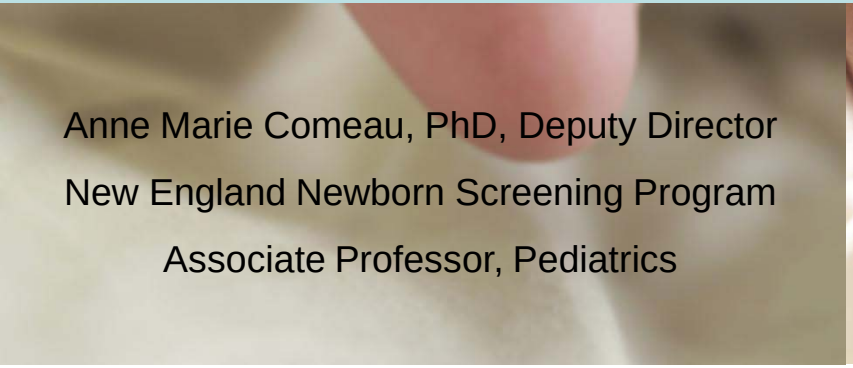



Post-Analytic Molecular Challenges:

algorithm development, clinical interpretation, reporting data and reporting risk



Anne Marie Comeau, PhD, Deputy Director
New England Newborn Screening Program
Associate Professor, Pediatrics

Molecular Training Workshop, CDC Atlanta 2012

Molecular Testing at

New England Newborn Screening Program

HIV (research) 1980's

CYSTIC FIBROSIS 1999 forward

GALACTOSEMIA → 2000's

MCADD → 2000's

SCID → 2009 forward

Purpose of the Testing

Context of the Reporting

Reporting SOP

Report Content

Educational Supplements

Record Keeping

Purpose of the Testing

Relating pre-analytic decisions to post-analytic reporting…

What are you looking for... and what do you hope to accomplish with molecular analyses?

Purpose of DNA in the NBS

data generated prior to full diagnostic evaluation

- Enhance sensitivity for conditions not otherwise included...

  TREC assay for SCID: First Tier molecular

- Enhance specificity of 1st tier test....CFTR mutation assay after IRT: Second Tier molecular

- Supplemental just-in-time

  Increase available information to aid diagnostic evaluation…

  GALT mutation assay: Second Tier molecular

Note on DNA testing:

Regardless of purpose, the DNA target might be

A specific allele

A specific structure

A foreign element

Qualitative or Quantitative

DNA Testing in the 2nd Tier

data generated prior to full diagnostic evaluation

- Enhance sensitivity for conditions not otherwise included… (Conventional genetic)

TREC assay for SCID: First Tier molecular

- Enhance specificity of 1st tier test….CFTR mutation assay after IRT: Second Tier molecular
- Supplemental just-in-time

Increase available information to aid diagnostic evaluation…

GALT mutation assay: Second Tier molecular

Context of the Reporting

Relating post-analytic reporting to the needs of the

report recipient

Context of the Reporting

- Routine outgoing reports

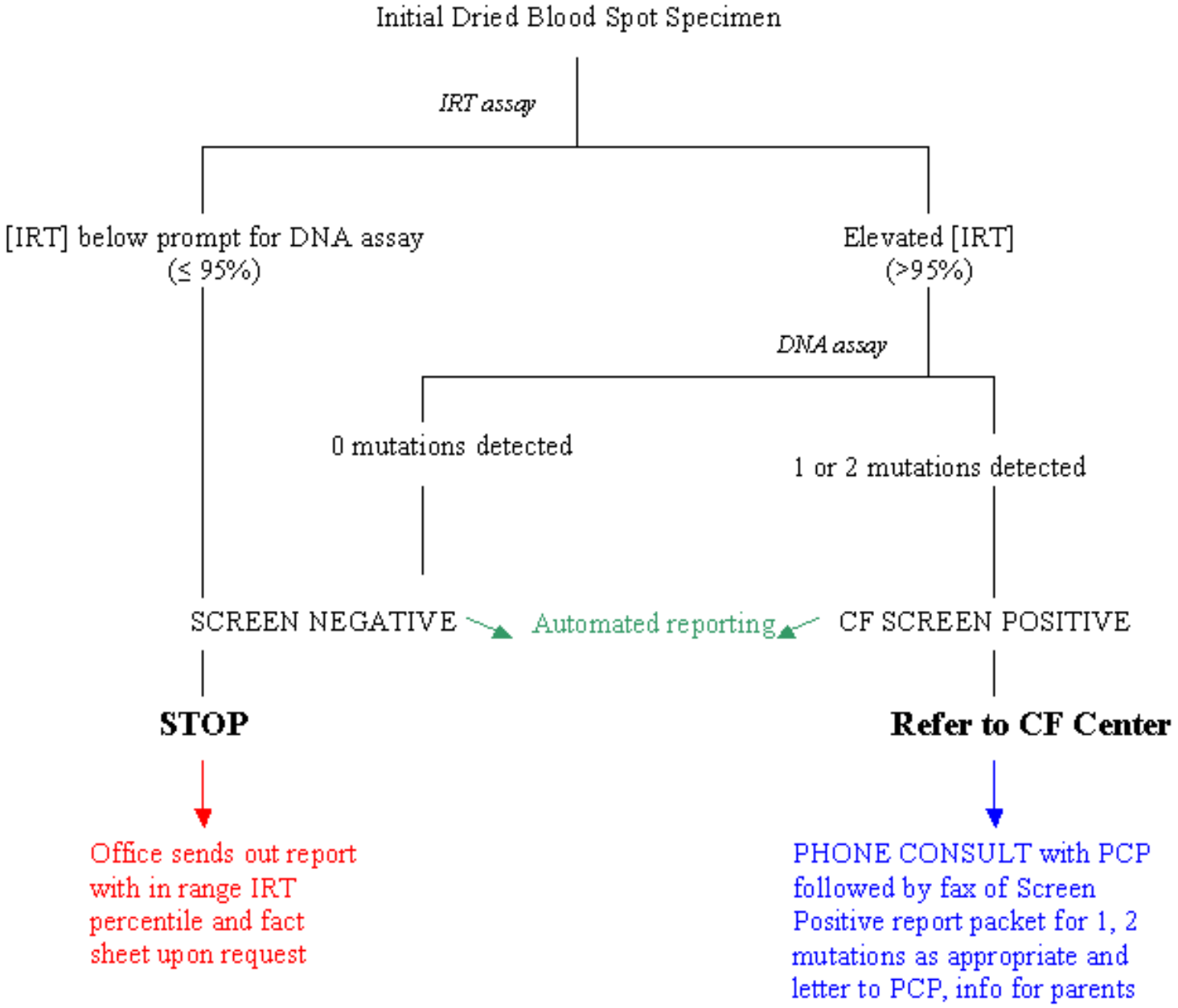
  Newborn screening result is “In Range”

  Newborn screening result is “OUT-OF-RANGE”

