Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

Vocabulary and Coding Team Update
Health Informatics Technology Workgroup

Developing New Codes for NBS Conditions:

Severe Combined Immunodeficiency, Lysosomal Storage Disorders, and the Hemoglobinopathies

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National Center for Environmental Health
Centers for Disease Control and Prevention

Vocabulary and Coding Team

Team Goal

Identify requirements to expand the newborn screening coding and terminology guide to include new requirements for data coding and language standardization

Initial Project

Request new LOINC variable codes for Newborn Screening methods available for:

- ❑ **Severe Combined Immunodeficiency (SCID)**
- ❑ **Lysosomal Storage Disorders (LSD)**

Request new LOINC Newborn Screening answer codes for:

- ❑ **Hemoglobinopathies (HGB)**

LOINC: Logical Observation Identifiers Names and Codes

General Process for Submitting Information for LOINC request

Submit with request:

- Name (i.e. What the submitter calls the Condition and Test)
- Brief Description of the Condition or Test and its use
  - If test is associated with discrete answers … what are typical answers?
- Clinical significance or significance of use
- Usual units of measure
- Typical Normal Range

LOINC Formal Name Parts:

LOINC Committee can help gather these details:

- Component
- Property
- Timing
- Sample
- Scale
- Method

LOINC Formal Name Parts

LOINC Elements
Component
Property
Timing
Sample
Scale
Method

1. Name of the Component or Analyte Measured

- **Analyte Name that is being measured**
  - Complete name of the analyte
  - Eg T-Cell Receptor Excision Circle (TREC) for the NBS SCID assay
- **Challenge Test if relevant**
  - Information necessary to interpret "challenge" tests
  - Includes time delay, substance of challenge, amount and route administered
  - E.g. oral glucose tolerance test

Does not apply for these NBS tests

- **Any Standardization or Adjustment**
  - Distinguishes uncorrected measurement from adjusted value
  - E.g. Ionized calcium adjusted to pH 7.4

Does not apply for these NBS tests

LOINC Formal Name Parts

LOINC Elements
Component
Property
Timing
Sample
Scale
Method

2. The Kind of Property or Quantity Observed

Property	Description
Mass	Reported with mass (milligrams, grams) in numerator of units of measure E.g. Mass content, mass concentration
Substance	Reported with moles or milliequivalents in numerator of units of measure
Catalytic Activity	Reports enzymatic activity Eg catalytic concentration, catalytic content
Arbitrary	Reported with arbitrary units in numerator
Number	Associated with counts or a number Eg white blood cell count per unit volume

LOINC Formal Name Parts

LOINC Elements
Component
Property
Timing
Sample
Scale
Method

3. The Timing of the Measurement

Abbrev	Description
Pt	Measures the property at a specific point or moment in time
Stdy	Duration of the study
Enctr	Duration of the encounter
Episode	Duration of the episode

For most NBS tests: Timing will be "Pt"

LOINC Formal Name Parts

LOINC Elements
Component
Property
Timing
Sample
Scale
Method

4. The Type of Sample Measured

Abbrev	Description
Ser	Serum
Bld	Whole Blood
Ur	Urine
Bld.dot	Blood Filter Paper

For most NBS tests: Sample will be "Bld.Dot"

LOINC Formal Name Parts

Required Elements
Component
Property
Timing
Sample
Scale
Method

5. The Scale of Measurement

Scale type	Abbrev	Description
Quantitative	Qn	The result of the test is a numeric value related to a continuous numeric scale. Reported either as an integer, a ratio, a real number, or a range.
Ordinal	Ord	Ordered categorical responses, e.g., 1+, 2+, 3+; positive, negative; reactive, indeterminate, nonreactive.
Quantitative or Ordinal	OrdQn	Reported as either Ord or Qn, e.g., an antimicrobial susceptibility that can be reported as resistant, intermediate, susceptible or as the mm diameter of the inhibition zone.
Nominal	Nom	Nominal or categorical responses that do not have a natural ordering, e.g., names of bacteria, categories of appearance without natural ordering, such as, yellow, clear, bloody.
Narrative	Nar	Text narrative, such as the description of a microscopic part of a surgical papule test.
Multi	Multi	Many separate results structured as one text — global, and reported as one observation, with or without imbedded display formatting.

