Newborn Screening 50th Year Celebration: the Utah experience

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The University of Utah
Department of Pathology

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Newborn screening

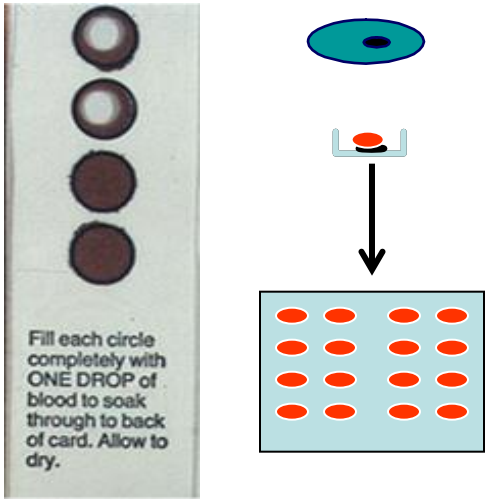
Public health activity aimed at the early identification of conditions for which timely intervention can lead to the elimination or reduction of mortality, morbidity, and disabilities associated with these conditions.

History of Newborn Screening

1961 Dr. Robert Guthrie (New York)

- First to use dried blood spot sample (often referred to as a Guthrie card)
- Developed Bacterial Inhibition Assay (BIA) to detect elevated levels of phenylalanine in dried blood spots
- Blood spots are placed on agar media containing B. subtilis spores and a chemical inhibitor
- Spores can not grow unless phenylalanine is present
- Measure diameter of bacterial growth around blood spot and compare to growth around blood spots enriched with known amounts of phenylalanine (semi-quantitative)

Newborn Screening: then



One spot

One test
(Bacterial Inhibition Assay)

One analyte
(Phe)

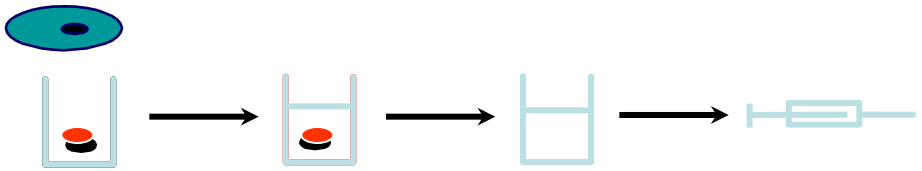
One disease
(Phenylketonuria)

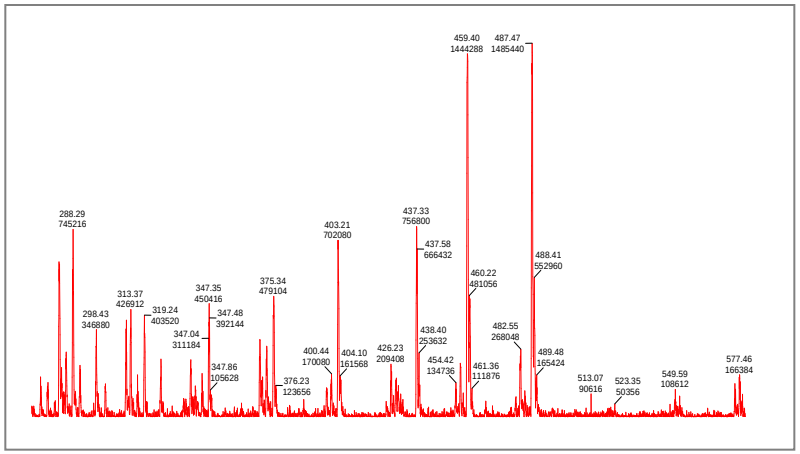
Tandem Mass Spectrometry

- **MS/MS can test a number of metabolites simultaneously, rather than one analyte at a time as in classic screening procedures.**

Newborn Screening: now

One spot → **One test (MS/MS)**





Multiple analytes

Many diseases

MS/MS analysis

Two main classes of metabolites can be detected using tandem mass spectrometry (MS/MS):

- **Amino acids**. *The level of one or more amino acids increases in disorders of amino acid metabolism (metabolic block close to the actual amino acid).*

- ***Aminoacidopathies and Urea Cycle defects:***
  - ***Phenylketonuria, Maple Syrup Urine Disease, Homocystinuria, Citrullinemia, Argininosuccinic aciduria, Tyrosinemia Type I***

- **Acylcarnitines**. *In disorders of the intermediary metabolism of amino acids or of fatty acid oxidation the abnormal metabolites are conjugated with carnitine to facilitate their excretion and to balance the Coenzyme A pool.*

- ***Organic acidemias and fatty acid oxidation defects:***
  - ***Glutaric acidemia Type I, Propionic acidemia, Methylmalonic acidemia***
  - ***MCADD, VLCADD, CUD, CPT-I and CPT-II deficiencies.***

Secretary Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

TANDEM MASS SPECTROMETRY (MS/MS)			Traditional methods (EIA, HPLC,etc.)		OTHERS
Acylcarnitines		*Amino acids*			
FAO (5)	OA (9)	AA (6)	Hematology (3)	Others (5)	
MCAD	*IVA*	*PKU*	*Hb SS*	*CH*	*SCID*
VLCAD	*GA-1*	*MSUD*	*Hb S/βThal*	*BIOT*	*HEAR*
LCHAD	*HMG*	*HCY*	*Hb S/C*	*CAH*	*CCHD* *Critical congenital heart disease*
TFP	*MCD*	*TYR I*		*GALT*	*Pompe*
CUD	*MUT*	*ASA*		*CF*	
	Cbl A,B	*CIT*			
	3MCC				
	PROP				
	BKT				

Newborn Screening in Utah (2006)

- PKU
- Congenital Hypothyroidism
- Galactosemia
- Hemoglobinopathies
- Newborn Hearing Screening

- MCAD Deficiency
- MSUD
- Homocystinuria
- Biotinidase deficiency
- Congenital adrenal hyperplasia
- Others detectable by MS/MS
- Cystic Fibrosis (2009)
- SCID (2013)
- CCHD (2014)

Utah's unique partnership

- ***A Pilot Project (2003-2005) was established with the purpose of:***

Evaluating the feasibility of expanding newborn screening in Utah with a private-public partnership involving the Department of Health, ARUP Biochemical Genetics laboratory, and the Metabolic Center/Medical Genetics at the University of Utah.