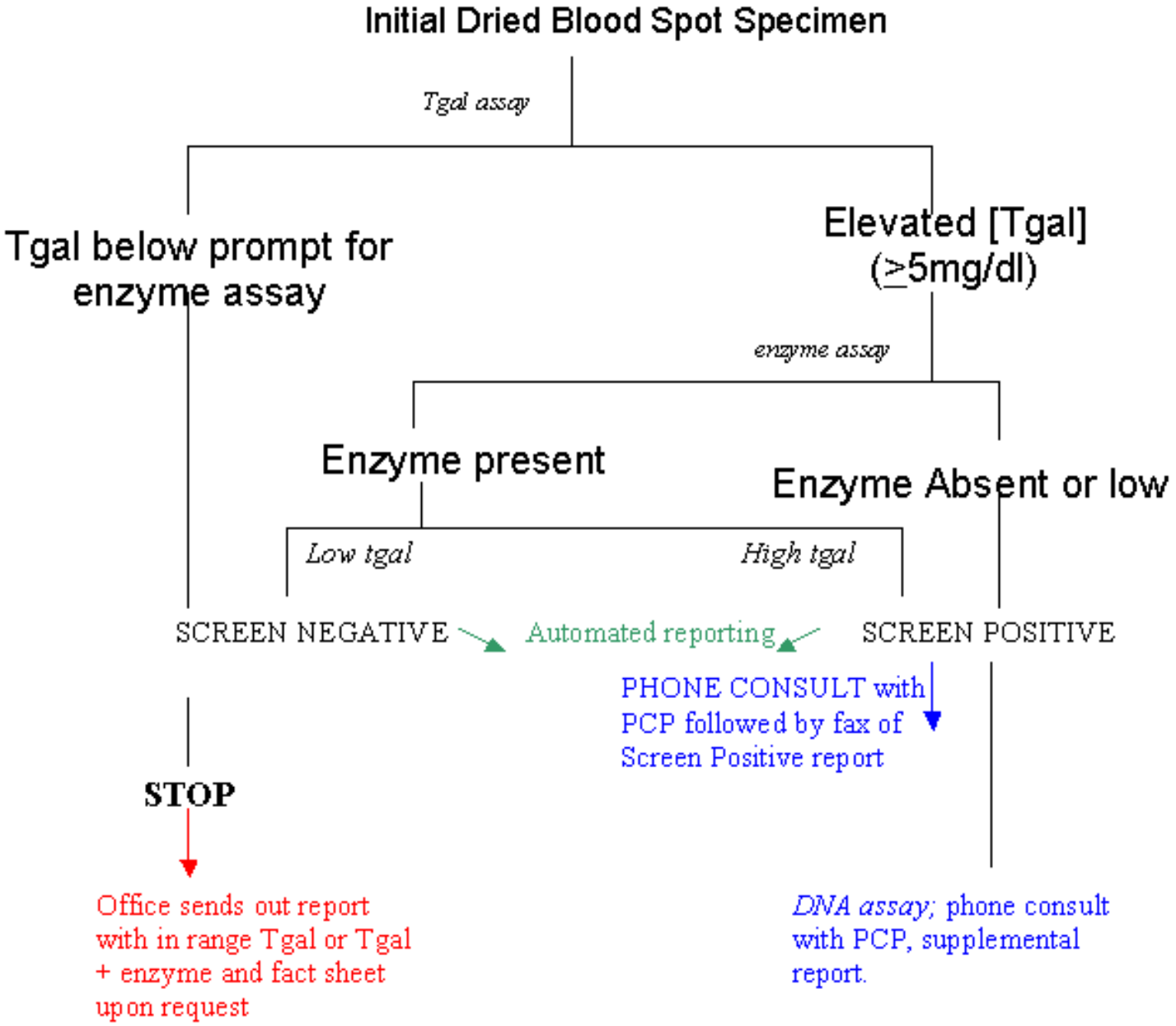
- Response to clinical inquiries

Reporting SOP

CF Reporting Overview



Galactosemia Reporting Overview



Reporting SOP

Staff roles

- data entry and second readers
- preparation of supplemental reports
- scripts

Report recipients

- to whom…

Report Content

Report Content

Technical Report

- CLSI demographics
- Reason for testing
- Disease locus tested
- Result is In Range or Out of Range

  Out of Range:

  Number of DNA sequence variants **detected** by the screen

Report Content

- **Names** of DNA sequence variants **detected** by the screen (colloquial and (?) HGVS)
- **Names** of DNA sequence variants **TESTED**.

nomenclature

- colloquial: Delta F508
- HGVS: c.1521_1523delCTT

Human Genome Variation Society

http://www.hgvs.org/

Report Content

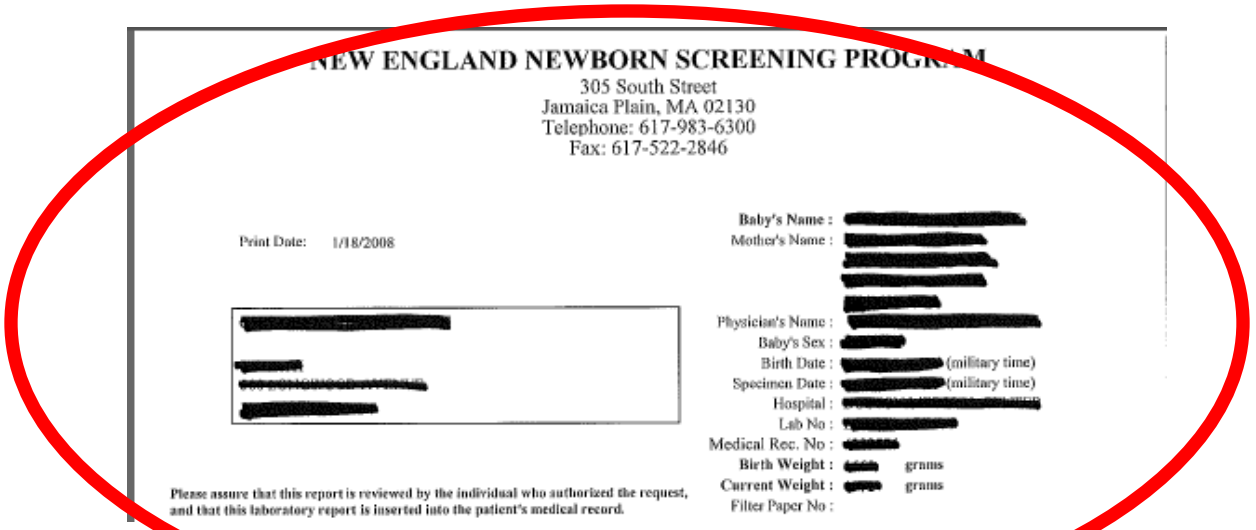
INTERPRETATION

- Interpretation of the overall NBS result for the condition
- State interpretation of the DNA result, e.g.,
  - *infant is (at least) a carrier*
  - *Infant with 2 variants is at high risk*

RECOMMENDED ACTION

Cystic Fibrosis

(enhance specificity of 1st tier)



NEW ENGLAND NEWBORN SCREENING PROGRAM

305 South Street
Jamaica Plain, MA 02130
Telephone: 617-983-6300
Fax: 617-522-2846

Print Date: 1/18/2008

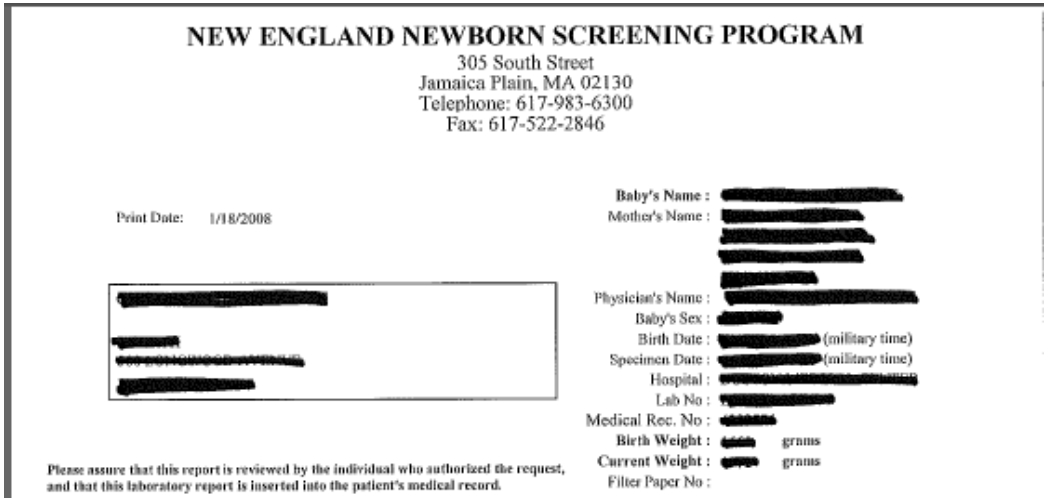
[redacted]

Baby's Name : [redacted]
Mother's Name : [redacted]
Physician's Name : [redacted]
Baby's Sex : [redacted]
Birth Date : [redacted] (military time)
Specimen Date : [redacted] (military time)
Hospital : [redacted]
Lab No : [redacted]
Medical Rec. No : [redacted]
Birth Weight : [redacted] grams
Current Weight : [redacted] grams
Filter Paper No :

Please assure that this report is reviewed by the individual who authorized the request, and that this laboratory report is inserted into the patient's medical record.

