), Texas Children's Hospital

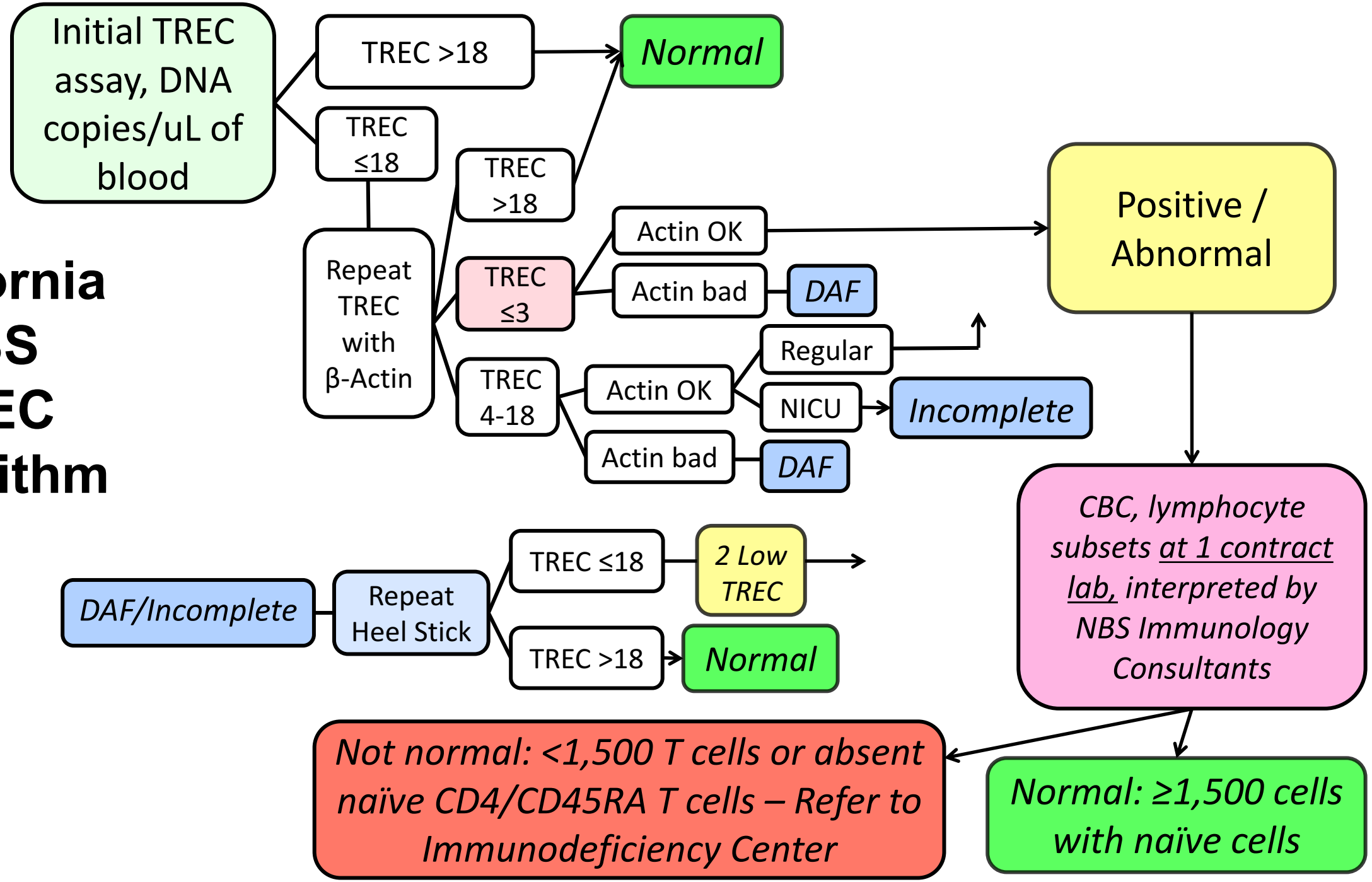
http://www.wired.com/news/images/full/bubbleboy3_f.jpg