Pilot Project: Study Design (1)

- **This study was approved by the Institutional Review Board of the University of Utah (IRB_00011072, Supplemental Newborn Screening for the Early Diagnosis of Inborn Errors of Metabolism in Utah).**

- ***Facility:*** **University of Utah hospital (3,000-4,000 births per year)**

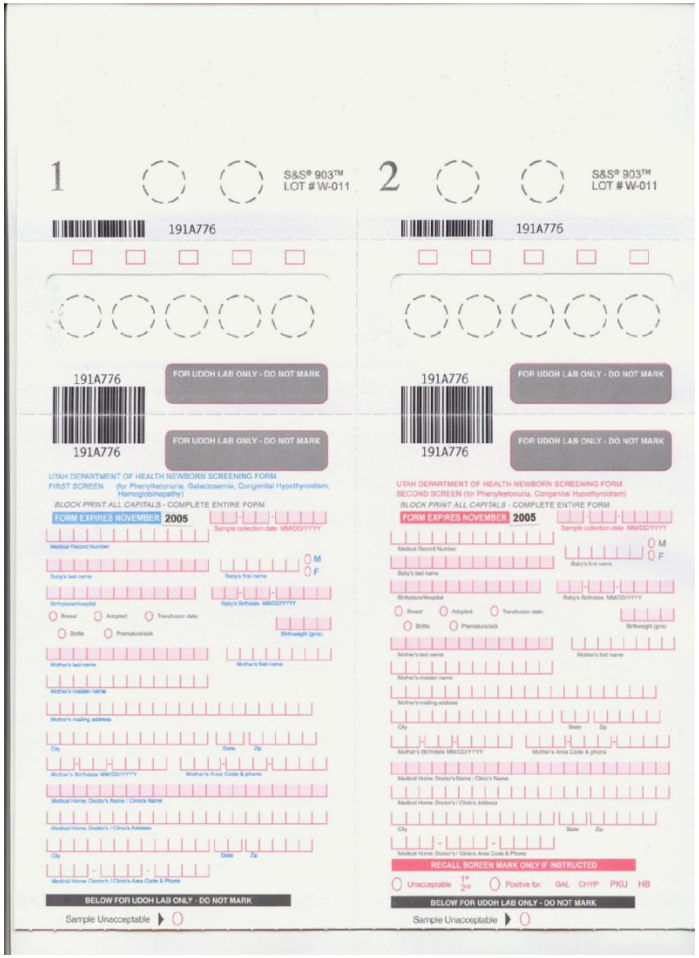
- ***Subjects:*** **Infants born at the U of U hospital (neonatal intensive care unit babies were excluded). Mothers had to sign a consent form.**

Pilot Project: Study Design (2)