LOINC Formal Name Parts

Required Elements
Component
Property
Timing
Sample
Scale
Method

6. The Method of the Measure

Method is only expressed as part of name when it provides distinction between 2 or more tests that measure the same component (analyte) but which can have either:

- **Different clinical significance**
- **Different clinical reference range**

Method type	Abbr	Comment
Molecular Genetics	Molgen	General class of methods used to detect genetic attributes on a molecular basis including RFLP, PCR and other methods
Coagulation Assay	Coag	To distinguish coagulation assays based on clotting methods
Chromogenic or Enzymatic Assay	Chromo	To distinguish coagulation assays based on chromogenic (enzymatic activity)
Enzyme Immunoassay	EIA	Subsumes variants such as ELISA

Overview of SCID – *the Condition*

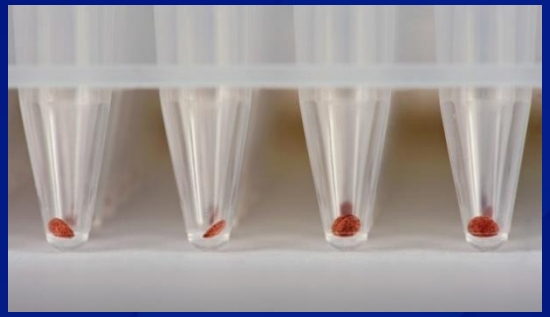
- Severe Combined Immunodeficiency (SCID) is characterized by the absence of both humoral and cellular immunity
  - At least 15 different genes known to cause SCID when mutated
  - All have profound defects in T lymphocyte differentiation and function
- As maternal antibodies wane during first months of life, affected infants develop infections due to common and opportunistic pathogens
- Treatment and prevention of infections can prolong life but are not curative
- Best hope for SCID patients is Hematopoietic Stem Cell Transplant before the onset of infections

SCID has been called "Bubble Boy Disease"

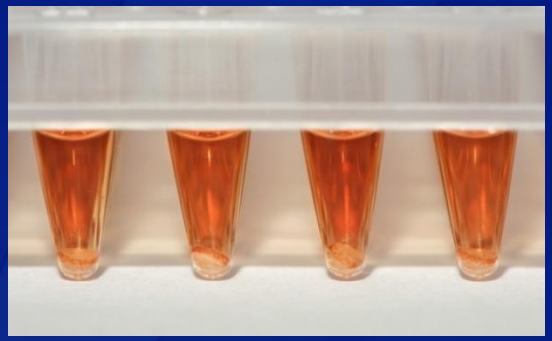
Overview of TREC Assay for SCID

- T cell receptor excision circles (TREC) are by-products of the rearrangement of T cell receptor (TCR) genes during thymocyte maturation in the thymus
- TRECs are episomal DNA and do not replicate during mitosis
- Peripheral blood TREC levels reflect T lymphocyte production in the thymus
- TREC Assay: Real Time PCR
- Variations in TREC Assay procedures can be based on:
  - Primers and Probes
  - DNA extraction procedures

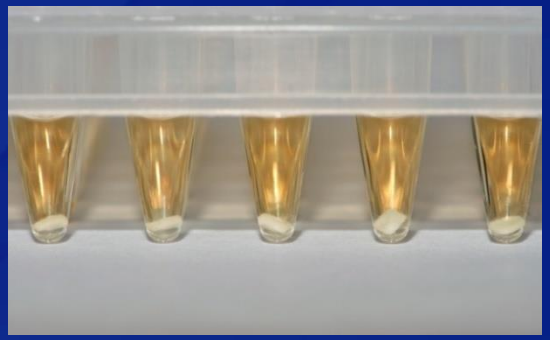
Overview of TREC Assay for SCID



Punch one 2.0 mm discs from DBS specimen into PCR tubes



Wash with 125 µl of DNA purification solution S1
(shake for 15 minutes at room temp)

