Newborn Screening for SCID and…?

Anne Marie Comeau, Ph.D
Deputy Director, NENSP
Professor of Pediatrics, UMMS

Molecular Advances
APHL Newborn Screening and Genetic Testing Symposium
October 27, Anaheim CA

University of Massachusetts Medical School
UMASS
umassmed.edu

ACKNOWLEDGEMENTS

Jaime Hale Jacalyn Thompson

Roger B Eaton Inderneel Sahai

New England Newborn Screening Program

Jessica Pagano-Therrien Beverly Hay

UMass Memorial Hospital UMMS

Catherine Biggs Francisco Bonilla

Children's Hospital, Boston

University of Massachusetts Medical School
UMASS
umassmed.edu

Jeffrey Modell Foundation | Curing PI. Worldwide.

National Institutes of Health

Laboratory Development, Retrieval and Testing

Grant # IV01-EH000362-03

Implementing SCID NBS with Multiplexed Assays in an Integrated Program Approach

CDC National Center for Environmental Health

Patient Recruitment and Consent

UMMS Life Sciences Moment Fund Grant # UL1TR000161

National Center for Advancing Translational Sciences

A Retrospective Study with Prospective Potential: evaluating specimens of children diagnosed with conditions that may e identifiable in the newborn period by molecular testing for measures of T and B cell development

New England Newborn Screening Program

University of Massachusetts Medical School

umassmed.edu

The Massachusetts SCID NBS Workgroup

Representatives from Newborn Screening, Immunology, Infectious Disease, Public Health and Transplantation