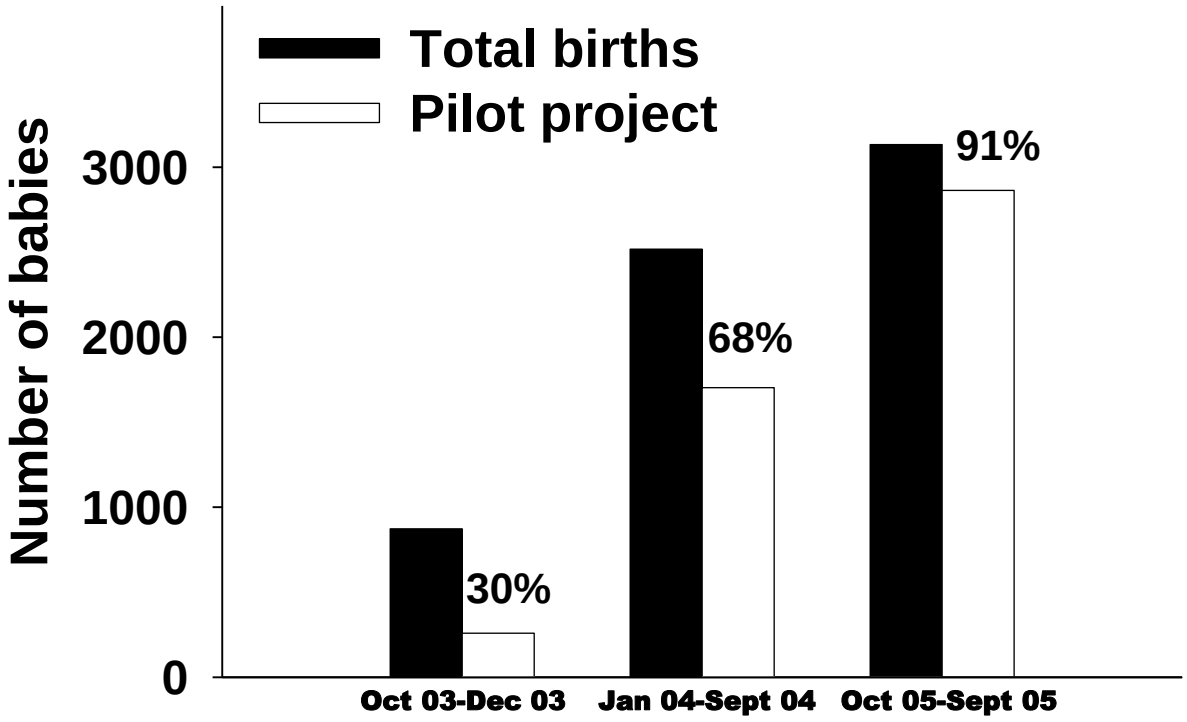
MS/MS

Filter paper

DoH



Pilot Project: Participation



Pilot Project: Results

- **4,827 first screen and 690 second screen samples were analyzed**
  - **1.7% first screen and 0.6% second screen needed follow-up**
  - **0.1% needed confirmatory testing**
  - **1 infant with Glutaric acidemia type I was identified and treated**

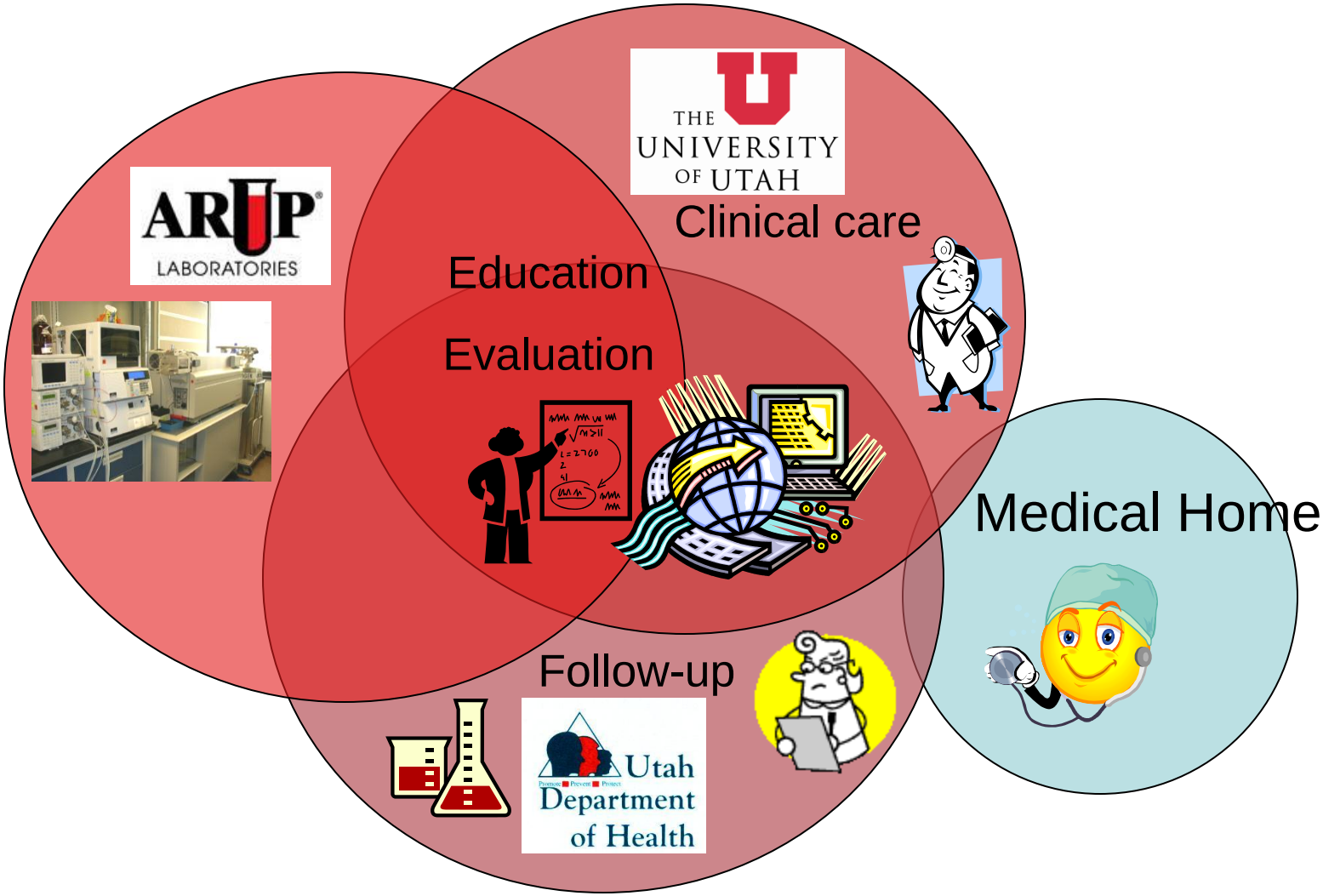
Pilot Project: Conclusions

- **Integration of private and public resources allows the prompt identification and treatment of children with metabolic disorders.**

- **Bidirectional data exchange between the State and the testing laboratory is necessary for good turnaround time.**

- **Education of health care professional and of the community is of paramount importance for a successful implementation of a new program.**

UTAH Newborn Screening Program



The efficiency and effectiveness of a newborn screening program is dependent upon the smooth integration of sample collection, laboratory testing, follow-up, diagnosis, timely treatment, and tracking of outcomes.

