LABORATORY STANDARDS AND PROCEDURES WORKGROUP

April 24, 2019

Co-chairs: Kellie Kelm, PhD & Susan Tanksley, PhD

Agenda

TOPIC	PRESENTER
Welcome and Roll Call (5 min)	Kellie Kelm Susan Tanksley
Welcome New Members (8 min) Nathalie Lepage, PhD, FCCMG, FCACB Laboratory Head, Inherited Metabolic Diseases, Newborn Screening Ontario Miriam Schachter, PhD Research Scientist, Newborn Screening Laboratory, New Jersey Department of Health Stan Berberich, PhD (returning) Program Manager, Medical Screening, State Hygienic Laboratory at The University of Iowa George Dizikes, PhD, HCLD/CC(ABB) (returning) Director, Knoxville Regional Laboratory, Division of Laboratory Services	Kellie Kelm Susan Tanksley
New conditions implementation update (12 min)	APHL
Lessons from the Field: SMA Screening New England (10 min) Utah (10 min) Discussion (10 min)	Anne Comeau Andy Rohrwasser All
Debrief and Discussion: RUSP Condition Nomination & Evidence Review Process (30 min)	All
Wrap-up/Next Steps (5 min)	Kellie, Susan

Workgroup Roster

Mei Baker
Carla Cuthbert
Tricia Hall
Scott McCandless
Scott Shone
Holly Winslow
Stan Berberich#
George Dizikes#
Travis Henry
Jelili Ojodu
Bonnie Taffe
Michele Caggana
Rosemary Hage
Nathalie Lepage*
Miriam Schachter*
Michael Watson

- Chair: Kellie Kelm
- Co-chair: Susan Tanksley
- HRSA staff: Kathryn McLaughlin

Workgroup Charge

Define and implement a mechanism for the periodic review and assessment of

1. The conditions included in the uniform panel
2. Laboratory procedures utilized for effective and efficient testing of the conditions included in the uniform panel.
3. Infrastructure and services needed for effective and efficient screening of the conditions included in the uniform panel

Project 1

- Laboratory procedures: Explore the role of next generation sequencing in newborn screening
  - Screening is currently based on phenotypic data. How do we accumulate the data to identify correlation between phenotypic & genotypic data?
  - Are there conditions for which sequencing is the only screening method?
  - What do you gain/lose from NGS?
  - Which data do you report?
    - What do you do with variants of unknown significance?
    - When do you report carrier status? Are there particular conditions where reporting carrier status is important?
  - What new infrastructure needs to be built for NGS?

Project 2

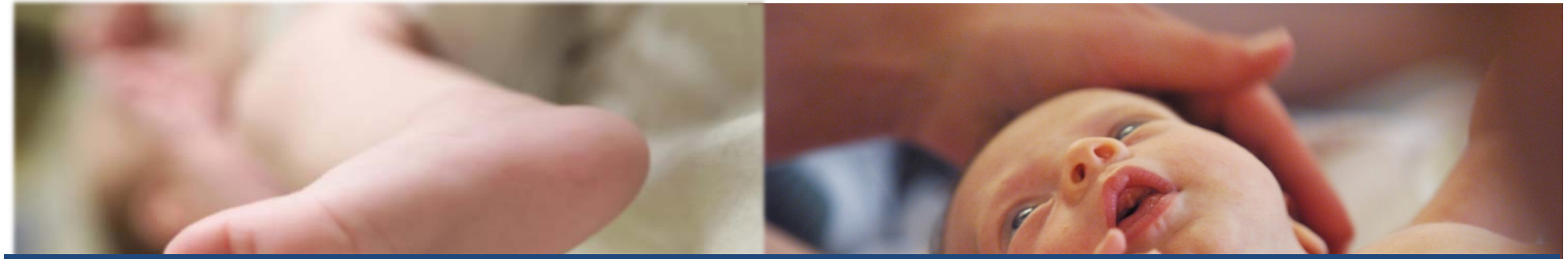
- Infrastructure and services: A portion of the timeliness initiatives fits here:
  - Review data related to testing (Timeliness 1.0)
  - What are the implications of earlier specimen collection (<24 hrs)?
  - What are the unforeseen consequences and costs of timeliness?