TREC: T Cell Receptor Excision Circle, a Biomarker for Thymic T Cell Production

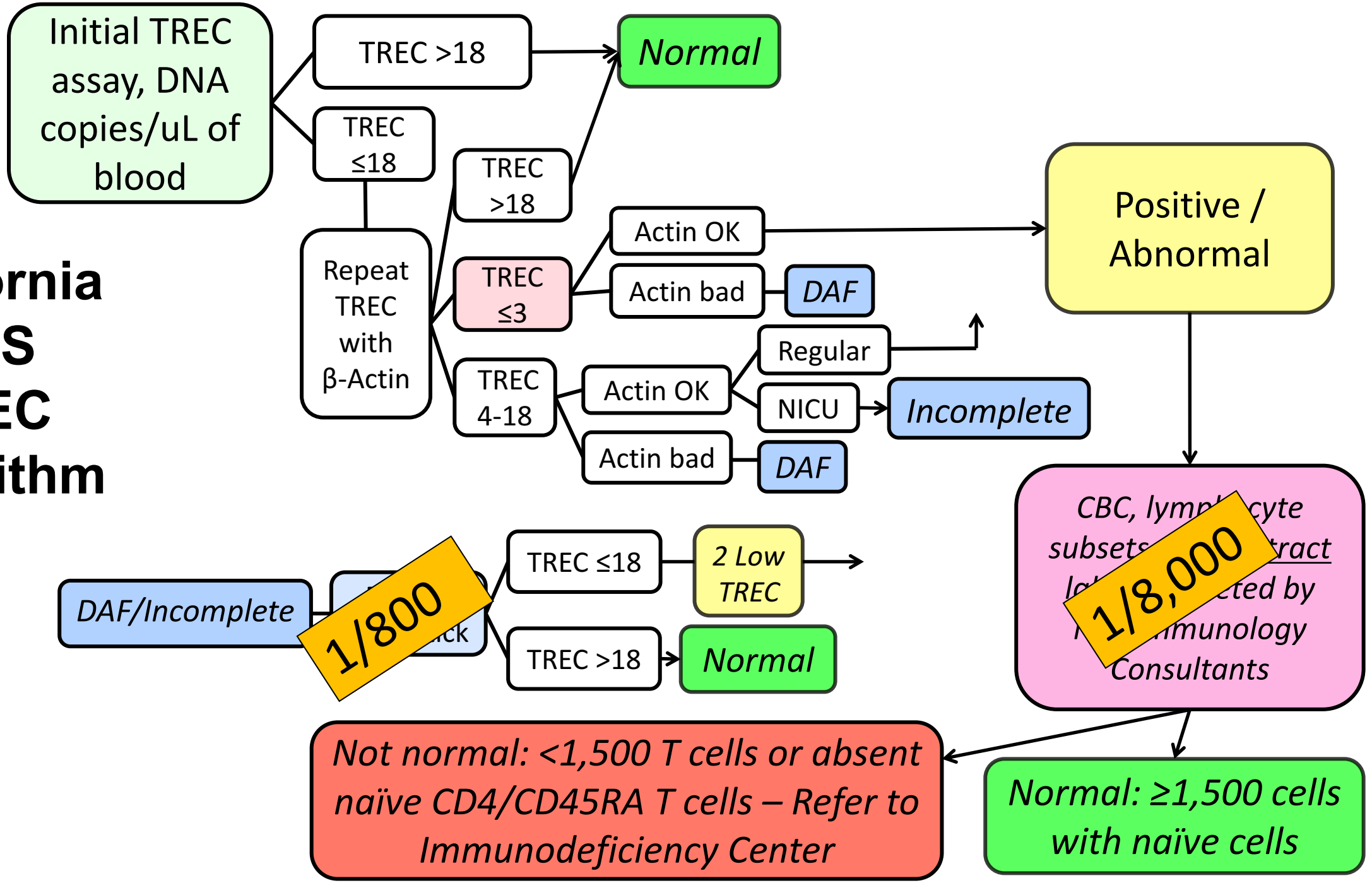
- Normal diverse T cell repertoire is made by cutting and pasting alternate DNA sections of receptor genes
- Excised DNA forms T Cell Receptor Excision Circles (TRECs) as a byproduct.
- TRECs can be detected by PCR.



California NBS TREC Algorithm



California NBS TREC Algorithm



Term male, 0 TREC, 473 Actin

39230704	6D	MALE	SCID#627	SCID#627

REMARKS

REFERRING PHYSICIAN: J PUCK MD/ J CHURCH

REPORTED 10/07/2016

STATUS DUPLICATE

CBC (DIFF/PLT)

TEST	RESULT (* = OUT OF RANGE)	UNITS	REFERENCE RANGE
WBC	6.9*	Thousand/uL	9.0-30.0
RBC	5.0	Million/uL	3.90-5.90
HGB	17.6	g/dL	13.4-19.9
HCT	54.7	%	42.0-65.0
MCV	108.6	fL	88.0-123.0
MCH	35.0	pg	31.0-37.0
MCHC	32.2	g/dL	28.0-36.0
PLT	356	Thousand/uL	150-400
MPV	9.7	fL	7.5-11.6
RDW	17.5*	%	11.5-16.0
Absolute Neutrophils	2600	cells/uL	1500-10000
Absolute Lymphocytes	1300*	cells/uL	2000-17000
Absolute Monocytes	2600*	cells/uL	300-2400
Absolute Eosinophils	300	cells/uL	15-800
Absolute Basophils	0	cells/uL	0-250
Neutrophils	38.0	%	
Lymphocytes	18.7	%	
Monocytes	38.4	%	
Eosinophils	4.7	%	
Basophils	0.2	%	
CD3 T-Cells, Absolute	78*	cells/uL	2500-5500
CD3 T-Cells, Percent	6*	% of lymphocytes	53-84
CD4 T-Helper, Absolute	65*	cells/uL	1600-4000
CD4 T-Helper, Percent	5*	%of lymphocytes	35-64
CD8 T-Cytotoxic, Absolute	<20*	cells/uL	560-1700
CD8 T-Cytotoxic, Percent	1*	% lymphocyte	12-28
CD19 B-Cells, Absolute	364	cells/uL	300-2000
CD19 B-Cells, Percent	28	% of lymphocytes	6-32
CD16/56 NK-Cell, Absolute	741	cells/uL	170-1100
CD16/56 NK-Cell, Percent	57*	% of lymphocytes	4-18
CD4/CD45RA, Absolute	<20*	cells/uL	1200-3700
CD4/CD45RA, Percent	5*	% of CD4 Cells	64-95
CD8/CD45RA, Absolute	<20*	cells/uL	450-1500
CD8/CD45RA, Percent	20*	% of CD8 Cells	80-99
CD3/CD4/CD45RO, Absolute	43*	cells/uL	60-900
CD3/CD4/CD45RO, Percent	55*	% of CD3 Cells	2-22
CD3/CD8/CD45RO, Absolute	<20*	cells/uL	30-330
CD3/CD8/CD45RO, Percent	1	% of CD3 Cells	1-9

Low total lymphocytes

T-

B+

NK+

No naïve T cells

SCID Definition

"Classic" SCID pre-Newborn Screening:

- No T cells; no specific antibody, failure to thrive, thrush, recurrent infections.