Baystate Children's Hospital

Boston Medical Center

Commonwealth of Massachusetts Department of Public Health

Children's Hospital Boston

Dana-Farber Cancer Institute

Floating Hospital for Children at Tufts Medical Center

MassGeneral Hospital for Children

UMassMemorial Medical Center
A Member of UMass Memorial Health Care

Dr. Alicia Johnston

Dr. Ellen Rae Cooper

Dr. Alfred DeMaria

Dr. Tony Bonilla

Dr. Luigi Notarangelo

Dr. Sung-Yun Pai

Dr. Cody Meissner

Dr. Paul Hesterberg

Dr. Mark Pasternak

Dr. Jolan Walter

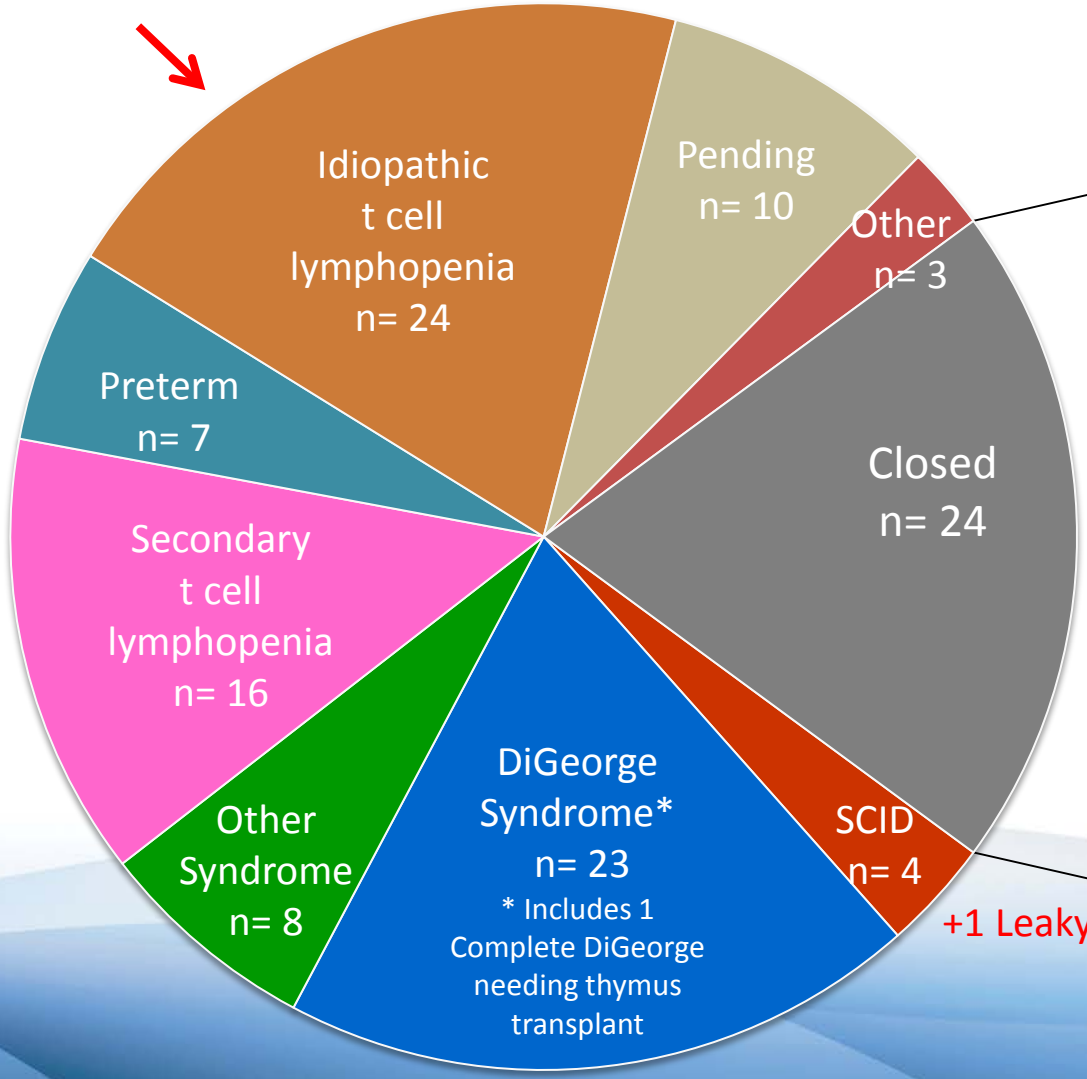
Dr. Beverly Hay

Dr. John Sullivan

Dr. Anne Marie Comeau **Dr. Roger Eaton** **Dr. Inderneel Sahai**

University of Massachusetts Medical School
UMASS
umassmed.edu

Status of 121 Infants Prompting Flow Cytometry



JAMA. 2014;312(7):729-738. doi:10.1001/jama.2014.9132

Table 1. Classification of Conditions With Low T-Cell Receptor Excision Circles and Low T-Cell Numbers Found by Newborn Screening

	Definition of Condition		
	CD3 T Cells/μL	Proliferation to PHA	Other Supporting Features
Primary Targets of Newborn Screening			
Typical SCID[a]	<300 (autologous)	<10% of normal	Detectable maternal T cells in peripheral blood; proven deleterious defect(s) in a known SCID gene
Leaky SCID[a]	300-1500, few naive T cells	Reduced (10%-50% of normal)	No maternal T cells detectable; incomplete defect(s) in a known SCID gene
Omenn syndrome	Oligoclonal T cells	Reduced (10%-50% of normal)	Erythroderma, hepatosplenomegaly, eosinophilia, and elevated levels of serum IgE antibody
Secondary Targets of Newborn Screening			
Syndrome with low T-cell numbers	Recognized genetic syndrome that includes low T-cell numbers within its spectrum of clinical findings		
Secondary T-cell lymphopenia	Congenital malformation or disease process without an intrinsic defect in production of circulating T cells		
Preterm birth alone	Preterm birth and low birth weight, with low T-cell numbers early in life that normalize over time		
Idiopathic T-cell lymphopenia, also called variant SCID	Low T-cell numbers without recognized cause; 6 programs used 300-1500 autologous T cells/μL plus evidence of functional immune cell impairment, while other programs included infants with higher T-cell numbers (see Table 4).[b]		

JAMA. 2014;312(7):729-738. doi:10.1001/jama.2014.9132

Table 5. Diagnoses of 411 Infants With Non-SCID T-Cell Lymphopenia Identified by Newborn Screening

Condition	No. of Infants
Unspecified T-cell lymphopenia[f]	117

To what extent is neonatal T-cell lymphopenia an early indicator of later diagnoses?

- Monitor infants identified with idiopathic T-cell lymphopenia
  - Long term – multi– year prospective follow up
- Retrieve and test NBS specimens of older children who carry specific diagnoses

To what extent would a TREC/KREC assay help to define later diagnoses associated with neonatal T-cell lymphopenia?