Project 3

- Impact of broad phenotypes on laboratories
  - Share lessons learned on identifying late onset Pompe disease, SMA cases with 2, 3, or 4 copies of SMN2, etc.
  - Use information to refine the target of the RUSP condition?

APHL New Conditions Implementation Update

- Funded 16 states for implementation projects and 3 states as Peer Network Resource Centers (PNRCs)
- PNRCs are early adopters of the 3 conditions (Pompe, MPS1, X-ALD) that would help the other states with either MS or digital microfluidics
- New conditions workgroup starting soon, George Dizikes and Amy Gaviglio, co-chairs
  - Webinars
  - Technical assistance
- Additional funding has been received for SMA and other disorders as they get added for the next 5 years



Newborn Screening for Spinal Muscular Atrophy

Massachusetts' experience

ACHDNC Laboratory Working Group
April 23, 2019

Anne Marie Comeau, Ph.D
Deputy Director, New England Newborn Screening Program
Professor of Pediatrics, UMass Medical School

University of Massachusetts Medical School
umassmed.edu

Assay Development for SMA NBS

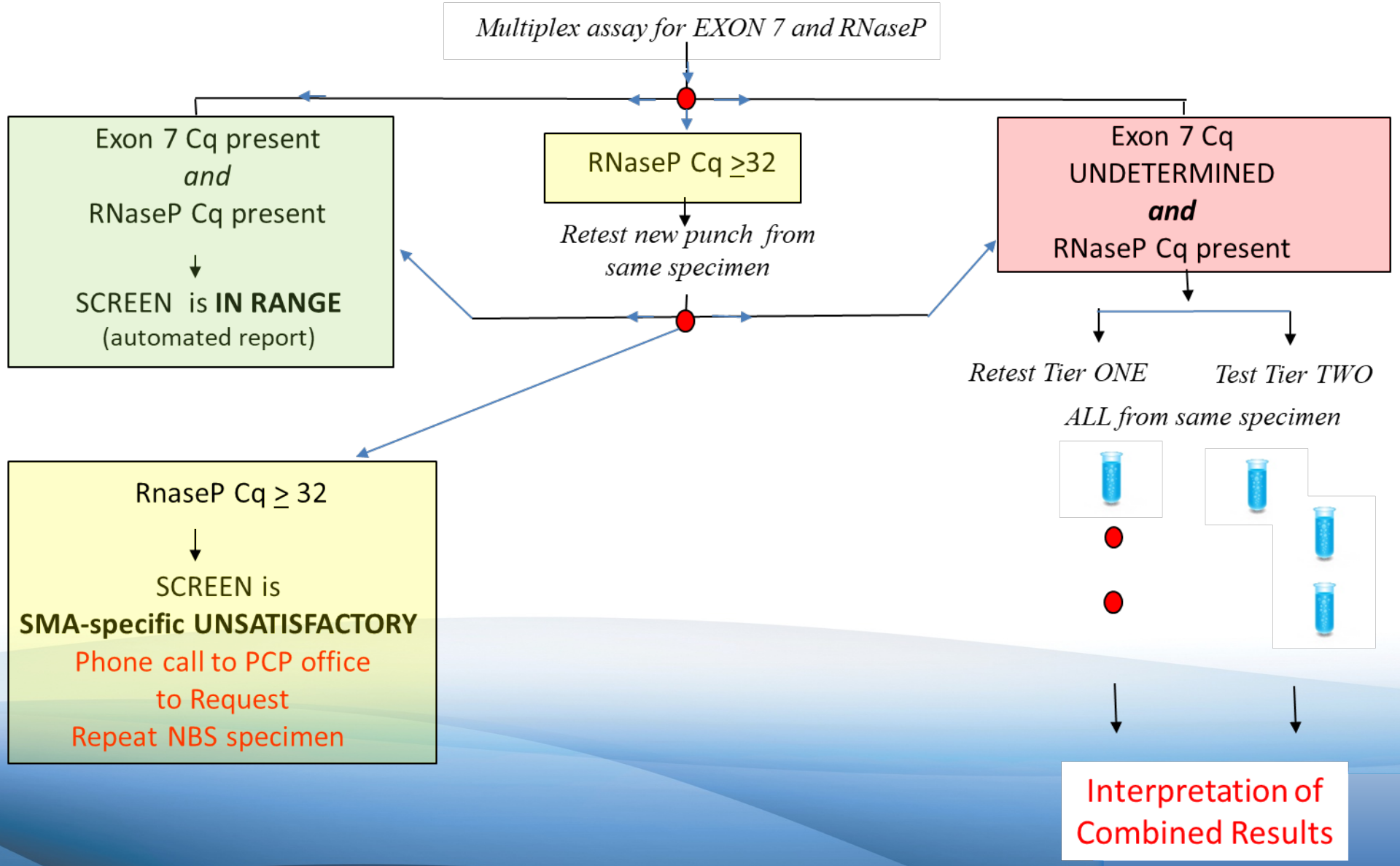
Two factors key to development:

- SMA is related to the absence of a fully functional gene that produces a Survival of Motor Neuron (SMN) protein, *SMN1*
- 95% SMA patients show homozygous loss of *SMN1* exon 7

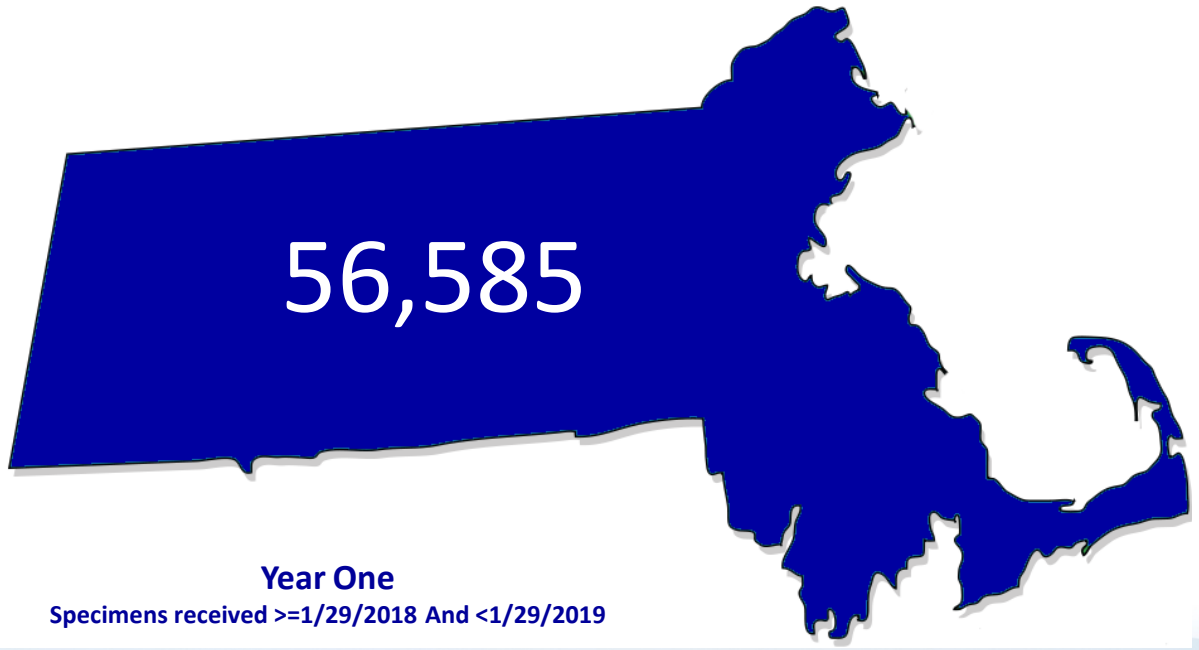
Assay is designed to detect
HOMOZYGOUS ABSENCE OF *SMN1* EXON 7.
It is not designed to detect carriers.