New definition with screening needs to be based on lab values:

- **"Typical" SCID**: <300/uL autologous T cells; <10% of normal proliferation to mitogens such as PHA; no production of specific antibodies. Proven with null mutation(s) in known SCID gene.
- **"Leaky" SCID** (includes Omenn syndrome): 300-1500 T cells or more, but low to absent naïve CD45RA T cells, impaired PHA, hypomorphic mutation(s) in SCID gene.

Primary Immune Deficiency Treatment Consortium (PIDTC)

>40 USA, Canadian and European Centers from 2009; uniform data collection

<u>Retrospective Study 6902:</u>

Cross-sectional evaluation

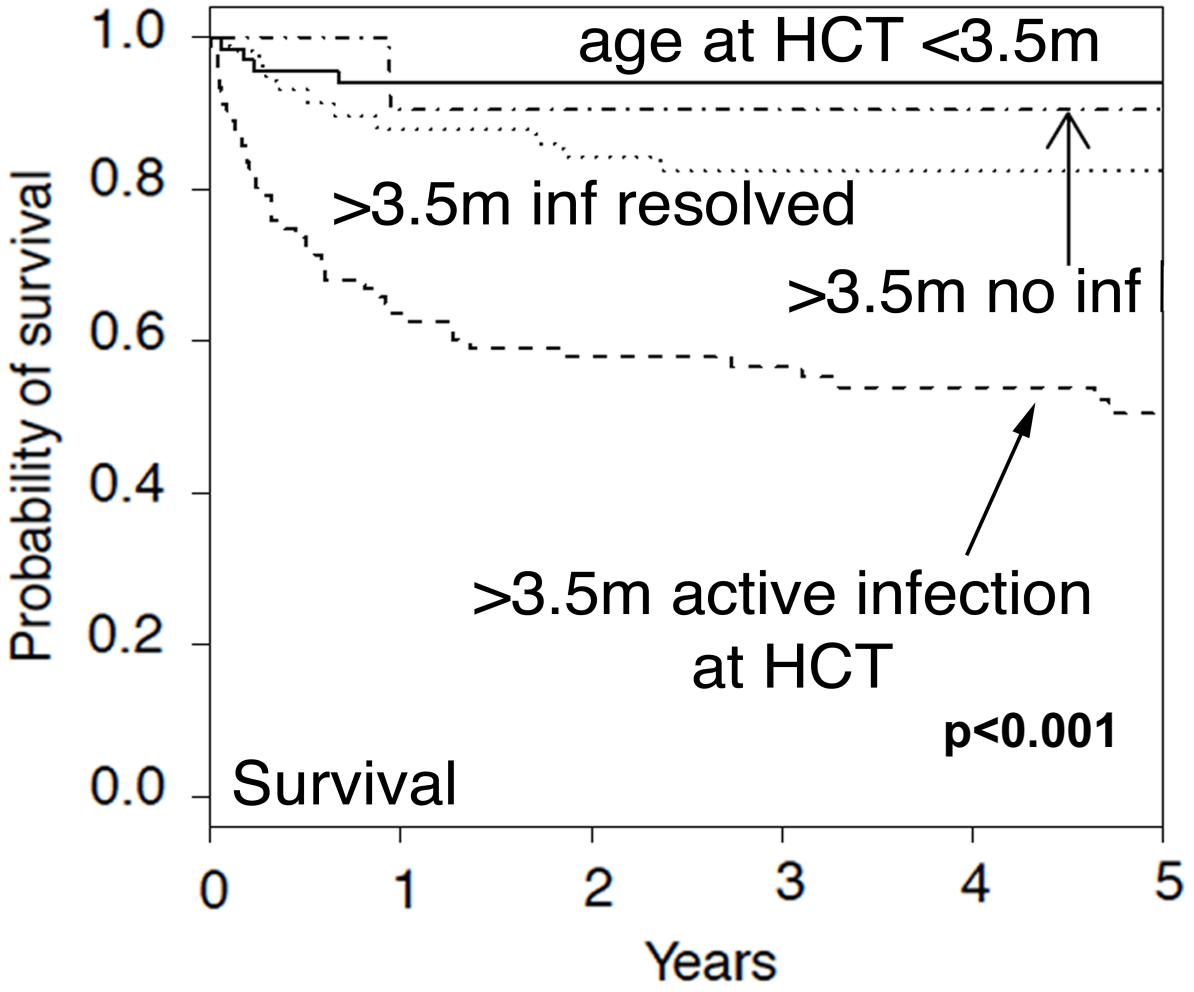
<u>Prospective Study 6901:</u>

Natural history, observational

Identify factors affecting outcomes of HCT, ERT, or GT