NEWBORN SCREENING TEST REPORT (Initial Blood Filter Paper Specimen)

Targeted Congenital Disorders / Analyte Tested	Results Within Range	Results Out of Range	Reference Range (for newborns)
Adrenal Hyperplasia(CAH) / 17-OH-Progesterone	<13.5 ng/mL		<60 ng/mL(weight dependent)
*Biotinidase Deficiency / Biotinidase	>=30%		>=30%
***Cystic Fibrosis_SCREEN**		**2 MUTATIONS**	IN RANGE
Galactosemia / Galactose,Total	<=2 mg/dL		<14 mg/dL
Hemoglobinopathies / Hemoglobin Isoelectric Focusing	FA		FA, AF, or A
Homocystinuria / Methionine	<1.5 mg/dL		< 1.5 mg/dL
Hypothyroidism (CH) / Thyroxine	17.2 ug/dL		>5.0 ug/dL
Maple Syrup Urine Disease (MSUD) / Leucine	<=4.5 mg/dL		<= 4.5 mg/dL
MCAD / Octanoylcarnitine	<0.80 uM		<0.80 uM
Phenylketonuria (PKU) / Phenylalanine (PHE)	<=2.3 mg/dL		<= 2.3 mg/dL
SCID/Ratio	0.0625		>=0.0100
SCID/RNaseP	49650 copies/uL		>=5435 copies/uL
SCID/TREC	3101 copies/uL		>=339 copies/uL
*Toxoplasma Infection / Toxoplasma IgG	0.041 O.D.		<0.1 OD
^Metabolic / MET SUPP 01 Panel	All in Range		All in Range



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Galactosemia / Galactose,Total	<=2 mg/dL		<14 mg/dL
Hemoglobinopathies / Hemoglobin Isoelectric Focusing	FA		FA - A Expected
Homocystinuria / Methionine	[redacted]		< 1.5 mg/dL
Hypothyroidism (CH) / Thyroxine	17.2 ug/dL		>5.0 ug/dL
Maple Syrup Urine Disease (MSUD) / Leucine	<=4.5 mg/dL		<= 4.5 mg/dL
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Attachment to Results for Routine Newborn Screening Testing

Result from Cystic Fibrosis Newborn Screening

Report Date: 5/5/09
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER		RESULT Screen Positive
CYSTIC FIBROSIS		Category C
Details for genetic counseling:	Name of the first mutation detected by the screen:	DF508
	Name of second mutation detected by the screen	S549N

INTERPRETATION: "Screen Positive"
Details for Category C:

- IRT > 95% and
- Two CFTR mutations were detected (39 mutation panel ASR*)
- Result is consistent with Cystic Fibrosis

IRT: Immunoreactive Trypsinogen; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator gene

RECOMMENDED ACTION:
All infants with "Screen Positive" Category C results should be referred to a CF Center for diagnostic evaluation (sweat test) and consultation with CF specialist.

Attention Health Care Provider: Newborn screening tests are intended to provide an early opportunity to detect disorders before symptoms appear. These tests are not diagnostic.

*ASR: Analyte Specific Reagent (CFTR 39+4) that includes 39 mutations with reflex analysis for I506V, I507V, F508C, 5, 7,9T as appropriate. The 39-mutation panel includes ΔF508, R117H, G551D, G542X, W1282X, N1303K, R334W, 621+1G>T, R553X, ΔI507, 1717-1G>A, R347P, R560T, 3849+10kbC>T, A455E, 3120+1G>A, 3659delC, R1162X, 711+1G>T, 2789+5G>A, G85E, 1898+1G>A, 2184del, 1078delT, 394delTT, Y122X, R347H, V520F, A559T, S549N, S549R(T>G), 1898+5G>T, 2183AA>G, 2307insA, Y1092X, M1101K, S1255X, 3876delA, 3905insT. This test has not been cleared or approved by the FDA. However, the New England Newborn Screening Program determined the performance characteristics of the test and the FDA has determined that its clearance and approval are not required for the NENSP-specific uses.

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Attachment to Results for Routine Newborn Screening Testing

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Report Date: 5/5/09
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER		RESULT Screen Positive
CYSTIC FIBROSIS		Category C
Details for genetic counseling:	Name of the first mutation detected by the screen:	DF508
	Name of second mutation detected by the screen	S549N

INTERPRETATION: "Screen Positive"
Details for Category C:

- IRT > 95% and
- Two CFTR mutations were detected (39 mutation panel ASR*)
- Result is consistent with Cystic Fibrosis

IRT: Immunoreactive Trypsinogen; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator gene

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Attachment to Results for Routine Newborn Screening Testing

Result from Cystic Fibrosis Newborn Screening

Report Date: 5/5/09
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER		RESULT Screen Positive
CYSTIC FIBROSIS		Category C
Details for genetic counseling:	Name of the first mutation detected by the screen:	DF508
	Name of second mutation detected by the screen	S549N

INTERPRETATION: "Screen Positive"

Details for Category C:

- IRT > 95% and
- Two CFTR mutations were detected (39 mutation panel ASR*)
- Result is consistent with Cystic Fibrosis

IRT: Immunoreactive Trypsinogen; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator gene

RECOMMENDED ACTION:

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305 South Street, Jamaica Plain, MA 02130
Telephone: 617-983-6300 Fax: 617-522-2846

Attachment to Results for Routine Newborn Screening Testing

Result from Cystic Fibrosis Newborn Screening

Report Date: 5/5/09
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER		RESULT Screen Positive
CYSTIC FIBROSIS		Category C
Details for genetic counseling:	Name of the first mutation detected by the screen:	DF508
	Name of second mutation detected by the screen	S549N

INTERPRETATION: "Screen Positive"
Details for Category C:

- IRT > 95% and
- Two CFTR mutations were detected (39 mutation panel ASR*)
- Result is consistent with Cystic Fibrosis

IRT: Immunoreactive Trypsinogen; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator gene

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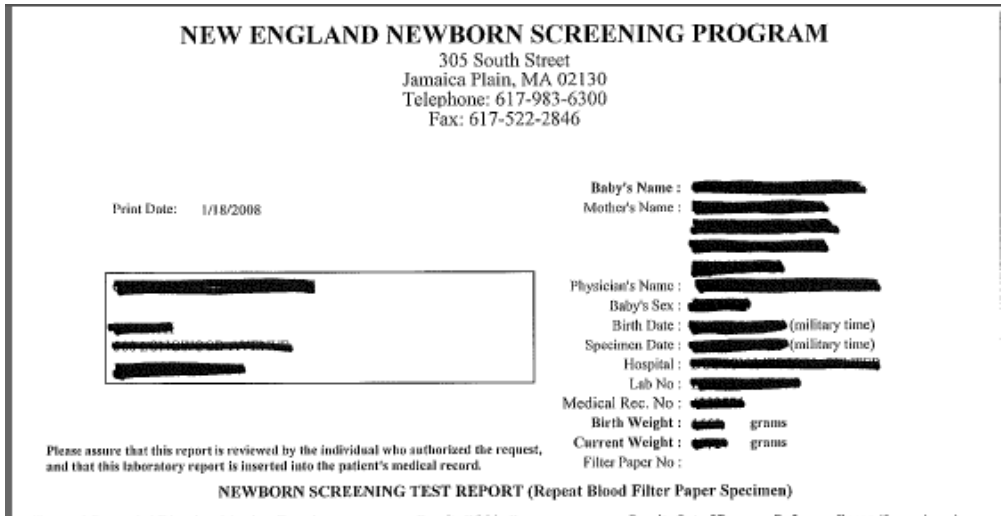