MS/MS screening in Utah: 2006-2013

- Total screens: 416,557
  - ***Total metabolic disorders: 188 1:2,216***
  - ***Total maternal cases: 24***
    - PKU/Hyperphe/Biopt
    - MCAD deficiency
    - 3-Methylcrotonylglycinuria
    - VLCAD deficiency
    - Glutaric acidemia type I
    - Primary carnitine deficiency (CUD)
    - LCHAD deficiency

Thank You

- **ARUP**
  - **Newborn Screening and Biochemical Genetics Laboratories**
  - **Dr. N. Kusukawa**
  - **Dr. C. Kjeldsberg**
- **Utah Department of Health**
  - **Kim Hart, Dr. H. Randall, Dr. R. Atkinson, N. Brown**
  - **Fay Keune, Dr. F. Tait**
- **University of Utah Metabolic Clinic**
  - **Dr. N. Longo, Dr. L. Botto, Dr. A. Warnock, S. Ernst, Krista Viau**

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SCID Newborn Screening in Utah

Patricia Slev, PhD, D(ABCC)
Medical Director, Serologic Hepatitis and Retrovirus Laboratory
Co-Director, Immunogenetics Laboratory
Assistant Professor of Pathology,
University of Utah, School of Medicine

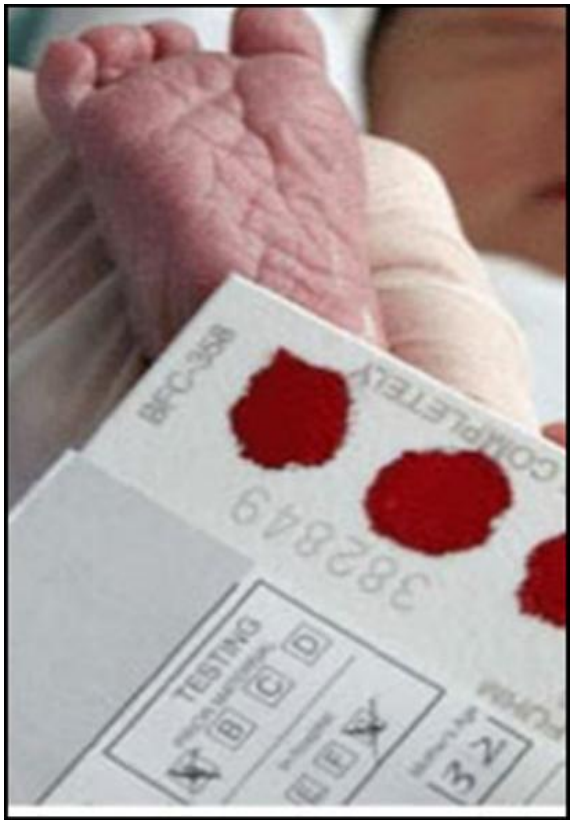
Timeline

- 2010 Uniform Panel Recommendation
- 2011 Utah SCID Subcommittee

  Parent Advocate, March of Dimes, Pediatric Immunology, Pediatric Bone Marrow Transplant Division
- 2012 Utah Genetics Advisory Committee and Newborn Screening Subcommittee recommend screening for SCID
- 2013 Governor approves kit fee increase
- 2013 Pilot
- 2013 Implementation (July)

Why Screen ?

- Fatal without treatment
- Asymptomatic at birth
- Effective Treatment
  - hematopoietic stem cell transplant (HSCT)
  - enzyme replacement
  - gene therapy
- Early intervention is key
  - <3 months = 95% survival
  - >3 months = 65% survival



March of Dimes

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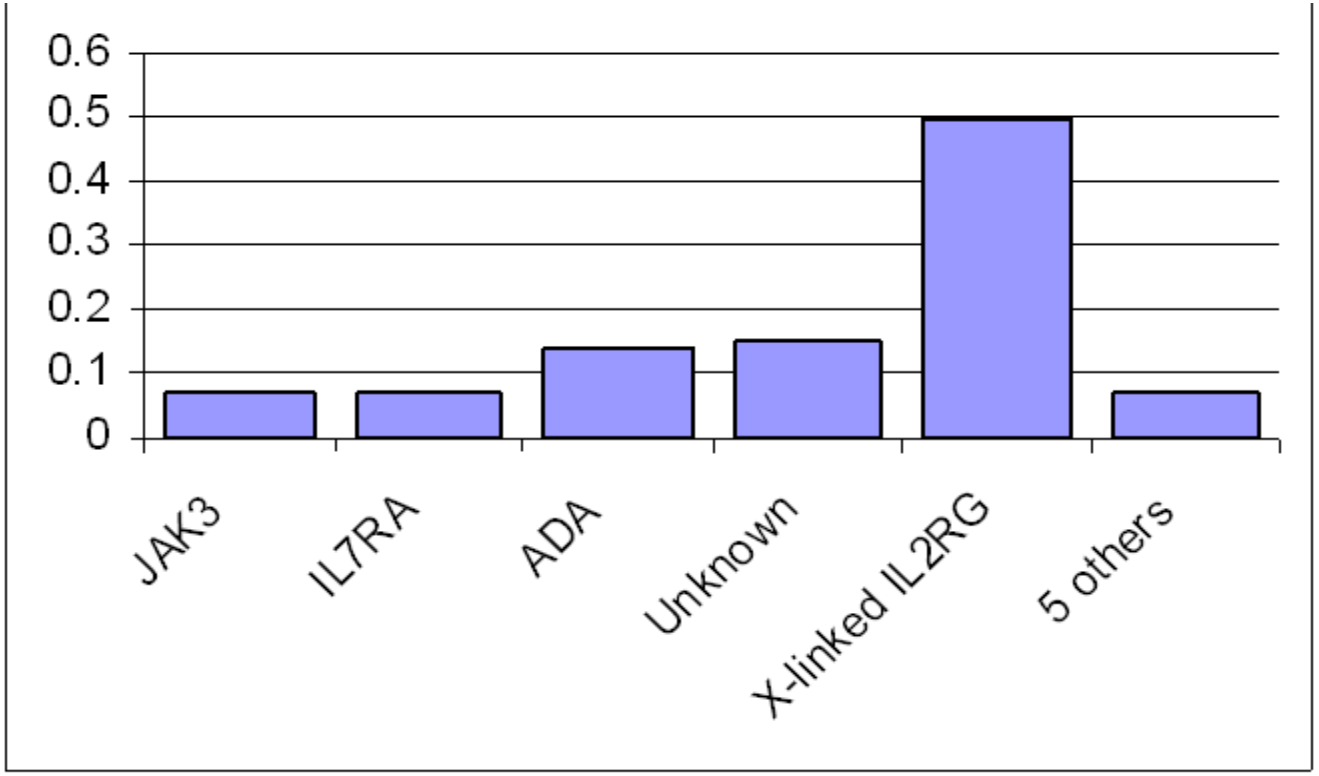
Severe Combined Immunodeficiency Genotypes