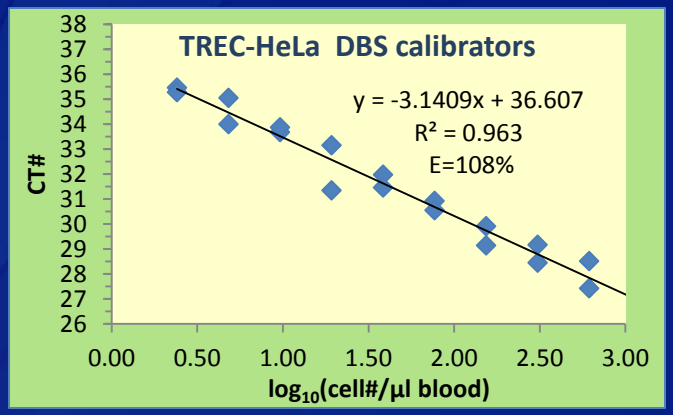


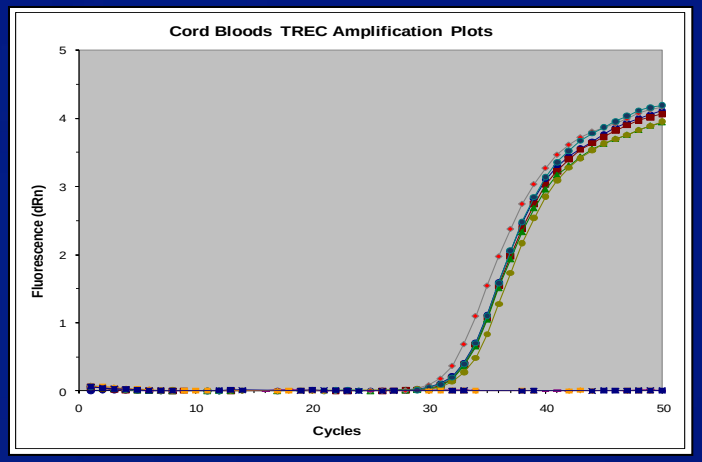
Wash with 125 µl of DNA elution solution S2
(shake for 5 minutes at room temp)

Overview of TREC Assay for SCID

Discard S2 wash buffer
Add 15 µl of qPCR mastermix
(contains complete mix of primers & probe)

Run qPCR in Stratagene MX3000p:
45 deg for 5 min, 95 deg for 20 min
45 cycles of [95 deg x 15 sec + 60 deg x 1 min]





Proposed Coding Information:

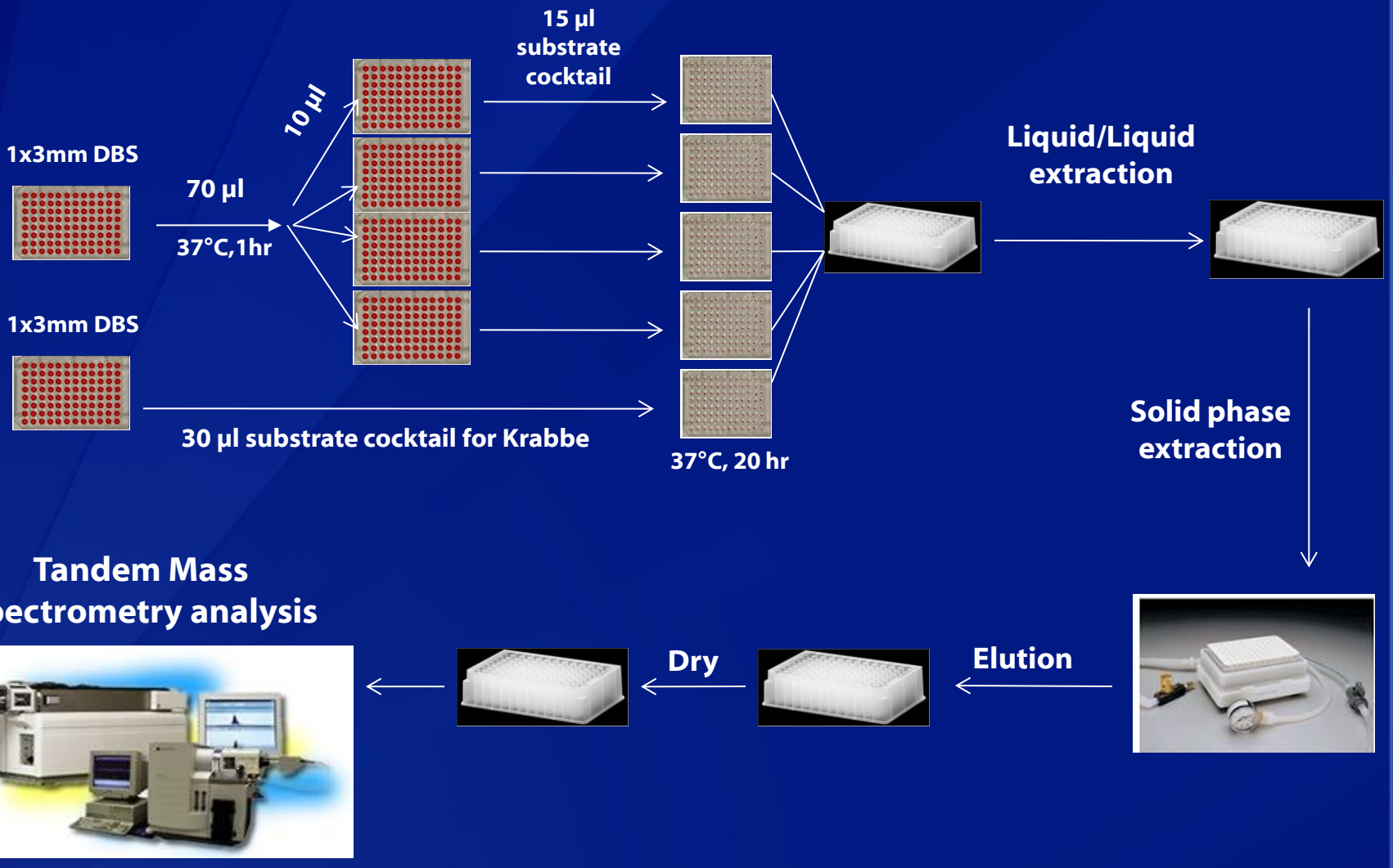
Test for SCID using the TREC Assay

Required Elements	SCID	Comments
Component	TREC	T-Cell Receptor Excision Circle
Property	NCnc	Number concentration (count/vol) Reported as number of TREC copies per microliter
Timing	Pt	Sample taken at a specific moment in time
Sample	Bld.dot	Blood Filter Paper
Scale	Qn	Quantitative assay
Method	PCR	Polymerase Chain Reaction

Overview of NBS Assays for LSDs

- Two main approaches currently available for NBS evaluation of LSDs
  - Mass Spectrometry (MSMS)
  - Fluorometry
- MSMS Evaluation of LSDs
  - Substrates available for 5 diseases and includes Fabry, Gaucher, Krabbe, Niemann-Pick A/B, Pompe
- Fluorometric Evaluation of LSDs
  - 4-methylumbelliferyl-based substrates available

LSD Enzyme Assay by MS/MS



(Zhang, XK etal, Clin Chem 2008; 54 (10):1725–1728)

Proposed Coding Information:

Tests for 5 different LSDs by MSMS

Required Elements	LSD (MSMS)	Comments
Component	GLA GAA GALC GBA ASM	GLA: Alphagalactosidase activity for Fabry Disease GAA: Alphaglucosidase activity for Pompe Disease GALC: Galactocerebrosidase activity for Krabbe Disease GBA: Glucocerebrosidase activity for Gaucher Disease ASM: Acid Sphingomyelinase activity for Niemann Pick A & B
Property	CCnc	Catalytic concentration Reported as mmol/L/hour
Timing	Pt	Sample taken at a specific moment in time
Sample	Bld.dot	Blood Filter Paper
Scale	Qn	Quantitative assay
Method	?	No appropriate method name yet for this assay

LSD Enzyme Assay by Fluorometry

Néstor A.Chamoles, MD (1938-2004)
Picture provided by Joan Keutzer, Genzyme

Courtesy of
Petra Olivova Ph.D.,
Genzyme

Proposed Coding Information:

Tests for 3 different LSDs by Fluorometry

Required Elements	LSD	Comments
Component	GLA GAA GBA	GLA: Alphagalactosidase activity for Fabry Disease GAA: Alphaglucosidase activity for Pompe Disease GBA: Glucocerebrosidase activity for Gaucher Disease
Property	CCnc	Catalytic concentration Reported as mmol/L/hour
Timing	Pt	Sample taken at a specific moment in time
Sample	Bld.dot	Blood Filter Paper
Scale	Qn	Quantitative assay
Method	?	No appropriate method name yet for this assay

New Answer Codes for the Hemoglobinopathies

- Harmonization Meeting held in Oakland, CA in May
- "Harmonizing laboratory reporting: Is It Possible?"
  - Presentation by Dr Roger Eaton (New England Newborn Screening Program)
  - 15 States participated … AK, HI, ID, NV, NM, PA, MS, NH, RI, VT, ME
  - Will be requesting new answer codes for differences in reporting NBS results for Hemoglobinopathies
  - Later phase: differences in confirmatory and diagnostic (2nd tier) testing

Request For New Answer Codes for the Hemoglobinopathies

Planned Outcome of Meeting

- Assemble workgroup to address harmonization of the "Hemoglobinopathy Answer List"
  - Build on strong foundation developed by Dr Eaton and colleagues
  - Several Oakland Meeting participants have indicated interest
- Task the group to develop a draft White Paper to serve as a working document for circulation to address "Harmonization of Electronic Reporting in the Hemoglobinopathies"
- Workgroup will report to the HITWG on progress

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