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Print Date: 1/18/2008

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Mother's Name : [redacted]
Physician's Name : [redacted]
Baby's Sex : [redacted]
Birth Date : [redacted] (military time)
Specimen Date : [redacted] (military time)
Hospital : [redacted]
Lab No : [redacted]
Medical Rec. No : [redacted]
Birth Weight : [redacted] grams
Current Weight : [redacted] grams
Filter Paper No :

Please assure that this report is reviewed by the individual who authorized the request, and that this laboratory report is inserted into the patient's medical record.

NEWBORN SCREENING TEST REPORT (Repeat Blood Filter Paper Specimen)

NEWBORN SCREENING TEST REPORT (Initial Blood Filter Paper Specimen)

Targeted Conditions / Analyte Tested	Results Within Range	Results Out of Range	Reference Range (for newborns)
Adrenal Hyperplasia(CAH) / 17-OH-Progesterone	18.9 ng/mL		<60 ng/mL(weight dependent)
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Hypothyroidism (CH) / Thyroxine	22.7 ug/dL		>5.0 ug/dL
Maple Syrup Urine Disease (MSUD) / Leucine	<=4.5 mg/dL		<= 4.5 mg/dL
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Phenylketonuria (PKU) / Phenylalanine (PHE)	<=2.3 mg/dL		<= 2.3 mg/dL
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Attachment to Results for Routine Newborn Screening Testing

Result from Cystic Fibrosis Newborn Screening

Report Date: 5/5/09
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER		**RESULT** **Screen Positive**
CYSTIC FIBROSIS		Category B
Details for genetic counseling	Name of the one mutation detected by the screen:	G551D

INTERPRETATION: "Screen Positive"
Details for Category B:

- IRT > 95% and
- one of 39 CFTR mutations were detected (39 mutation panel ASR*)
- infant is *at least* a carrier for Cystic Fibrosis

IRT :Immunoreactive Trypsinogen; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator gene

RECOMMENDED ACTION:
All infants with "Screen Positive" results should be referred to a CF Center for diagnostic evaluation (sweat test). Families of Category B infants should be offered genetic counseling.

Attention Health Care Provider: Newborn screening tests are intended to provide an early opportunity to detect disorders before symptoms appear. These tests are not diagnostic. Regardless of screening test results, a physician should immediately evaluate any infant who exhibits findings consistent with cystic fibrosis.

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Result from Cystic Fibrosis Newborn Screening

Report Date: 5/5/09
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER		**RESULT** **Screen Positive**
CYSTIC FIBROSIS		Category B
Details for genetic counseling	Name of the one mutation detected by the screen:	G551D

INTERPRETATION: "Screen Positive"
Details for Category B:

- IRT > 95% and
- one of 39 CFTR mutations were detected (39 mutation panel ASR*)
- infant is *at least* a carrier for Cystic Fibrosis

IRT :Immunoreactive Trypsinogen; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator gene

RECOMMENDED ACTION:
All infants with "Screen Positive" results should be referred to a CF Center for diagnostic evaluation (sweat test). Families of Category B infants should be offered genetic counseling.

Attention Health Care Provider: Newborn screening tests are intended to provide an early opportunity to detect disorders before symptoms appear. These tests are not diagnostic. Regardless of screening test results, a physician should immediately evaluate any infant who exhibits findings consistent with cystic fibrosis.

*ASR: Analyte Specific Reagent (CFTR 39+4) that includes 39 mutations with reflex analysis for I506V, I507V, F508C, 5, 7,9T as appropriate. The 39-mutation panel includes ΔF508, R117H, G551D, G542X, W1282X, N1303K, R334W, 621+1G>T, R553X, ΔI507, 1717-1G>A, R347P, R560T, 3849+10kbC>T, A455E, 3120+1G>A, 3659delC, R1162X, 711+1G>T, 2789+5G>A, G85E, 1898+1G>A, 2184del, 1078delT, 394delTT, Y122X, R347H, V520F, A559T, S549N, S549R(T>G), 1898+5G>T, 2183AA>G, 2307insA, Y1092X, M1101K, S1255X, 3876delA, 3905insT. This test has not been cleared or approved by the FDA. However, the New England Newborn Screening Program determined the performance characteristics of the test and the FDA has determined that its clearance and approval are not required for the NENSP-specific uses.

New England Newborn Screening Program University of Massachusetts Medical School
305 South Street, Jamaica Plain, MA 02130
Telephone: 617-983-6300 Fax: 617-522-2846

Attachment to Results for Routine Newborn Screening Testing

Result from Cystic Fibrosis Newborn Screening

Report Date: 5/5/09
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER		RESULT **Screen Positive**
CYSTIC FIBROSIS		Category B
Details for genetic counseling	Name of the one mutation detected by the screen:	G551D

INTERPRETATION: "Screen Positive"

Details for Category B:

- IRT > 95% and
- one of 39 CFTR mutations were detected (39 mutation panel ASR*)
- infant is *at least* a carrier for Cystic Fibrosis

IRT :Immunoreactive Trypsinogen; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator gene

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Attachment to Results for Routine Newborn Screening Testing

Result from Cystic Fibrosis Newborn Screening

Report Date: 5/5/09
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER		RESULT **Screen Positive**
CYSTIC FIBROSIS		Category B
Details for genetic counseling	Name of the one mutation detected by the screen:	G551D

INTERPRETATION: "Screen Positive"

Details for Category B:

- IRT > 95% and
- one of 39 CFTR mutations were detected (39 mutation panel ASR*)
- infant is *at least* a carrier for Cystic Fibrosis

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Attachment to Results for Routine Newborn Screening Testing

Result from Cystic Fibrosis Newborn Screening

Report Date: 5/5/09
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER		**RESULT** **Screen Positive**
CYSTIC FIBROSIS		Category B
Details for genetic counseling	Name of the one mutation detected by the screen:	G551D

INTERPRETATION: "Screen Positive"
Details for Category B:

- IRT > 95% and
- one of 39 CFTR mutations were detected (39 mutation panel ASR*)
- infant is *at least* a carrier for Cystic Fibrosis

IRT: Immunoreactive Trypsinogen; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator g...

