Nomination of Severe Combined Immune Deficiency (SCID)--T Lymphocyte Defects

Follow-up Discussion
January 21, 2010

Jennifer Puck, *University of CA San Francisco*
Jack Routes, *Medical College of Wisconsin*
Anne Comeau, *University of Massachusetts*
Bob Vogt, *Center for Disease Control and Prevention*

SCID Fulfills Requirements for Consideration by the Evidence Review Group (2009).

"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 beyond Wisconsin to implement newborn screening for SCID.
3. Test reproducibility, continuance of false positive rate of <0.1%.
4. Standardization; laboratory proficiency testing.
5. Costs and availability of resources to appropriately address the costs.

1. Prospective identification of “real” SCID cases

- **SCID**, the original **primary target** of TREC screening, is defined by very low or absent T lymphocytes produced by an infant, such that ability to resist infection is severely compromised. There are over a dozen known and additional unknown SCID genes.
- **Related conditions** also can have very low T cells and therefore a risk of life-threatening susceptibility to infections. Examples are:

  Severe DiGeorge syndrome, Folate receptor deficiency

  Lymphangiectasia or chylothorax with T cell sequestration and loss
- **Omenn syndrome** and **SCID with maternal T cell engraftment** are conditions with oligoclonal T cells instead of a diverse repertoire of newly minted thymic emigrant T cells.

Infants with any of the above should receive prophylactic anti-infective therapy and <u>should not receive live rotavirus vaccine</u>, which is now recommended for infants <3 months of age.

<u>Infants with any of the above can be detected by very low TRECs</u>.

<u>TRECs are a good physiological correlate with a diverse T cell pool</u>.

2. Willingness and capacity of states beyond Wisconsin to implement screening for SCID
3. Test reproducibility, continuance of false positive rate of <0.1%.

- Wisconsin has 2 years of experience
- Massachusetts has an ongoing pilot program
- A targeted trial in the Navajo Indian population is under way
- Several additional states have indicated they are ready to run pilot programs; funds for pilot screening of larger numbers of infants were recommended by this Committee a year ago.

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WSLH Wisconsin Newborn Screening Laboratory

Newborn Screening (NBS) for T cell Lymphopenia in Wisconsin Jan. 1 - Dec. 31, 2008

Jack Routes

2008 WI NBS for T cell lymphopenia

Routes et al., JAMA 2009

- **Number Screened:** **71,000**
  - Full term 64,397
  - Premature (< 37 wks) 6,603
- Premature infants were rescreened until they reached the equivalent of 37 weeks gestational age.
- Abnormal Results (TREC <25, actin normal, infants ≥ 37 weeks gestational age) underwent flow cytometry (preferred) or repeat TREC assay on new NBS card
- Number abnormal: 17
  - 4 had normal repeat TREC assay from new DBS card
  - 1 died (metabolic cause)
  - 1 parents refused further evaluation
  - 11 had flow cytometry
    - 3 “Third spacing,” lymphocyte loss
    - 2 DiGeorge syndrome/22q11 deletion
    - 2 Idiopathic T cell lymphopenia
    - 1 Rac2 mutation (successfully treated with transplantation)

WI Summary: TREC assay

- Detected significant T cell lymphopenia with low number of false positive results.
- Inexpensive ($5.50/assay).
- Assay easily incorporated into existing screening algorithm used by Wisconsin State Hygiene Laboratory.

SCID NBS in Massachusetts

- **Multiplexed Assays and an Integrated Program**
- **Training of other state laboratories**

January 21, 2010

Anne Marie Comeau

MA SCID NBS Working Group and NENSP Molecular Laboratory

CDC National Center for Environmental Health
Grant # IV01-EH000362-01

UMASS MEDICAL SCHOOL | COMMONWEALTH MEDICINE
NEW ENGLAND NEWBORN SCREENING PROGRAM

Massachusetts SCID NBS

February 1, 2009 – December 31, 2009

- > 77,000 specimens
- > 68,000 infants
  - 272 requests for repeat
    - 51 recommendations for Flow
    - 19 T cell Lymphopenia
  - DiGeorge, Jacobsen Syndromes
  - Thymectomies, pending final diagnoses

TRAINING

Multiplex TREC and Quality Assurance

New England Newborn Screening Program

Dec. 7-11, 2009

Texas Department of State Health Services

California Department of Public Health

Minnesota Department of Health

+ MA + WI = 750K-1.2M infants

Next training: early March at CDC

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NEW ENGLAND NEWBORN SCREENING PROGRAM

4. Standardization; lab proficiency testing.

CDC Laboratory Support for NBS-SCID TREC Assay

Update: January 18, 2010 (prepared by R Vogt, NSMBB/CDC)

QC Materials Available to Any NBS Lab

- High-Range Normal & Mid-Range Normal
- Low-Range / “Gray Zone”
- SCID-Like *(TREC undetectable; Genomic DNA normal)*
- Unsatisfactory Specimen *(TREC and Genomic DNA undetectable)*