Massachusetts' SMA NBS **Laboratory Testing** Algorithm

Dried Blood Spot Specimen, DNA from 3 mm punch/20



Number of Babies Screened for SMA

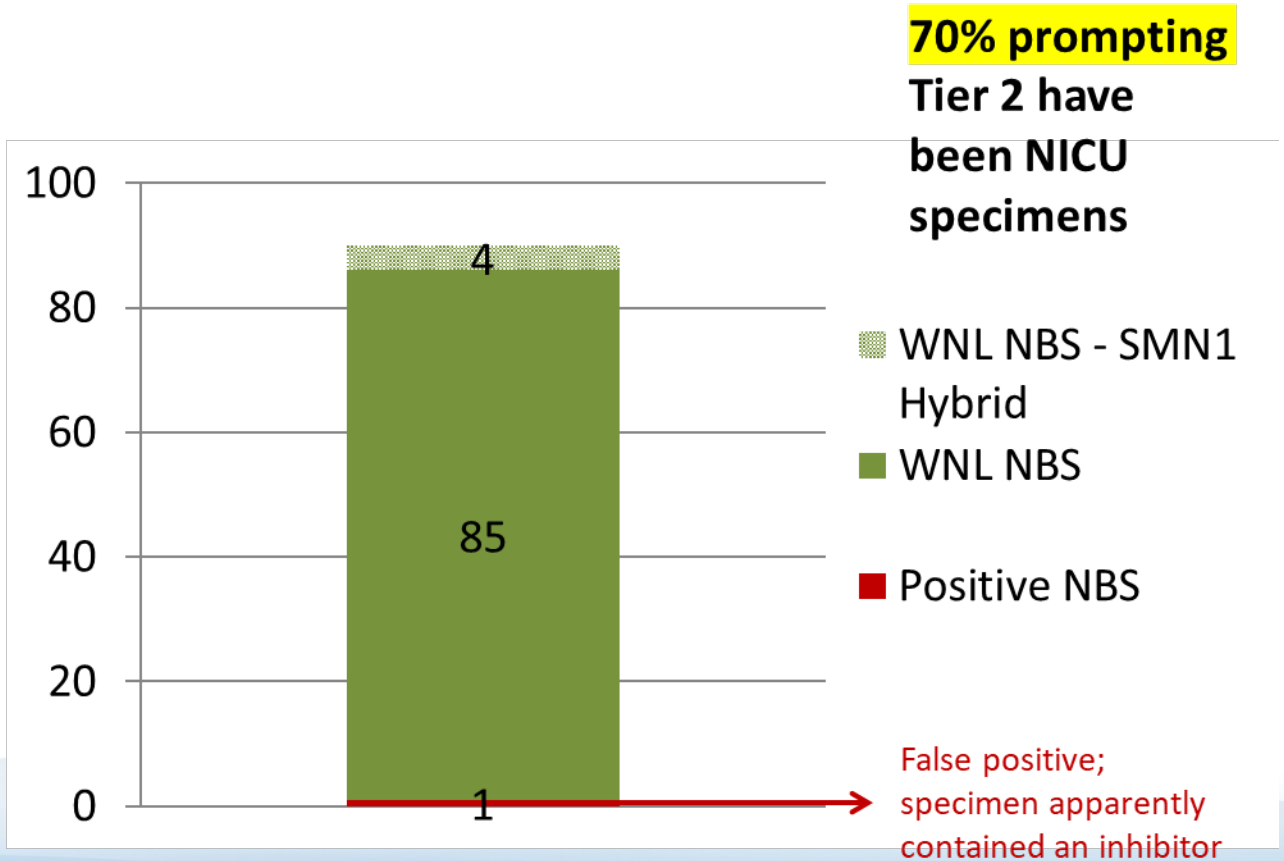


Year One

Specimens received >=1/29/2018 And <1/29/2019

69,169 as of April 16

Infants with a specimen prompting Tier 2
n = 90



SMA screening in Utah: One year update

Andy Rohrwasser
arohrwasser@utah.gov

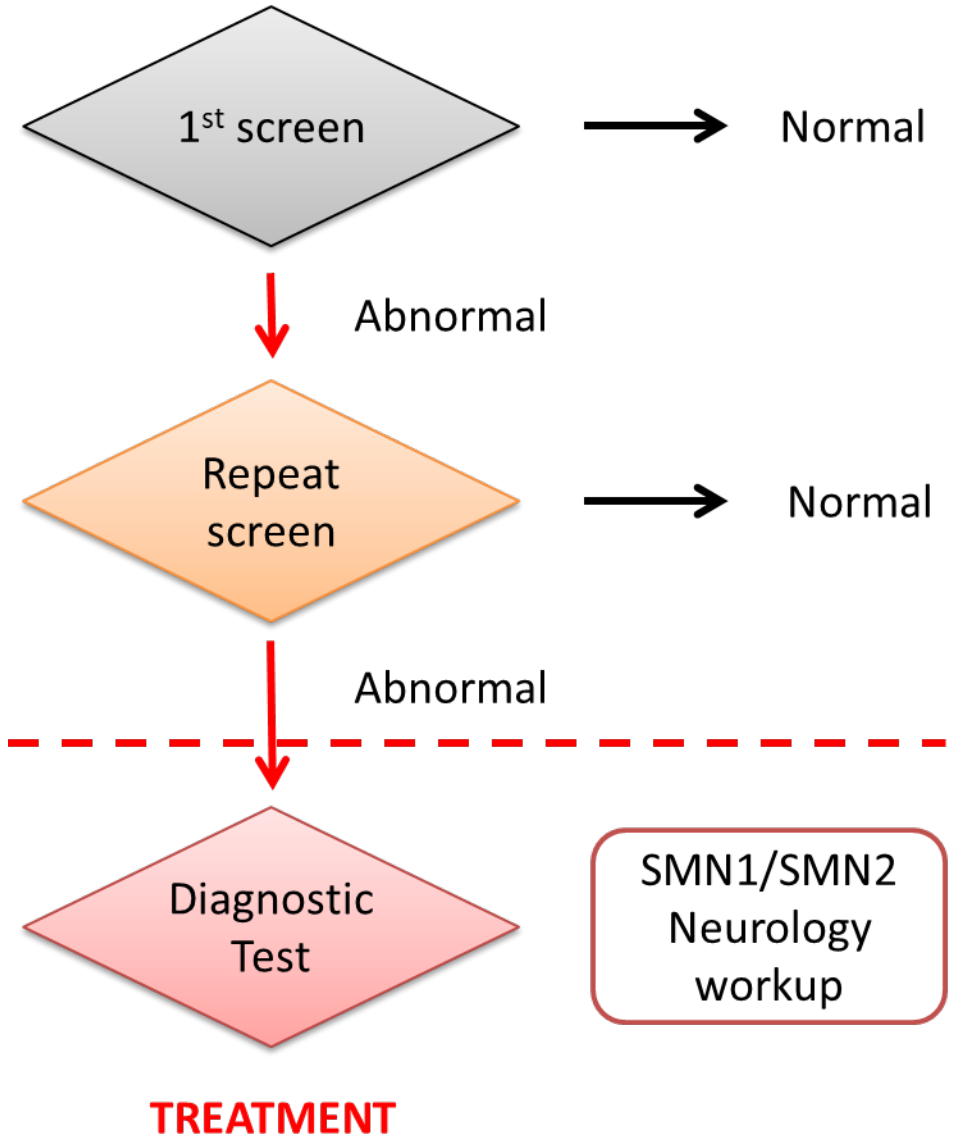