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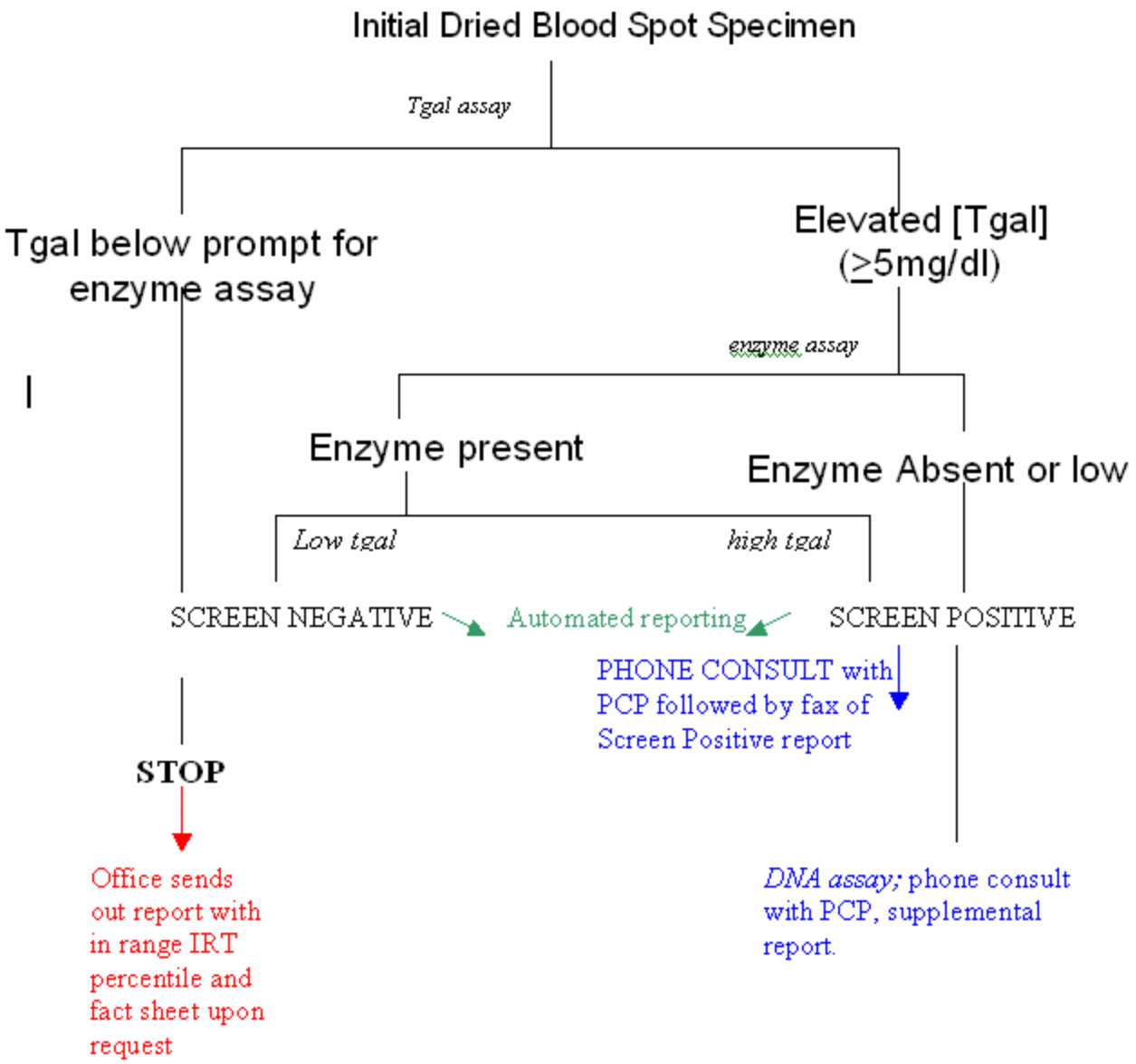
Galactosemia

Supplemental just-in-time

Galactosemia Reporting Overview



New England Newborn Screening Program University of Massachusetts Medical School
305 South Street, Jamaica Plain, MA 02130
Telephone: 617-983-6300 Fax: 617-522-2846

Result from Assays for
DNA MUTATIONS that may be associated with GALACTOSEMIA

Report Date: [redacted]
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER GALACTOSEMIA		Result Two mutations detected
Details for genetic counseling	Name of the first mutation detected by the screen	**Q188R**
	Name of second mutation detected by the screen	**Q188R**

INTERPRETATION:

- **"Positive Newborn Biochemical Screen" with "two mutations"**
- **consistent with CLASSICAL GALACTOSEMIA**
  Two mutations in the gene for the enzyme galactose-1-phosphate uridyl transferase (GALT or UT) were detected*. Observation of this genotype is consistent with severe impairment of the GALT enzyme and classical galactosemia.

RECOMMENDED ACTION:
All infants with specimens showing a "Screen Positive with Two Mutations" result should be 'in the care of' or 'referred immediately' to a Metabolic Specialist for diagnostic evaluation and treatment.

Attention Health Care Provider: Newborn screening tests are intended to provide an early opportunity to detect disorders before symptoms appear. These tests are not diagnostic.

*ASR: Analyte Specific Reagent that includes assays for detection of Q188R, N314D, S135L, K285N, L195P, Y209C, F171S, T138M and IVS2-2A>G. For screening purposes, detection of 2 mutations assumes that the mutations are in trans; diagnostic testing is indicated. This test has not been cleared or approved by the FDA. However, the New England Newborn Screening Program determined the performance characteristics of the test. The FDA has determined that its clearance and approval are not required for the NENSP-specific uses.

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Result from Assays for
DNA MUTATIONS that may be associated with GALACTOSEMIA

Report Date: [redacted]
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER GALACTOSEMIA		Result Two mutations detected
Details for genetic counseling	Name of the first mutation detected by the screen	**Q188R**
	Name of second mutation detected by the screen	**Q188R**

INTERPRETATION:

- **"Positive Newborn Biochemical Screen" with "two mutations"**
- **consistent with CLASSICAL GALACTOSEMIA**
  Two mutations in the gene for the enzyme galactose-1-phosphate uridyl transferase (GALT or UT) were detected*. Observation of this genotype is consistent with severe impairment of the GALT enzyme and classical galactosemia.

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Result from Assays for DNA MUTATIONS that may be associated with GALACTOSEMIA

Report Date: [redacted]
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER GALACTOSEMIA		Result Two mutations detected
Details for genetic counseling	Name of the first mutation detected by the screen	**Q188R**
	Name of second mutation detected by the screen	**Q188R**

INTERPRETATION:

- **"Positive Newborn Biochemical Screen" with "two mutations"**
- **consistent with CLASSICAL GALACTOSEMIA**
  Two mutations in the gene for the enzyme galactose-1-phosphate uridyl transferase (GALT or UT) were detected*. Observation of this genotype is consistent with severe impairment of the GALT enzyme and classical galactosemia.

RECOMMENDED ACTION:

All infants with specimens showing a "Screen Positive with Two Mutations" result should be 'in the care of' or 'referred immediately' to a Metabolic Specialist for diagnostic evaluation and treatment.

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Result from Assays for
DNA MUTATIONS that may be associated with GALACTOSEMIA

Report Date:
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER GALACTOSEMIA		**Result** One mutation and one DNA variant detected by the screen
Details for genetic counseling	Name of mutation detected by screen	**Q188R**
	Name of DNA variant detected by the screen	**N314D**

INTERPRETATION and RECOMMENDED ACTION

"Positive Newborn Biochemical Screen" with "one mutation and one variant"

- **consistent with DUARTE phenotype Galactosemia**
- One mutation and one variant in the gene for the enzyme galactose-1-phosphate uridyl transferase (GALT or UT) were detected*. Observation of this compound heterozygote is consistent with medium to low activity of the GALT / UT enzyme and a mild (Duarte) form of the disorder, but
- The presence of other mutations or other blocks in the galactose metabolic pathway have not been ruled out by this assay.
- *DNA results do not alter the interpretation of biochemical results. In addition to any recommendations that are based on the infant's biochemical results, the infant's family should be offered genetic counseling.*

Attention Health Care Provider: Newborn screening tests are intended to provide an early opportunity to detect disorders before symptoms appear. These tests are not diagnostic.