T-Cell Lymphopenia

TREC Assay for SCID

- **Marker/Target – T-cell Receptor Excision Circle (TREC)**

  Circular, episomal, DNA fragment formed as a byproduct of successful T-cell receptor rearrangement, during maturation in the thymus

  TREC do not replicate with mitosis and therefore are diluted with cell division

  Peripheral concentrations correlate with T-cell production in the thymus

  Marker for T- cell lymphopenia not SCID

- **Assay**

  Real-time PCR

  Reported cut-offs and concentrations vary by laboratory due to differences in reagents, calibrators and instrumentation

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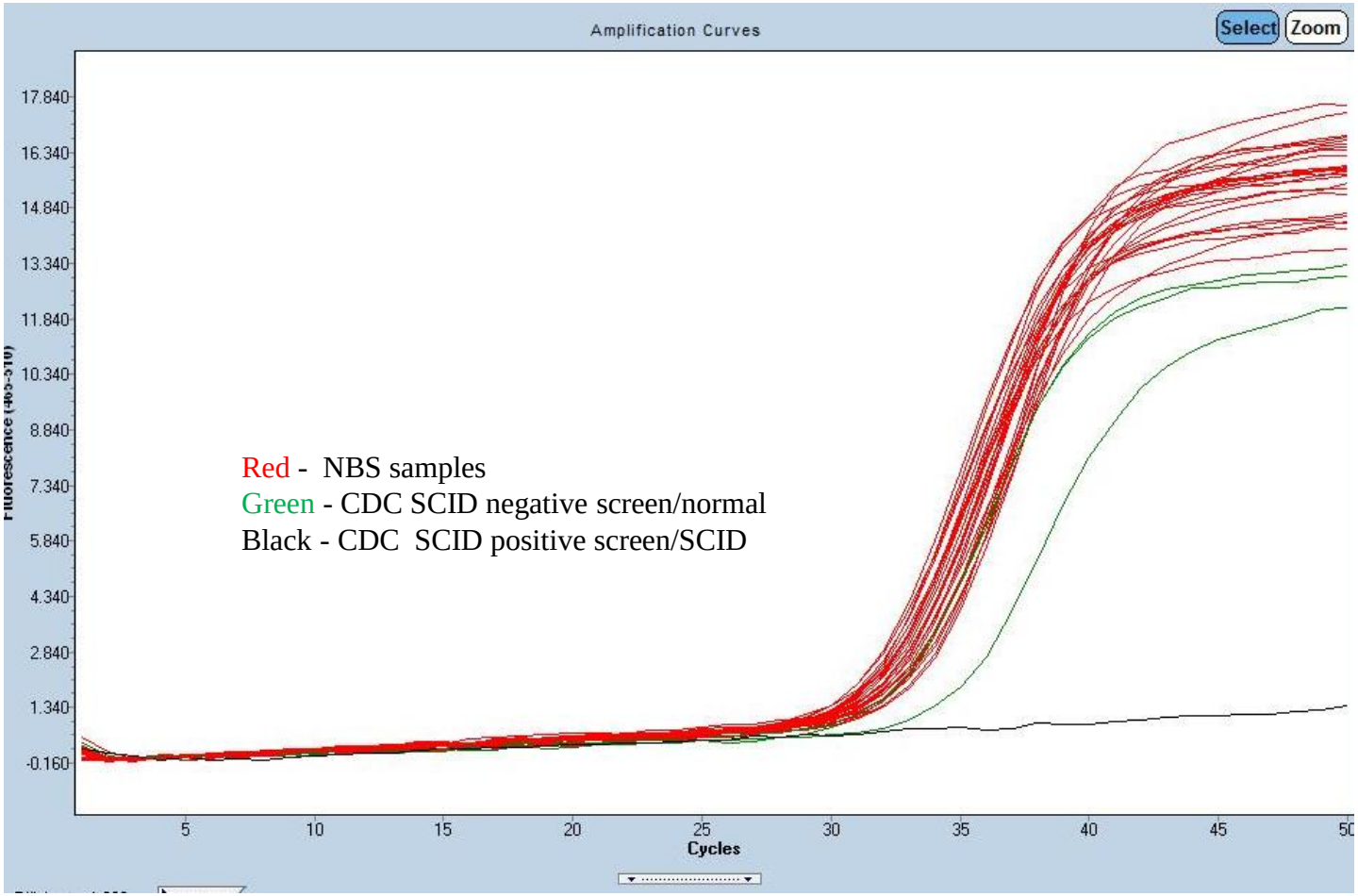
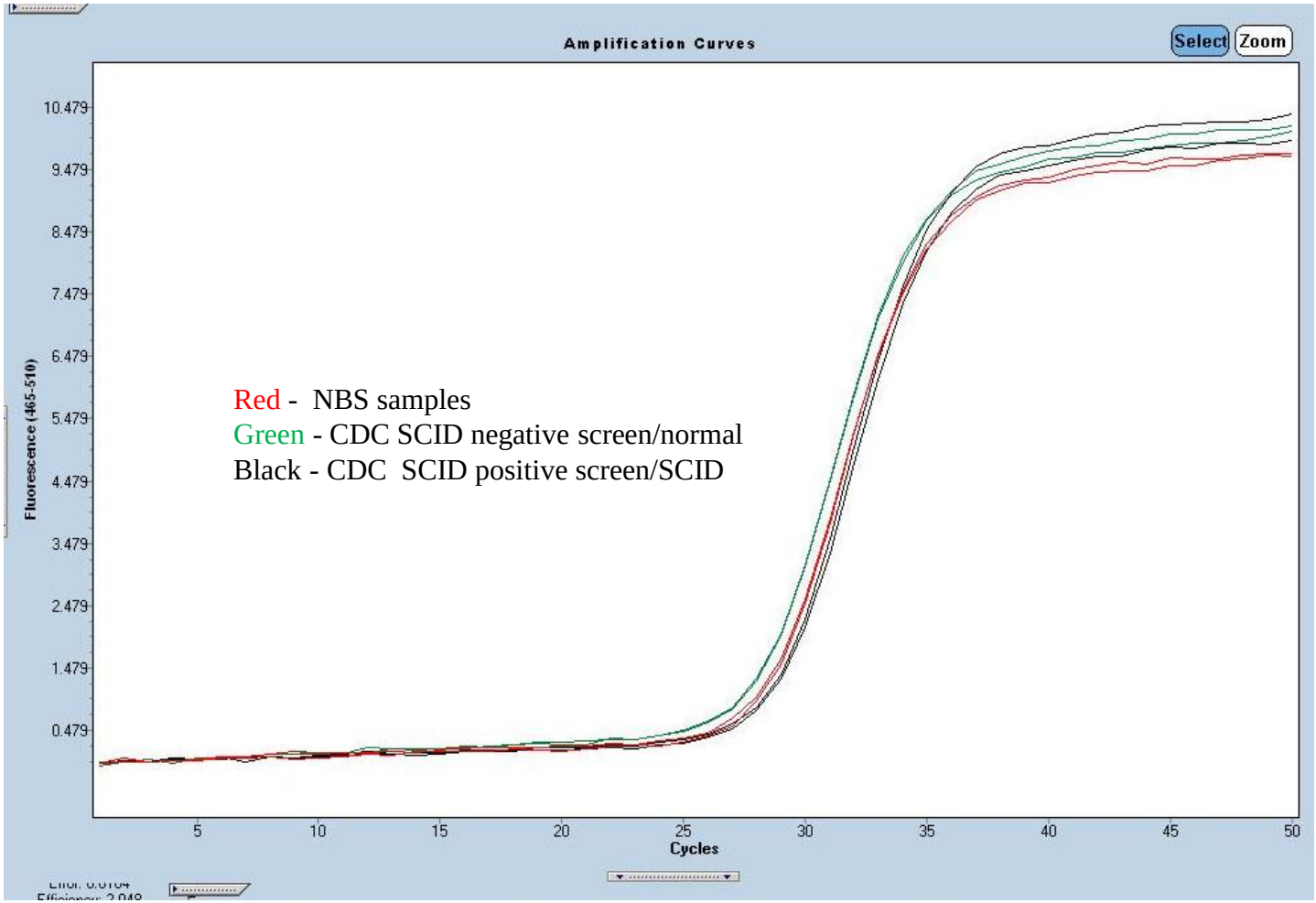
Retrospective Utah Pilot Study

- 4,999 dried blood samples (DBS)
  - 4,665 non- NICU
  - 344 NICU
- TREC Singleplex Assay
  - TREC concentrations
  - β -actin concentrations