- Evaluate T and B cell profiles of older children with specific diagnoses
  - Representative of neonatal profile?
- Retrieve and test NBS specimens of older children who carry specific diagnoses

Retrieve and test NBS specimens of older children who carry specific diagnoses

Retrospective Study with Prospective Potential

Retrieve and test NBS specimens of older children who carry specific diagnoses

- assays for TREC and KREC

  multiplex TREC/KREC/RNaseP

- Patient cohort

  Patients with defined diagnoses and likely T or B cell dysfunction

TREC and KREC for SCID NBS

van Zelm MC, van der Burg M, Langerak AW, van Dongen JJ. PID comes full circle: applications of V(D)J recombination excision circles in research, diagnostics and newborn screening of primary immunodeficiency disorders. Front Immunol 2011;2:12

Nakagawa N, Imai K, Kanegane H et al. Quantification of κ-deleting recombination excision circles in Guthrie cards for the identification of early B-cell maturation defects. J Allergy Clin Immunolo 2011;128:223-5

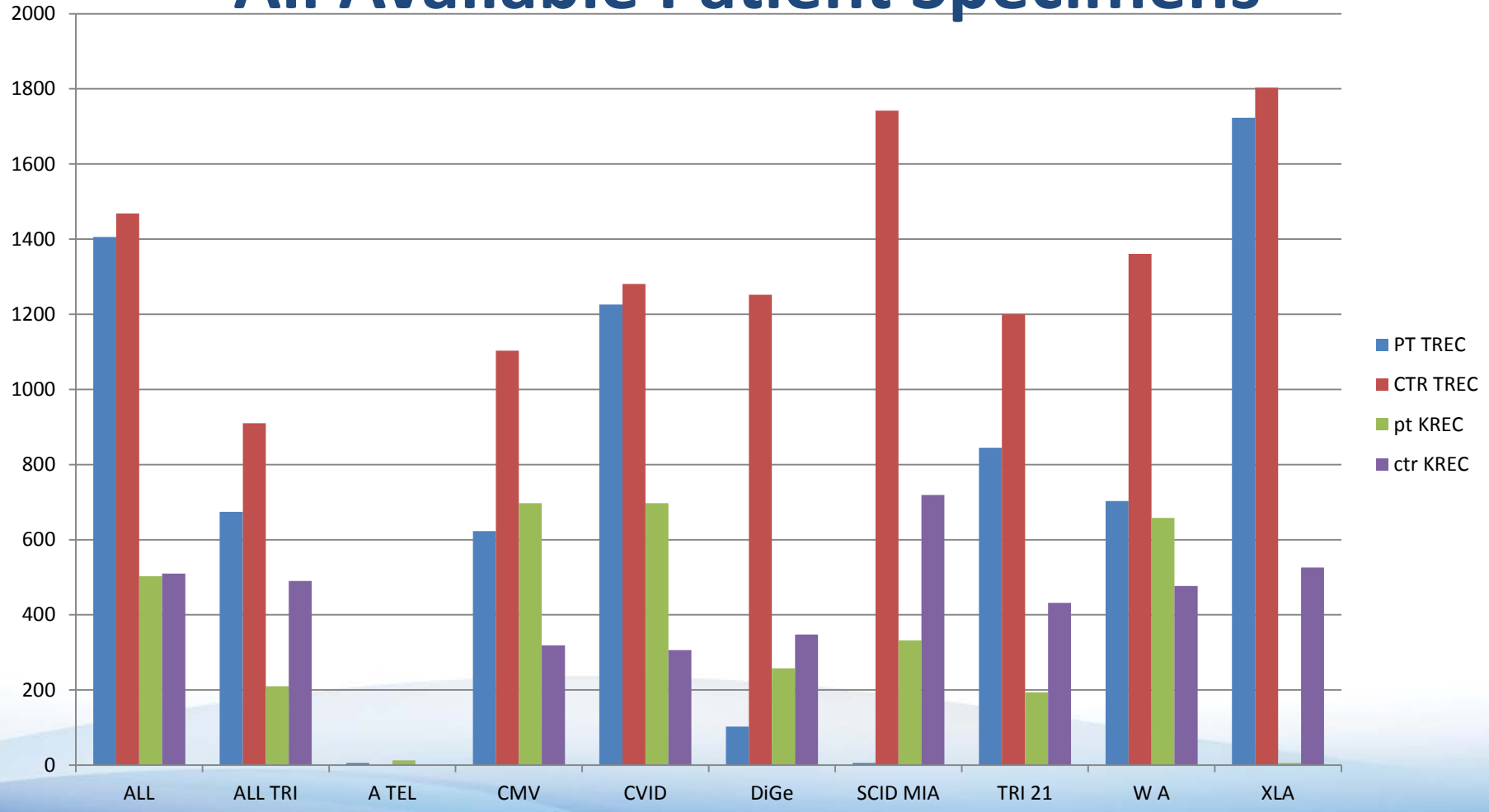
Sottini A, Ghidini C, Zanotti C et al. Simultaneous quantification of recent thymic T-cell and bone marrow B-cell emigrants in patients with primary immunodeficiency undergone to stem cell transplantation. Clin Immunolo 2010:136:217-27

Borte S, von Dobeln U, Fasth A et al. Neonatal screening for severe primary immunodeficiency diseases using high throughput triplex real-time PCR. Blood 2012;119:2552-5.