Pilot Proficiency Testing (PT) Program

- Initial Evaluation w/ WI and MA
- Will be generally available to NBS labs in April 2010
- Specimen Types Similar to QC Materials
- Accelerated Frequency Available for Pilot Programs

Laboratory Training and Education

- First session convened by MA
- Sessions in CDC and WI to follow

Newborn Screening
Translation Research Initiative

CDC
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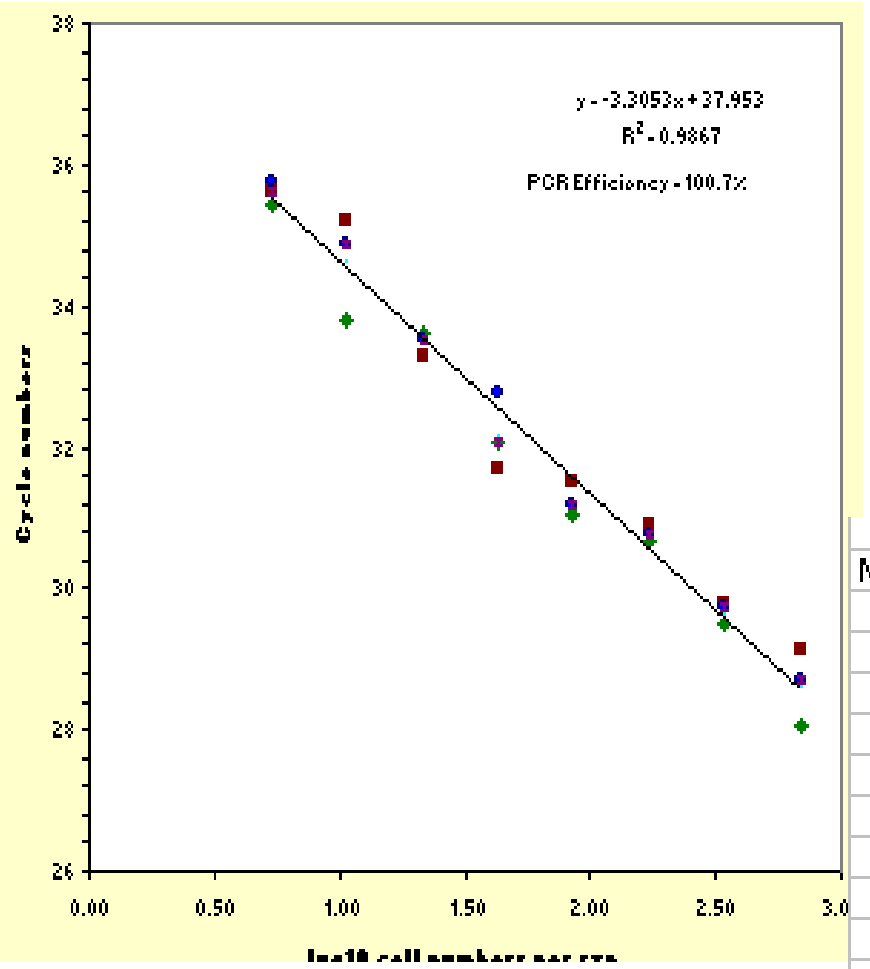

Dried Blood Spot Calibrators

Primary Calibrators Based on Cell Count :
TREC-Transfected HeLa Cells

Secondary Calibrators: Cord Blood Dilutions *(Values Assigned by Comparison w/ Primary Calibrators)*

Evaluation w/ WI and MA Plasmid Calibrators *(=> Concordant)*

Number of cells	log10	Ct#1	Ct#2	Ct#3	Mean	Median
685	2.84	28.06	29.14	28.70	28.63	28.70
343	2.53	29.5	29.76	29.73	29.66	29.73
171	2.23	30.65	30.89	30.75	30.76	30.75
86	1.93	31.04	31.53	31.18	31.25	31.18
43	1.63	32.09	31.69	32.78	32.19	32.09
21	1.33	33.59	33.28	33.53	33.47	33.53
11	1.03	33.78	35.19	34.88	34.62	34.88
5	0.73	35.41	35.64	35.75	35.60	35.64
0		No Ct	No Ct	No Ct	No Ct	No Ct

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5. Costs and availability of resources to appropriately address the costs.

Wisconsin: $5.50
UCSF (CA archived and Navajo): $5.00
MA: similar to other screening tests

[6.] Follow-up of screened infants, treatment
Primary Immune Deficiency Treatment Consortium (PIDTC): a new rare disease network funded in 2009.

Cost of not performing newborn screening?

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 qualifiedexpert in immunology who finds that it would be safe;

2. assure that infants with low TRECs are evaluated by such an expert without delay;

3. track ultimate outcomes to measure effectiveness of screening, diagnosis and management.