*ASR: Analyte Specific Reagent that includes assays for detection of Q188R, N314D, S135L, K285N, L195P, Y209C, F171S, T138M and IVS2-2A>G. For screening purposes, detection of one mutation and one sequence variant assumes that they are in trans. This test has not been cleared or approved by the FDA. However, the New England Newborn Screening Program determined the performance characteristics of the test. The FDA has determined that its clearance and approval are not required for the NENSP-specific uses.

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Result from Assays for
DNA MUTATIONS that may be associated with GALACTOSEMIA

Report Date:
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER GALACTOSEMIA		**Result** One mutation and one DNA variant detected by the screen
Details for genetic counseling	Name of mutation detected by screen	**Q188R**
	Name of DNA variant detected by the screen	**N314D**

INTERPRETATION and RECOMMENDED ACTION:
"Positive Newborn Biochemical Screen" with "one mutation and one variant"

- **consistent with DUARTE phenotype Galactosemia**
- One mutation and one variant in the gene for the enzyme galactose-1-phosphate uridyl transferase (GALT or UT) were detected*. Observation of this compound heterozygote is consistent with medium to low activity of the GALT / UT enzyme and a mild (Duarte) form of the disorder, but
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Result from Assays for
DNA MUTATIONS that may be associated with GALACTOSEMIA

Report Date: [redacted]
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER	RESULT
GALACTOSEMIA	No mutations or variants detected by the screen

INTERPRETATION and RECOMMENDED ACTION:
"Positive Newborn Biochemical Screen" with "no mutation or variant"
DNA findings do not alter interpretation of biochemical results

- Of the eight mutations and one sequence variant assayed, none were observed in the gene for the enzyme galactose-1-phosphate uridyl transferase (GALT or UT) *. Observation of this genotype is consistent with normal enzyme activity but
- *The presence of other mutations in GALT or other blocks in the galactose metabolic pathway have not been ruled out by this assay.*
- Follow any recommendations that are based on the infant's biochemical results.

Attention Health Care Provider: Newborn screening tests are intended to provide an early opportunity to detect disorders before symptoms appear. These tests are not diagnostic.

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Result from Assays for
DNA MUTATIONS that may be associated with GALACTOSEMIA

Report Date: [redacted]
Lab ID# of baby: [redacted]
Name of baby: [redacted] Date of birth: [redacted]
Name of mother: [redacted]

TARGETED DISORDER	RESULT
GALACTOSEMIA	No mutations or variants detected by the screen

INTERPRETATION and RECOMMENDED ACTION:
"Positive Newborn Biochemical Screen" with "no mutation or variant"
DNA findings do not alter interpretation of biochemical results

- Of the eight mutations and one sequence variant assayed, none were observed in the gene for the enzyme galactose-1-phosphate uridyl transferase (GALT or UT) *. Observation of this genotype is consistent with normal enzyme activity but
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DNA testing in 1st Tier NBS

data generated prior to full diagnostic evaluation

- Enhance sensitivity for conditions not otherwise included...

  TREC assay for SCID: First Tier molecular

- Enhance specificity of 1st tier test....CFTR mutation assay after IRT: Second Tier molecular

- Supplemental just in time

(unconventional quantitative)

Increase available information to aid diagnostic evaluation…

GALT mutation assay: Second Tier molecular

SCID Testing and Follow up Algorithms

Regardless of purpose, the DNA target might be

A specific allele

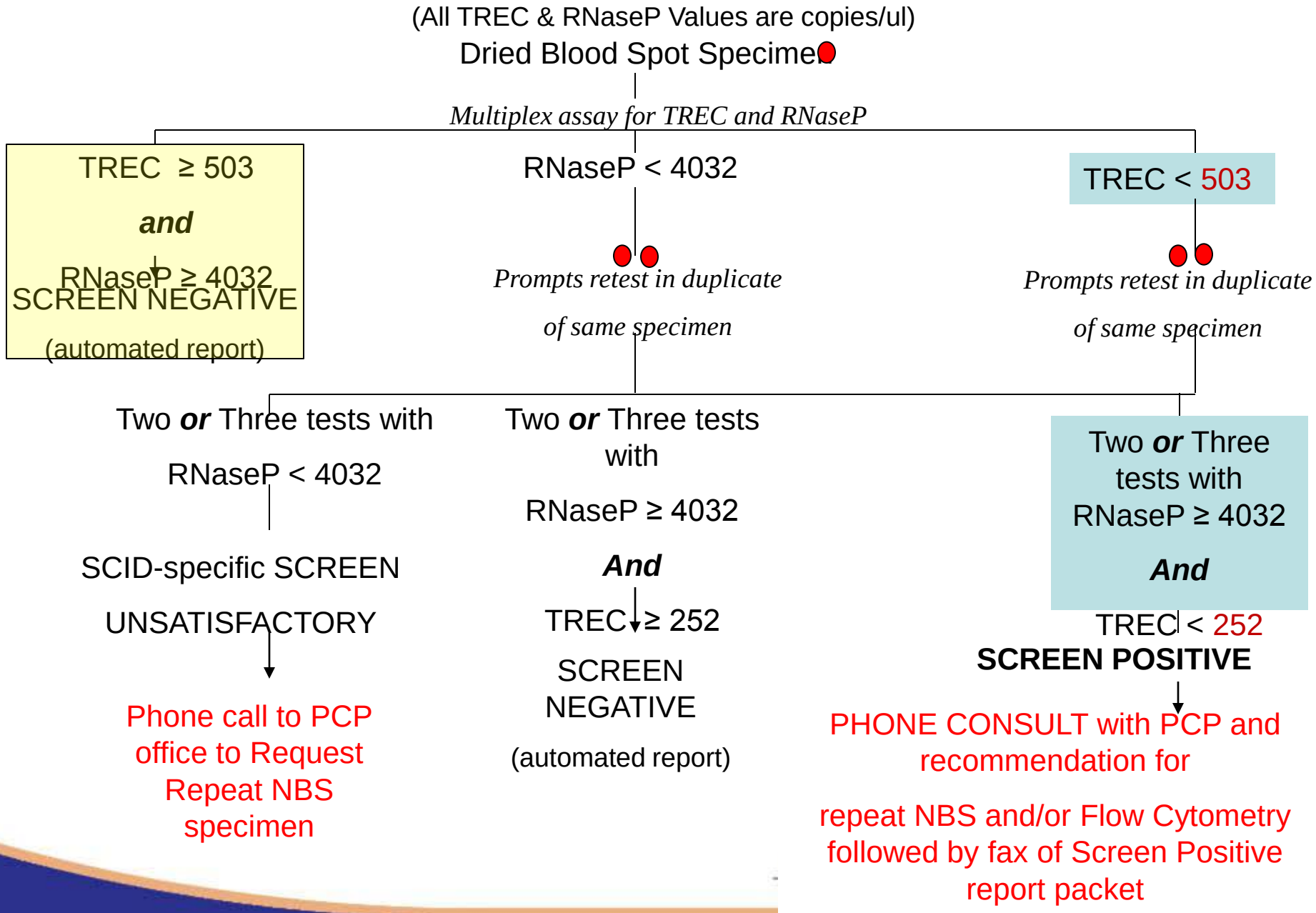
A specific structure

A foreign element

Qualitative or Quantitative

And ABSENCE!