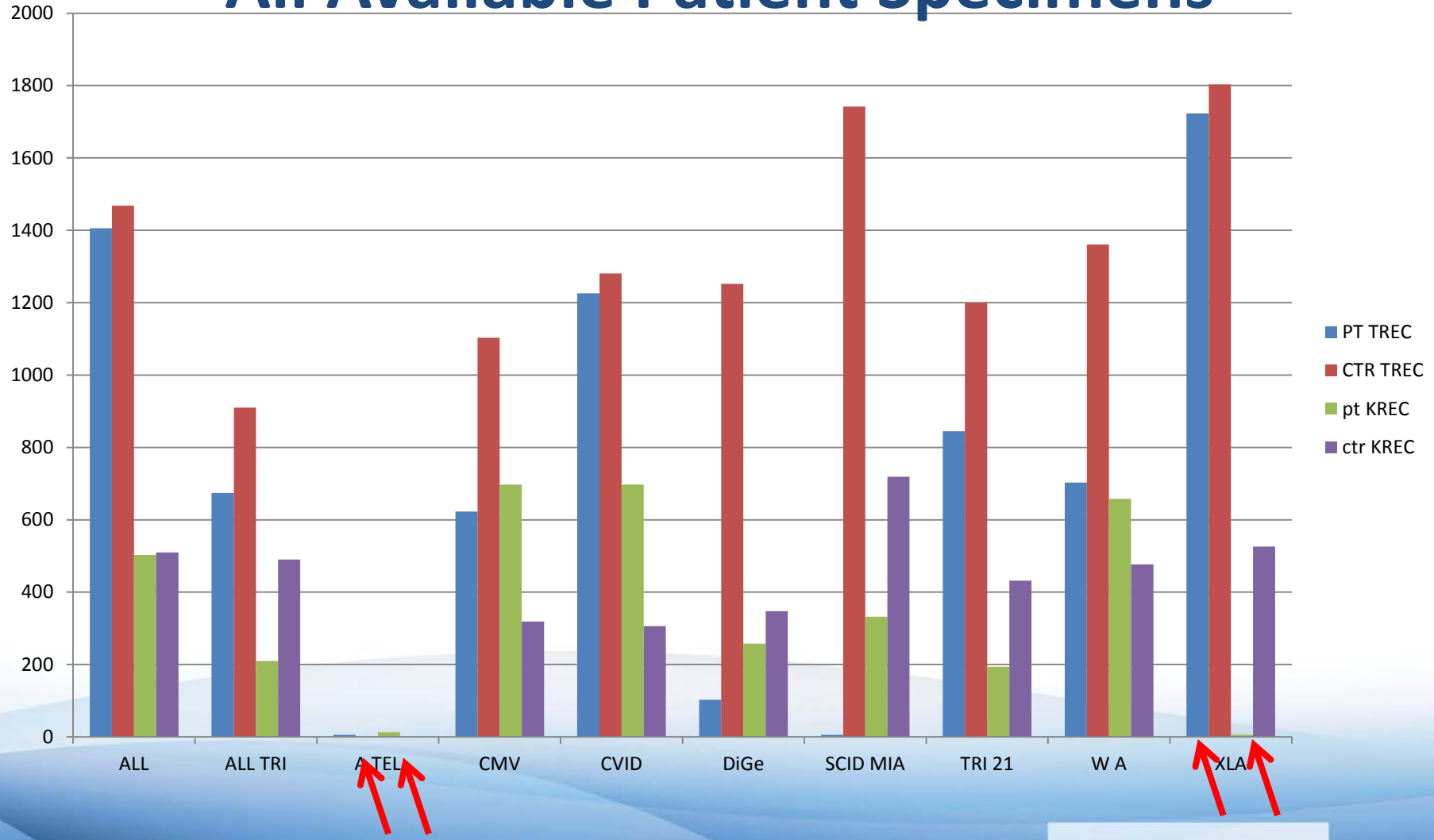
VALIDATION OF MULTIPLEX ASSAY WITH RESIDUAL SAMPLES FROM SCID PATIENTS

SCID TYPE	PHENOTYPE	TREC	KREC	RNaseP
IL7RA	T-B+NK+	0	387	37761
ADA	T-B-NK-	0	0	9006
IL2RG	T-B+NK-	0	542	32071
PNP	progressive loss T	0	6	33316
ADA	T-B-NK-	0	0	58987
IL2RG+MAT engraft	T-B+NK-	0	742	59968
CD3D	T-B+NK+	0	219	33413