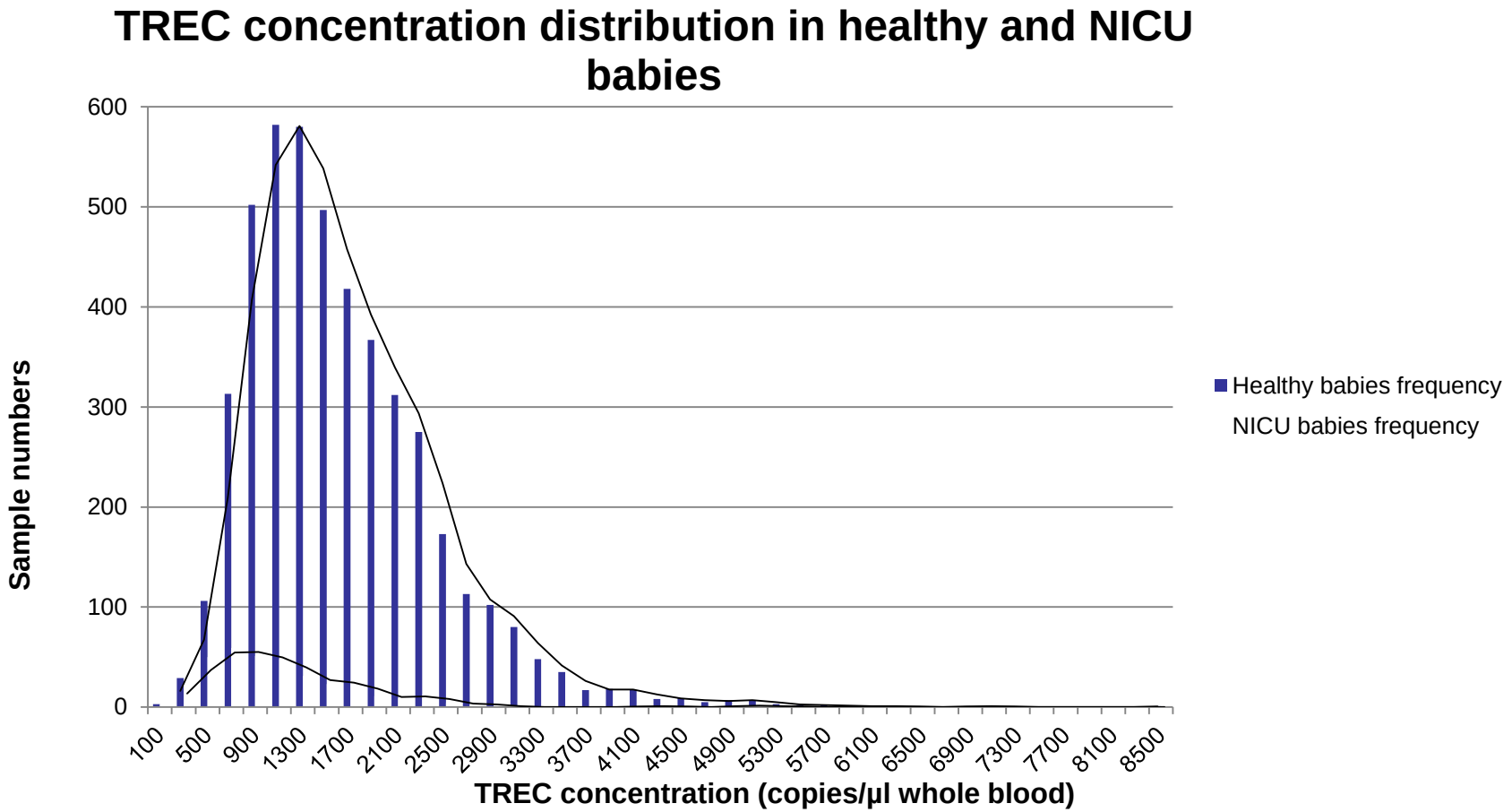
TREC Concentrations



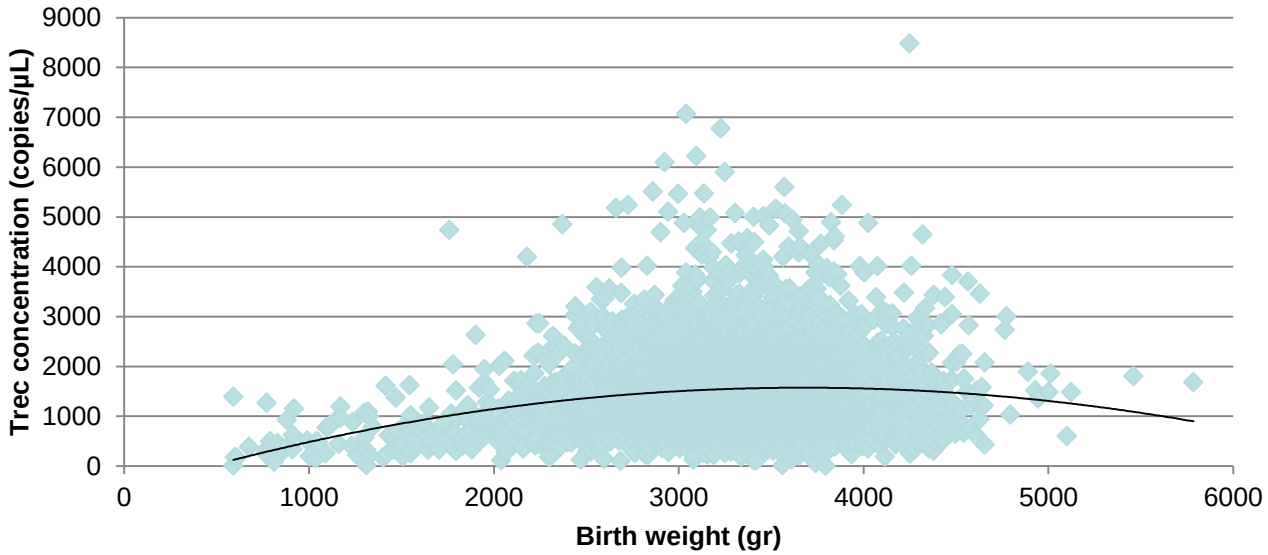
Reference Gene Concentrations (β -actin)