Primary Immune Deficiency Treatment Consortium

5 year survival for *Typical SCID* depends more on infection than age at HCT

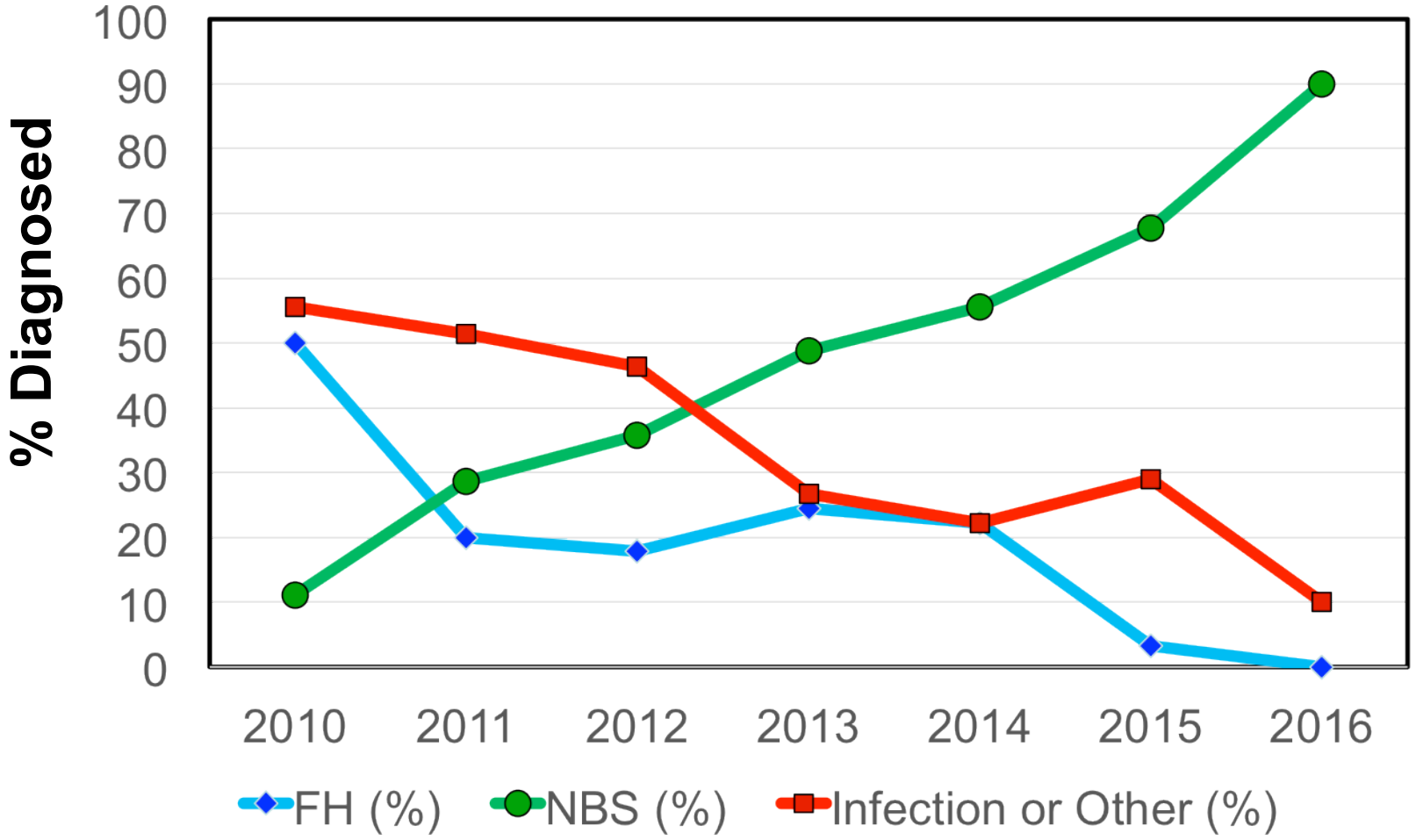


- >3.5 months with active infection worse than any other group.
- <3.5 months and >3.5 months with no infection had best survival;
- >3.5 months with infection resolved same as <3.5 months or uninfected.

Pai et al, NEJM, 2014 371:434-46.

Primary Immune Deficiency Treatment Consortium

PIDTC SCID Diagnosis by Screening vs. Infection, Family History

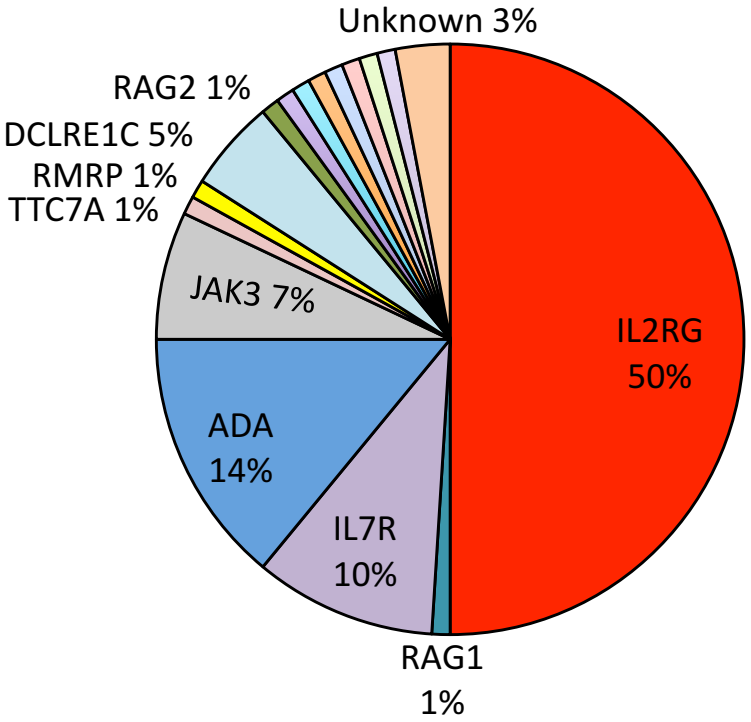


Primary Immune Deficiency Treatment Consortium

Genotypes of Typical and Leaky SCID

Reports from Transplant Centers, no Screening

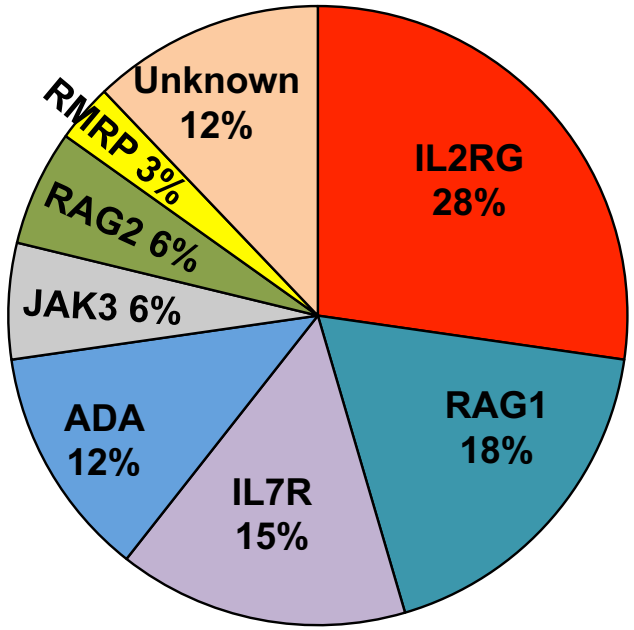
Duke University, European centers (estimates)