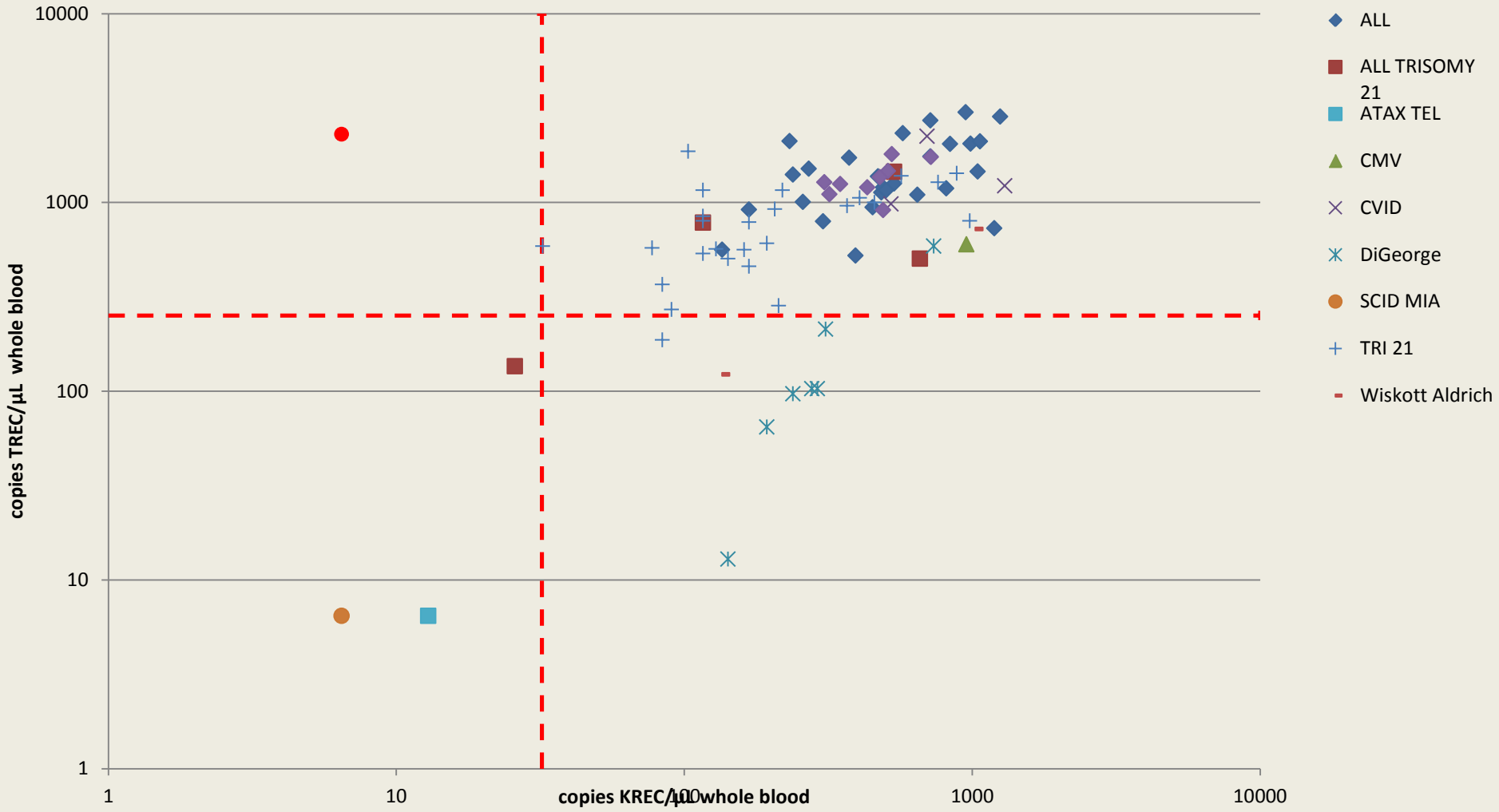
Median TREC and KREC values by Condition
All Available Patient Specimens