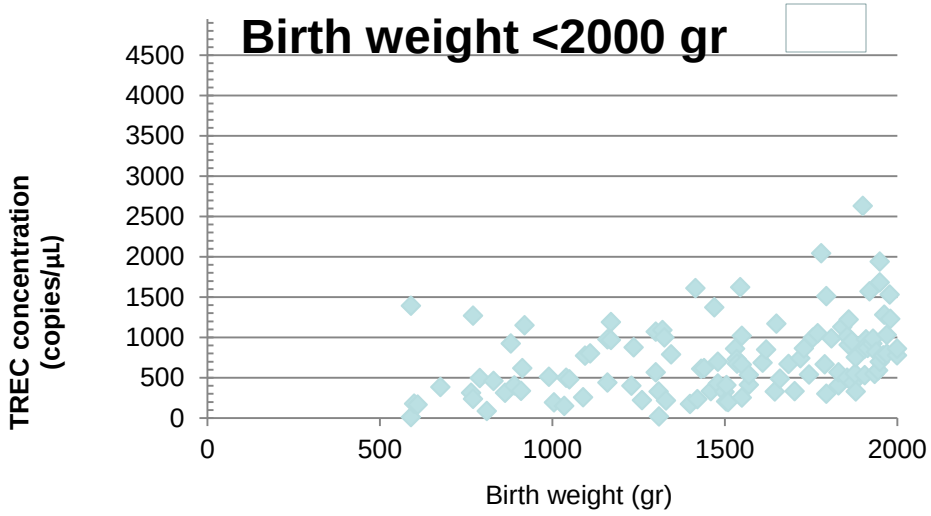


Pilot Study Results



TREC Concentrations vs. Birth Weight





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Detecting SCID

- Established Cutoff
- Detected CDC SCID positive DBS
- Detected SCID DBS
  - Reticular Dysgenesis
  - Adenosine Deaminase Deficiency

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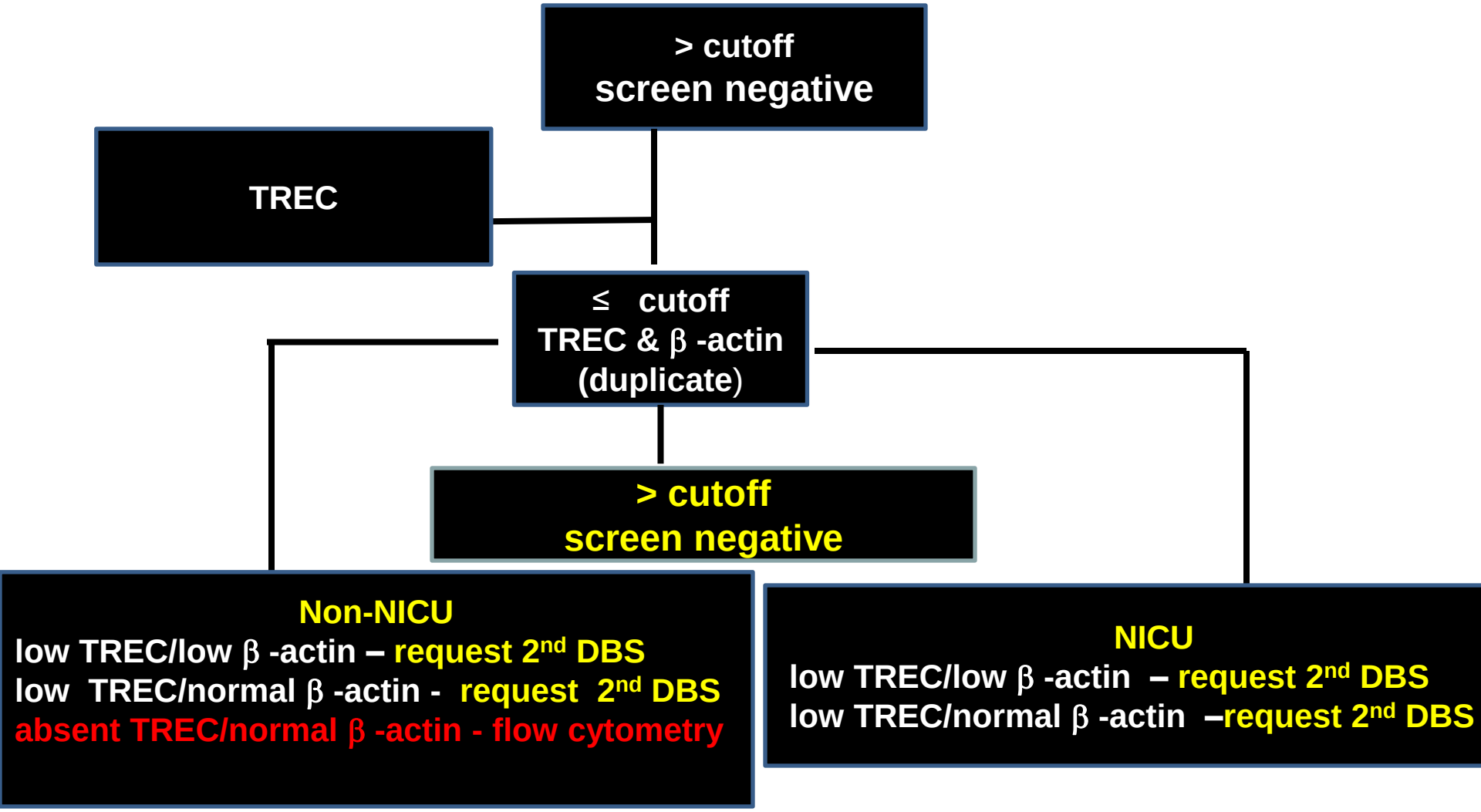
Algorithm



The First Quarter

- Screened 13,200 babies
- NICU population accounts for the majority of repeat DBS testing
- Confirmatory Testing – 3 babies
  - 1 mild lymphopenia
  - 2 profound lymphopenia

Acknowledgements

- **Utah Department of Health**
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- **Primary Children's Medical Center, Immunology Division**
  Dr. Karin Chen

- **SCID Subcommittee**
  Dr.Rich Harward *(UDOH),* Julie Drake *(March of Dimes),* Michael Pulsipher *(Bone Marrow Transplant)* Nan Streeter *(UDOH)*, Jill Heaps *(Parent Advocate)*