Overall Survival ~74%

California, with TREC Screening

3½ years, 1.7 ×10⁶ infants



Overall Survival 94%

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

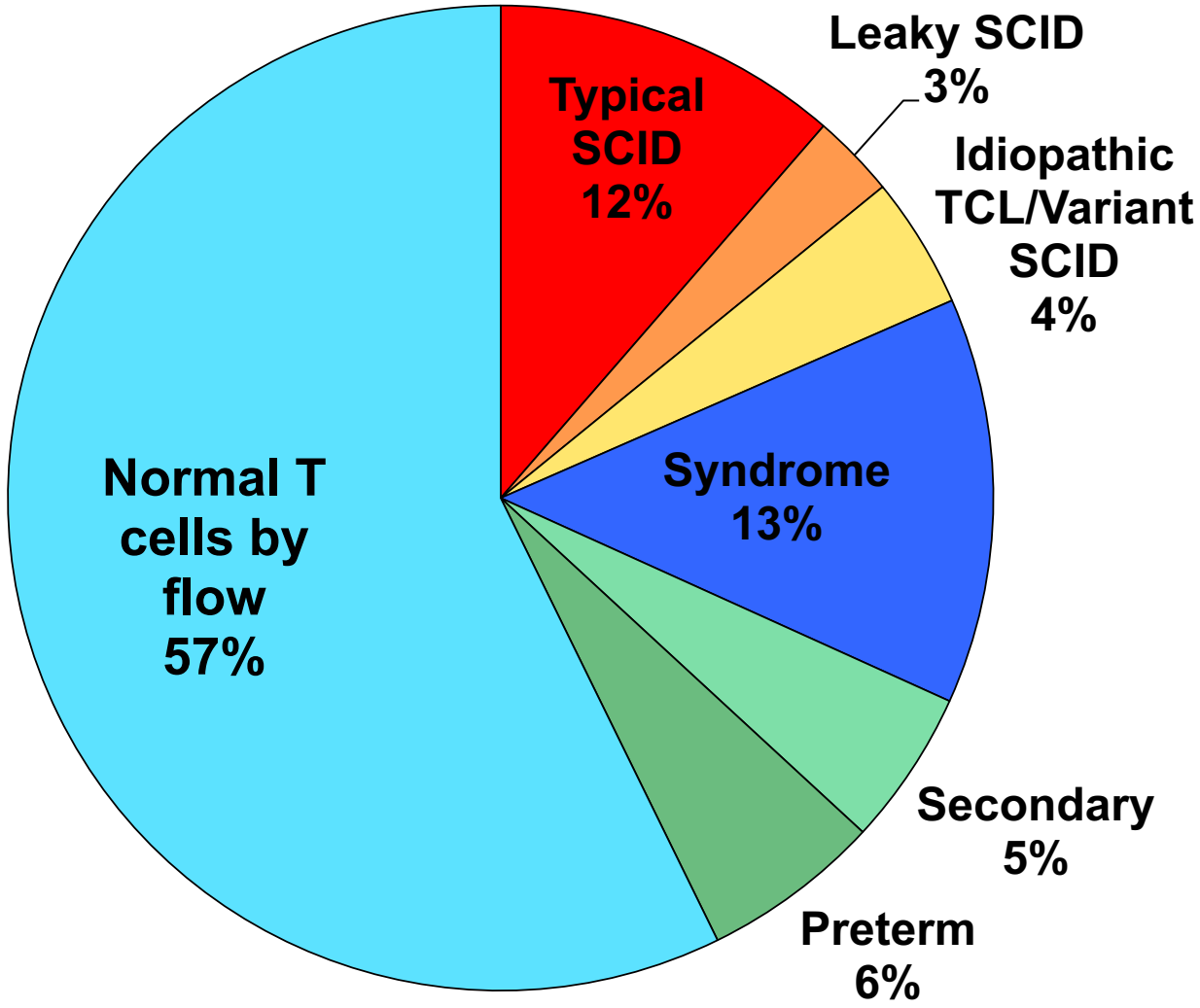
2 million infants screened.

255 flow cytometry 2nd tier tests. (1/8,000 infants)

109/255 had <1500 T cells/uL (43%).