Massachusetts' SCID NBS **Laboratory Testing** Algorithm



In range report

NEWBORN SCREENING TEST REPORT (Initial Blood Filter Paper Specimen)

Targeted Congenital Disorders / Analyte Tested	Results Within Range	Results Out of Range	Reference Range (for newborns)
Adrenal Hyperplasia(CAH) / 17-OH-Progesterone	<13.5 ng/mL		<25 ng/mL(weight dependent)
*Biotinidase Deficiency / Biotinidase	>=30%		>=30%
Cystic Fibrosis / IRT PERCENTILE	71.4%		<95.1%
*Galactosemia / Galactose,Total	2.9 mg/dL		<14 mg/dL
*Hemoglobinopathies / Hemoglobin Isoelectric Focusing	FA		FA, AF, or A
*Homocystinuria / Methionine	<1.5 mg/dL		< 1.5 mg/dL
Hypothyroidism / Thyroid-Stimulating Hormone	2.7 uU/mL		< 15 uU/mL (age dependent)
Hypothyroidism (CH) / Thyroxine	12.9 ug/dL		>5.0 ug/dL
*Maple Syrup Urine Disease (MSUD) / Leucine	<=4.5 mg/dL		<= 4.5 mg/dL
*MCAD / Octanoylcarnitine	<0.80 uM		<0.80 uM
*Phenylketonuria (PKU) / Phenylalanine (PHE)	<=2.3 mg/dL		<= 2.3 mg/dL
*SCID/TREC	715 copies/uL		>=252 copies/uL
*Toxoplasma Infection / Toxoplasma IgG	0.023 O.D.		<0.1 OD
*^Metabolic / MET SUPP 01 Panel	All in Range		All in Range

^Met Supp 01 Panel:

Amino Acid- TYR, (also CIT II)
Urea Cycle- ARG, ASA, CIT, CPS, HHH, OTC
FAOD- CPT II, CUD, LCHAD, VLCAD, M/SCHAD, DE-RED (also CACT, GA2, MCKAT, SCAD, TFP)
Organic Acid- BKT, Cbl Defects,CPT1A, GA1, HMG, IVA , MAL, MUT, PROP, (also IBG, 2M3HBA, 2MBG, 3MCC,MCD, 3MGA)

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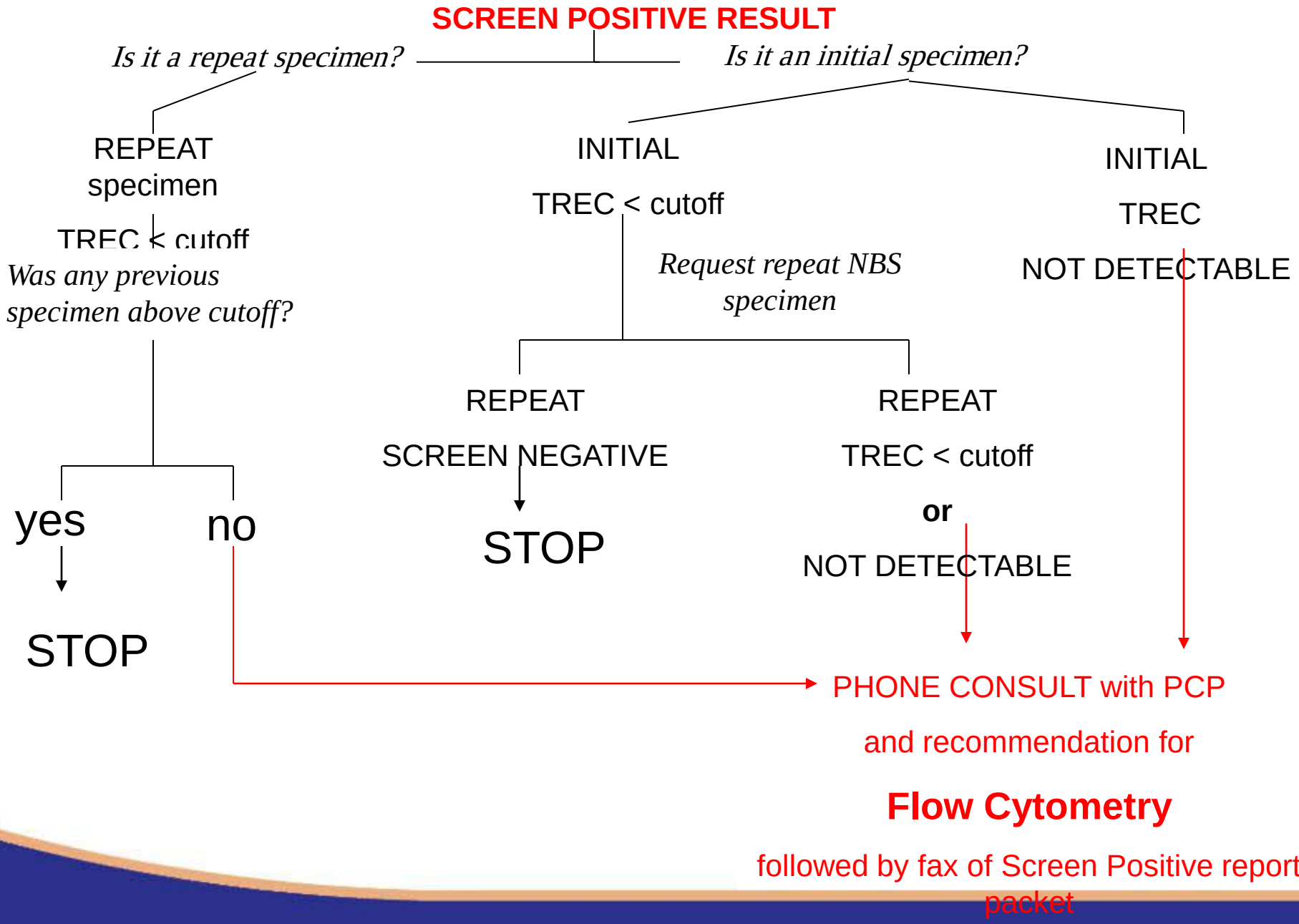
Tests Performed by New England Newborn Screening Program, 305 South Street, Jamaica Plain, MA 02130 Roger Eaton, Ph.D., Director.

Please contact the Newborn Screening Program at 617-983-6300 if you have any questions or clinical concerns.

Massachusetts' SCID NBS **Interpretation and Notification** Algorithm

Effective as of 2009/10



Out of range report

NEWBORN SCREENING TEST REPORT (Initial Blood Filter Paper Specimen)

Targeted Congenital Disorders / Analyte Tested	Results Within Range	Results Out of Range	Reference Range (for newborns)
Adrenal Hyperplasia(CAH) / 17-OH-Progesterone	<13.5 ng/mL		<45 ng/mL(weight dependent)
*Biotinidase Deficiency / Biotinidase	>=30%		>=30%
Cystic Fibrosis_SCREEN	IN RANGE ~		IN RANGE
*Galactosemia / Galactose,Total	<=2 mg/dL		<14 mg/dL
*Hemoglobinopathies / Hemoglobin Isoelectric Focusing	FA		FA, AF, or A
*Homocystinuria / Methionine	<1.5 mg/dL		< 1.5 mg/dL
Hypothyroidism / Thyroid-Stimulating Hormone	10.8 uU/mL		< 20 uU/mL (age dependent)
Hypothyroidism (CH) / Thyroxine	10.6 ug/dL		>5.0 ug/dL
*Maple Syrup Urine Disease (MSUD) / Leucine	<=4.5 mg/dL		<= 4.5 mg/dL
*MCAD / Octanoylcarnitine	<0.80 uM		<0.80 uM
*Phenylketonuria (PKU) / Phenylalanine (PHE)	<=2.3 mg/dL		<= 2.3 mg/dL
*SCID/TREC		<252 copies/uL	>=252 copies/uL
*Toxoplasma Infection / Toxoplasma IgG	0.000 O.D.		<0.1 OD
*^Metabolic / MET SUPP 01 Panel	All in Range		All in Range

Another blood filter paper specimen should be obtained and submitted to this laboratory for testing immediately. There is no charge for this servic

^Met Supp 01 Panel:

Amino Acid- TYR, (also CIT II)
Urea Cycle- ARG, ASA, CIT, CPS, HHH, OTC
FAOD- CPT II, CUD, LCHAD, VLCAD, M/SCHAD, DE-RED (also CACT, GA2, MCKAT, SCAD, TFP)
Organic Acid- BKT, Cbl Defects,CPT1A, GA1, HMG, IVA , MAL, MUT, PROP, (also IBG, 2M3HBA, 2MBG, 3MCC,MCD, 3MGA)

~ None of Tag-It 39+4 mutations detected.