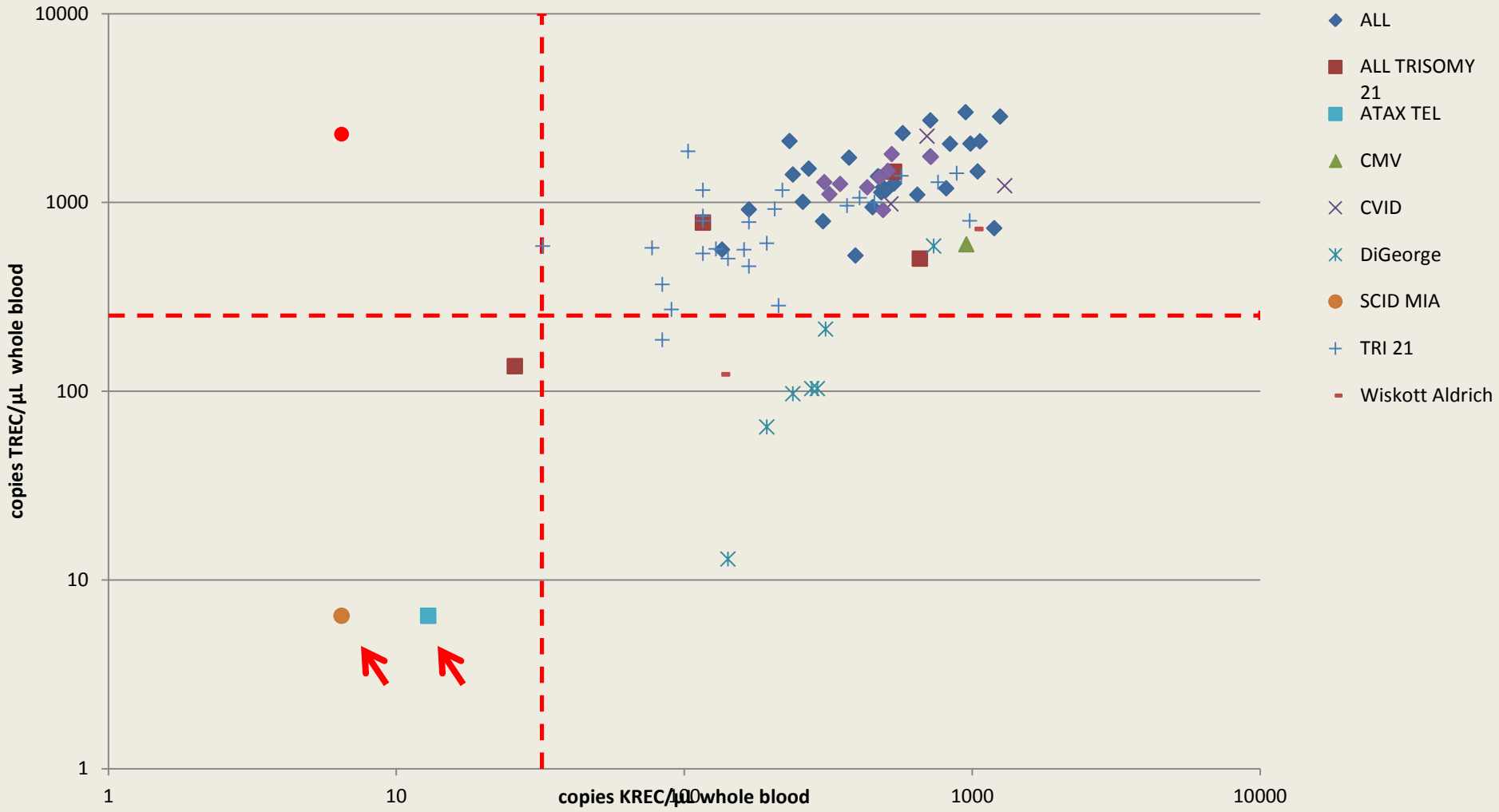
Median TREC and KREC values by Condition
All Available Patient Specimens



TREC and KREC profiles in neonatal specimen of each infant



TREC and KREC profiles in neonatal specimen of each infant



TREC and KREC profiles in neonatal specimen of each infant

Conclusions

- KREC in first tier is necessary to identify XLA
- Other non-SCID PID show early profile T-B- PID
- Multiplex TREC KREC shows early profile indicative of B- SCID
- Population data needed