UTAH DEPARTMENT OF HEALTH

NEWBORN SCREENING

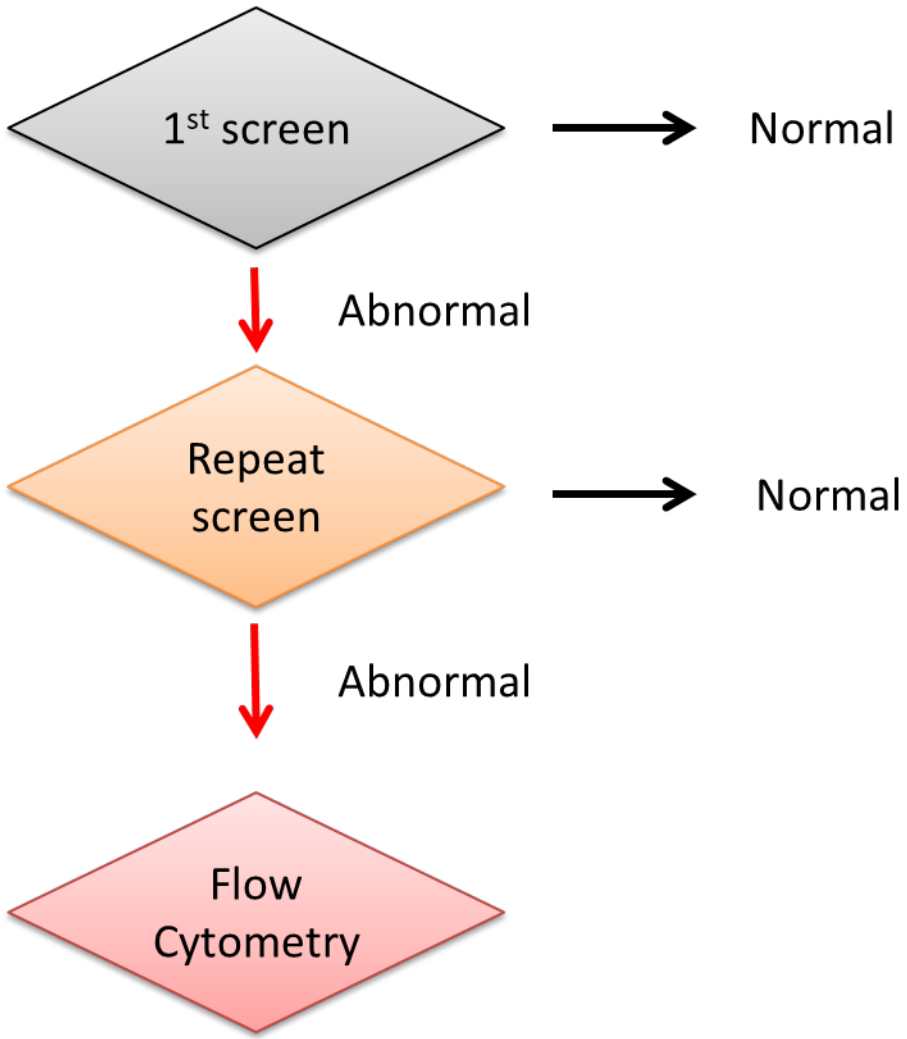
SMA/TREC Assay Method

- PCR-Based Triplex Assay: modified CDC protocol
  - SMN1 – Deletion of exon 7 of SMN1 gene (SMA)
  - TREC – T-cell receptor excision circles (SCID)
  - RPP30 – Internal control
- Automated Extraction Tecan Evo 200
  - 2 step washing protocol
    - PBS/Tween 20 (room temperature)
    - Qiagen Solution 2 (room temperature)
  - Qiagen Solution 2 (70C) elution
  - 96 well to 384 well transition
- Real-Time PCR
  - Roche LightCycler 480 II
  - 384 well format

SMA Screening and Diagnostic Workflow



SCID Screening and Diagnostic Workflow



Case	Age at NBS report	Age at clinic evaluation	Age at confirmatory testing result	Confirmatory Result	Treatment type
Case 1	6 days	7 days	13 days	SMN1 = 0 SMN2 = 3	Gene therapy trial
Case 2	7 days	8 days	14 days	SMN1 = 0 SMN2 = 3	Gene therapy trial