<u>1/55,000 Typical and Leaky SCID.</u>

1/180,000 Idiopathic T Cell Lymphopenia



Non-SCID Conditions with Low TRECs

Multisystem syndromes with variable T cell deficiency

57% DiGeorge/chromosome 22q11.2 deletion
15% Trisomy 21
3% Ataxia telangiectasia
2% CHARGE syndrome, *and many more…*

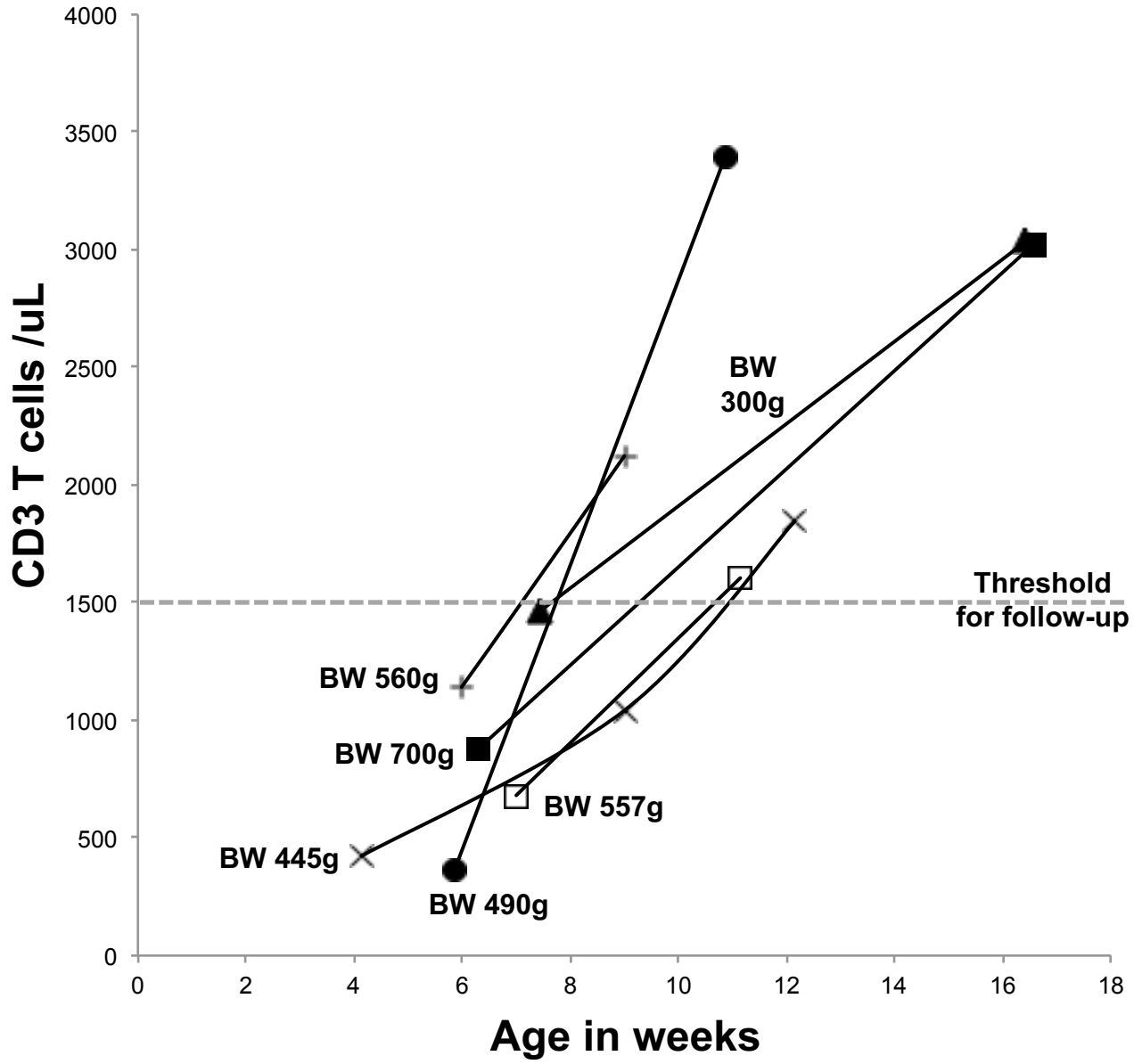
Secondary T lymphopenia

25% Congenital cardiac anomalies
38% Other congenital anomalies
13% Vascular leakage, third spacing, hydrops
3% Neonatal leukemia
3-5% Maternal immunosuppressive medications

Extreme preterm birth — T cells become normal over time

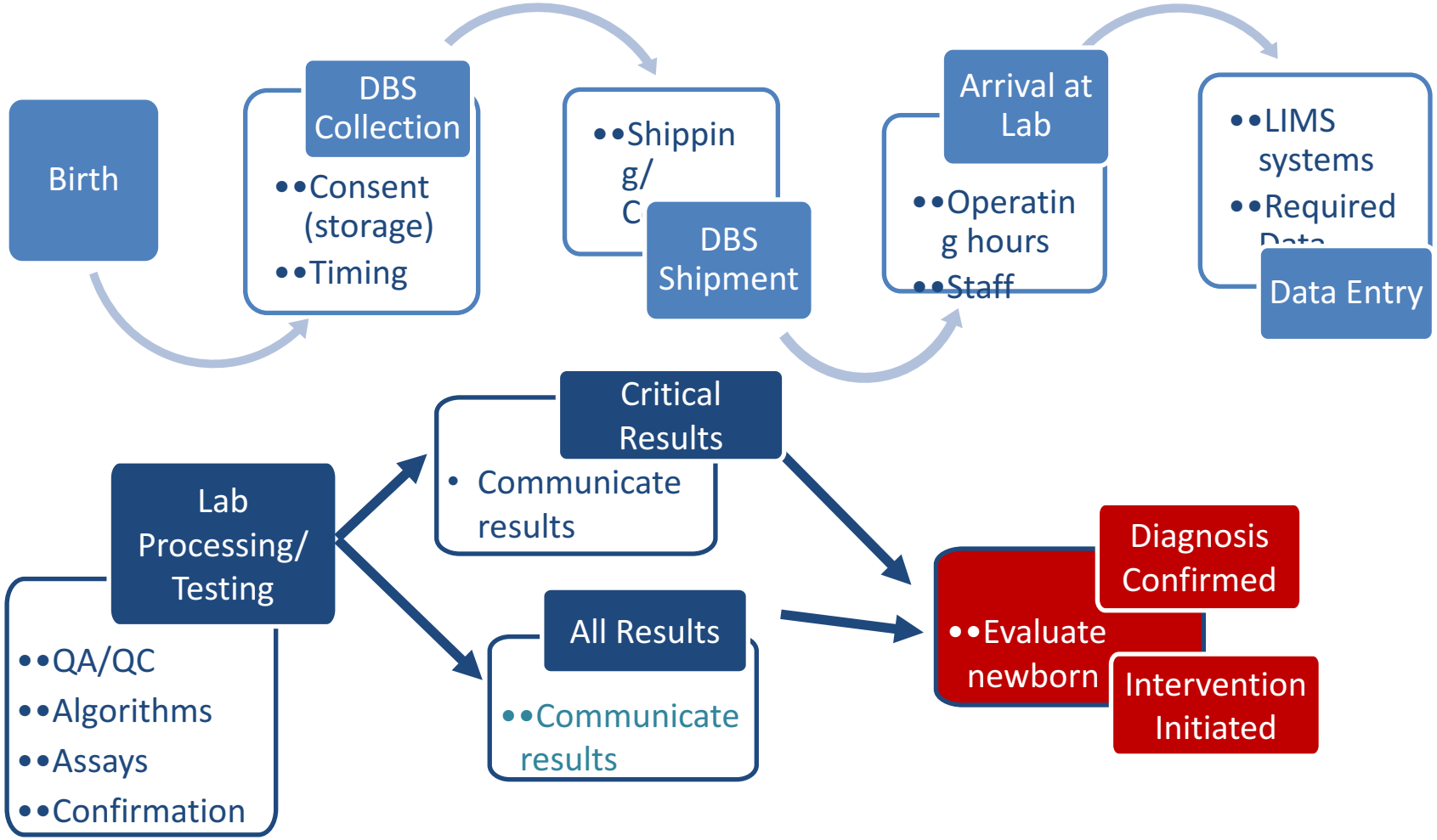
Idiopathic T lymphopenia — few or no naïve T cells, no maternal cells; when solved move to correct category

Preterm Low Birthweight Infants with Low TRECs and T Lymphopenia



Idiopathic T Lymphopenia (Variant SCID)

- **Persistently low 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.**

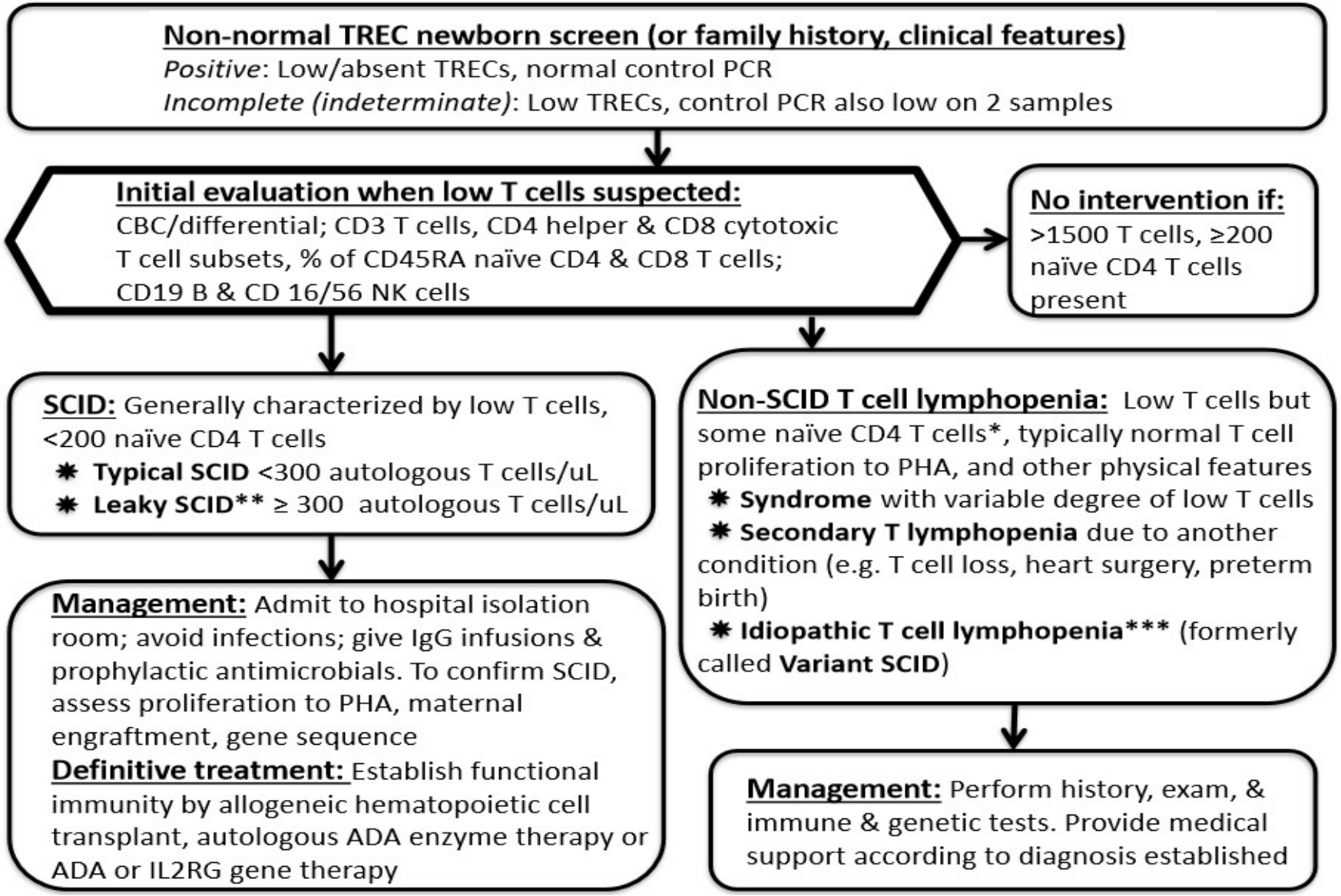


••Immune Evaluation
Varies by State

Flow cytometry in NBS Program eliminates half of cases!