Statistics

SMA/ repeat	n	Percent SMA
SMA	48,557	-
repeat	466	0.96%

SCID/ repeat	n	Percent SCID	Percent SCIDC
SCID	22,525	-	-
repeat	708	3.14%	-

SMA: you have the deletion or you don’t/binary

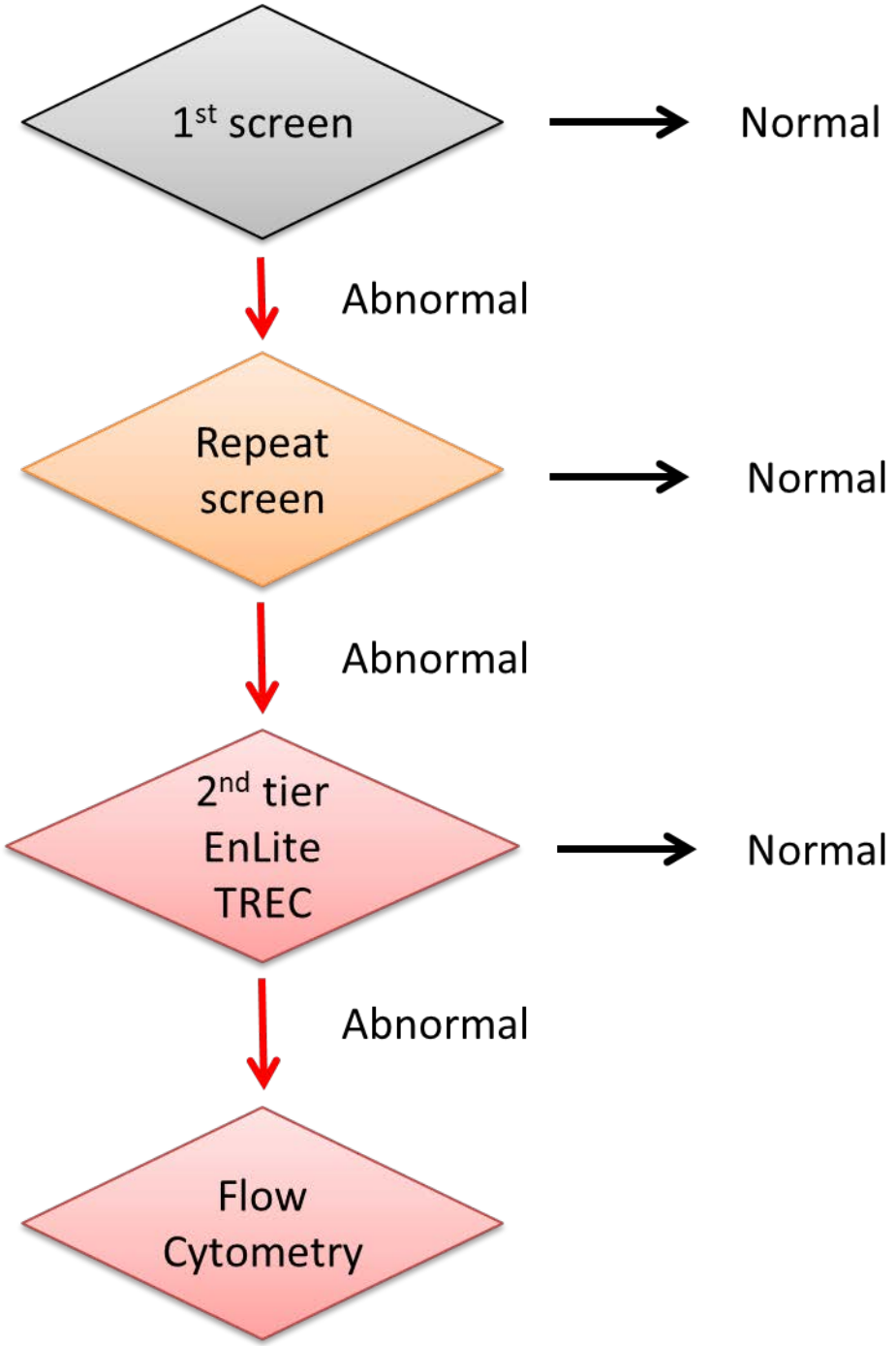
TREC as a SCID marker: continuous or quantitative trait phenotype

Problem: 2 false positive SCID cases

- *2 cases abnormal on 1st NBS; referred for flow cytometry; results normal/not consistent with SCID*
  - Retested SCID cases using EnLite TREC: Normal/low TREC levels

- Hypothesis: differential binding/elution kinetics TREC/gDNA

SCID Screening and Diagnostic Workflow



Debrief and discussion:
RUSP Condition Nomination & Evidence Review Process

- Need to define the terminology for the evidence review process (e.g. what is a case definition)
- Set the case definition for the condition under consideration – it's what the laboratory is supposed to find
- Is identifying carriers a benefit or a harm?
- Very difficult to find published evidence of harm (doesn't mean we shouldn't look for it)
- Need better assessment of the availability of the confirmatory test and turnaround time, specialty care availability
- Systematic way to measure family experiences e.g. Maslow's hierarchy of needs