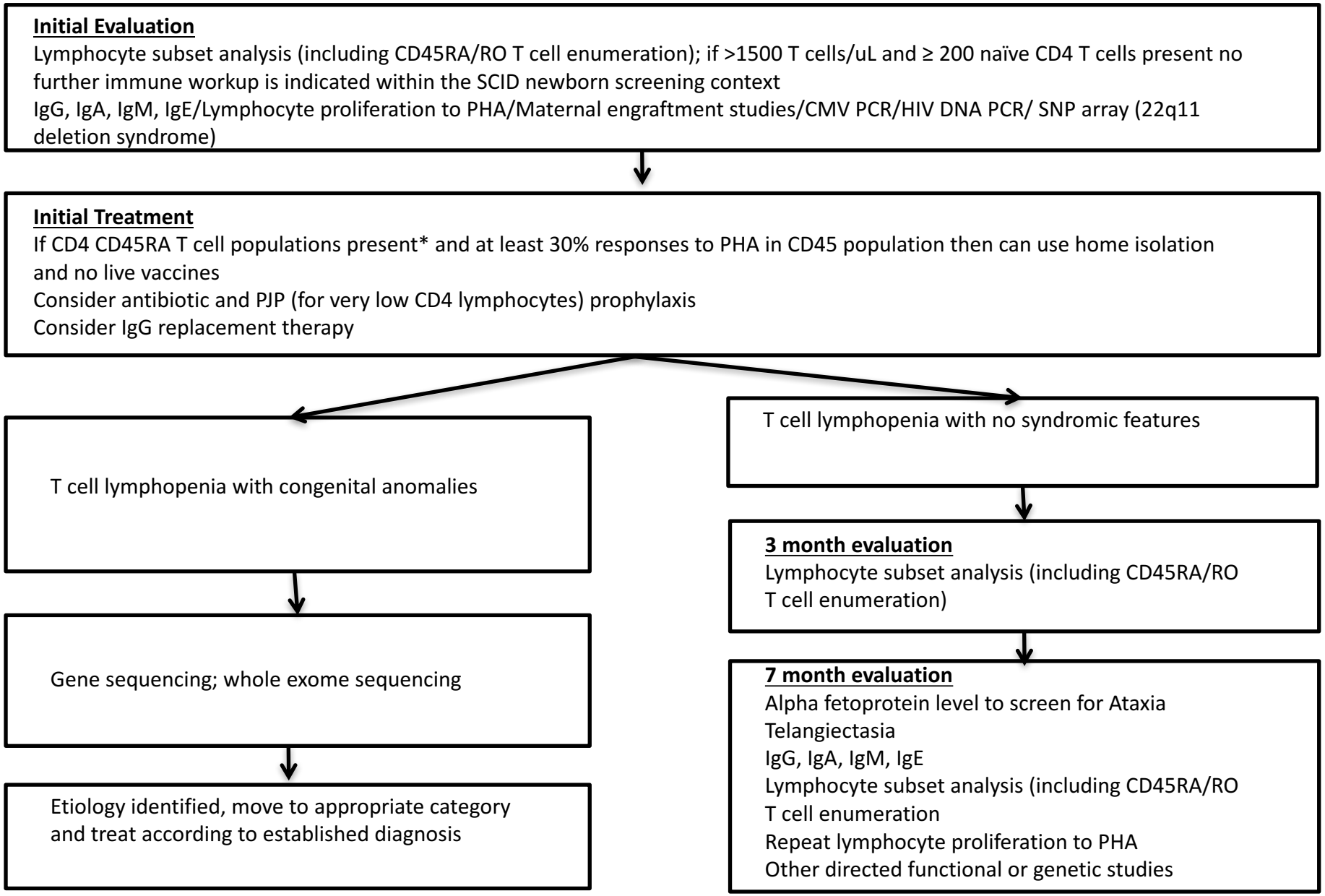
For SCID, direct hospital admit
Pursue genetic cause
Evaluate donors for transplant
Protect from infectious exposure
CMV & breastfeeding
Hospitalization, isolation
Transfusion precautions
Antibody infusions
Antimicrobial prophylaxis

For T cells <1500 do outpatient workup
Physical exam: syndrome?
Repeat lymphocyte subsets
Antibody levels
PHA proliferation
No live vaccines



*Variable can be < 200 naïve CD4 T cells.**__Omenn syndrome__ is a form of leaky SCID with rash; eosinophilia; autoreactive, oligoclonal T cells; and variable CD3 T cell count which can be >1500. ***Some infants never leave this group but some move out of this category when other diagnoses are made. These infants need to be followed over time.

Dorsey et al. JACI 139:733-42, 2017



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Conclusions

1. SCID comprises treatable, serious, immune deficiencies affecting 1/50,000-1/60,000 births. TREC screening for SCID is sensitive.
2. Early diagnosis has identified more cases, saved lives, compared to historical data.
3. Incorporation of CBC/diff and flow cytometry testing into the screening program can be effective to increase specificity.
4. TREC screening also detects non-SCID conditions with low T cells, offering clinical benefit and opportunities to study the spectrum of disorders.
5. New data suggests that infections are a problem for newborns with SCID despite screening, particularly CMV transmission from breastfeeding.

Thanks to Many Collaborators

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Other
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