* This test has not been cleared or approved by the FDA. However, the test was developed and its performance characteristics determined by the New England Newborn Screening Program, and the FDA has determined that its clearance and approval are not required.

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Tests Performed by New England Newborn Screening Program, 305 South Street, Jamaica Plain, MA 02130 Roger Eaton, Ph.D., Director.

Please contact the Newborn Screening Program at 617-983-6300 if you have any questions or clinical concerns.

First OOR, copies detected

New England Newborn Screening Program

ACTION SHEET

for Primary Care Provider

INTERPRETATION OF NEWBORN SCREENING REPORT:

Your patient has a positive (Out of Range) result from SCID NBS. This means that the infant may be at increased risk for SCID.

- **TREC < 252 copies/ul**

We are requesting a **new filter paper specimen.** This will help us to determine whether the finding reflects a transient immunologic status or one that would prompt further evaluation.

RECOMMENDED NEXT STEPS BY PRIMARY CARE PHYSICIAN:

- Contact family. Report positive newborn screening result.
  - Well infants may stay at home safely during preliminary diagnostic testing as they have some protection from maternal antibodies.
  - *Infants with congenital or neonatal infections should be immediately evaluated by a specialist at one of the participating centers.*
- Obtain a repeat newborn screening specimen (filter paper) and send to NENSP.

Prompts for Referral to Flow Cytometry

- Undetectable TREC on initial NBS specimen
- Two out of range TREC results (<252 copies/ul) from two independent NBS specimens in the absence of a normal TREC result

  if a subsequent specimen has a normal TREC result prior to flow cytometry being done, then the recommendation for flow cytometry will be withdrawn in the absence of clinical concerns (helpful in NICU)

- Persistent SCID-specific unsatisfactory result due to failed amplification of RNaseP and assurance of good collection

NEWBORN SCREENING TEST REPORT (Initial Blood Filter Paper Specimen)

Targeted Congenital Disorders / Analyte Tested	Results Within Range	Results Out of Range	Reference Range (for newborns)
Adrenal Hyperplasia(CAH) / 17-OH-Progesterone	<13.5 ng/mL		<45 ng/mL(weight dependent)
*Biotinidase Deficiency / Biotinidase	>=30%		>=30%
Cystic Fibrosis_SCREEN	IN RANGE ~		IN RANGE
*Galactosemia / Galactose,Total	<=2 mg/dL		<14 mg/dL
*Hemoglobinopathies / Hemoglobin Isoelectric Focusing	FA		FA, AF, or A
*Homocystinuria / Methionine	<1.5 mg/dL		< 1.5 mg/dL
Hypothyroidism / Thyroid-Stimulating Hormone	10.8 uU/mL		< 20 uU/mL (age dependent)
Hypothyroidism (CH) / Thyroxine	10.6 ug/dL		>5.0 ug/dL
*Maple Syrup Urine Disease (MSUD) / Leucine	<=4.5 mg/dL		<= 4.5 mg/dL
*MCAD / Octanoylcarnitine	<0.80 uM		<0.80 uM
*Phenylketonuria (PKU) / Phenylalanine (PHE)	<=2.3 mg/dL		<= 2.3 mg/dL
*SCID/TREC		<252 copies/uL	>=252 copies/uL
*Toxoplasma Infection / Toxoplasma IgG	0.000 O.D.		<0.1 OD
*^Metabolic / MET SUPP 01 Panel	All in Range		All in Range

Another blood filter paper specimen should be obtained and submitted to this laboratory for testing immediately. There is no charge for this servic

^Met Supp 01 Panel:

Amino Acid- TYR, (also CIT II)
Urea Cycle- ARG, ASA, CIT, CPS, HHH, OTC
FAOD- CPT II, CUD, LCHAD, VLCAD, M/SCHAD, DE-RED (also CACT, GA2, MCKAT, SCAD, TFP)
Organic Acid- BKT, Cbl Defects,CPT1A, GA1, HMG, IVA , MAL, MUT, PROP, (also IBG, 2M3HBA, 2MBG, 3MCC,MCD, 3MGA)

~ None of Tag-It 39+4 mutations detected.

* This test has not been cleared or approved by the FDA. However, the test was developed and its performance characteristics determined by the New England Newborn Screening Program, and the FDA has determined that its clearance and approval are not required.

Attention Health Care Provider: Newborn screening tests are intended to provide an early opportunity to detect disorders before symptoms appear. These tests are not diagnostic. Regardless of screening test results, a physician should immediately evaluate any infant who exhibits findings consistent with the targeted disorders noted above.

Tests Performed by New England Newborn Screening Program, 305 South Street, Jamaica Plain, MA 02130 Roger Eaton, Ph.D., Director.

Please contact the Newborn Screening Program at 617-983-6300 if you have any questions or clinical concerns.

Notification of need for flow

New England Newborn Screening Program

ACTION SHEET

for Primary Care Provider

INTERPRETATION OF NEWBORN SCREENING REPORT:

Your patient has a positive (Out of Range) result from SCID NBS. This means that the infant is at increased risk for SCID.

- ***TREC < 252 copies/ul***

Your patient requires a specially designed flow cytometry blood test. Note that particular laboratories have pre-qualified for the testing. Note also that the type and scheduling of blood collection must follow specific instructions to ensure that the appropriate blood arrives at the pre-qualified laboratory in time for processing. If the blood is too old by the time it arrives at the lab, another blood specimen will be required.

RECOMMENDED NEXT STEPS BY PRIMARY CARE PHYSICIAN:

- Contact family. Report positive newborn screening result.
  - Well infants may stay at home safely during preliminary diagnostic testing as they have some protection from maternal antibodies.
  - ***Infants with congenital or neonatal infections should be immediately evaluated by a specialist at one of the participating centers.***
- Obtain a repeat newborn screening specimen (filter paper) and send to NENSP.
- Obtain "Preliminary Diagnostic Test for Well Infants with Out-of-Range Newborn Screening Result for SCID" *see page 5*

Basic Facts about Severe Combined Immunodeficiency (SCID)

SCID is the name of a spectrum of Primary Immunodeficiencies. These immunodeficiencies are characterized by severe defects in cellular and humoral immunity and comprise > 15 independent genetic conditions.

Natural history, treatments and outcomes

- If untreated, SCID results in near uniform mortality by age 1.
  - The most common presenting symptoms are recurrent severe infections, chronic diarrhea, and failure to thrive.
  - Infants with SCID are particularly susceptible to complications from routine infant vaccinations with live virus vaccines.
  - Without NBS, the average age at diagnosis is 6 months.
  - Without NBS, infants with SCID are likely to miss the opportunity for early diagnosis and early treatment.
- SCID *can be cured* by Hematopoietic Stem Cell Transplantation (HSCT).
  - Transplant prior to the onset of severe infections yields the most promising outcomes.
  - Infants diagnosed with SCID immediately after birth have the best chance of survival and fewer medical complications after transplant compared to those diagnosed after clinical presentation.

Incidence and risk factors

- The true incidence of SCID is unknown; a conservative estimate is 1/100,000 births.
- SCID can occur in all ethnic groups.
- Infants with a family history of SCID are at high risk; family history is not required though, for an infant to have SCID.

Genetics and Immunology

- The most common form of SCID is X-linked, but there are also multiple autosomal recessive forms.
- Infants with SCID universally have extremely low or absent T cells.
- Infants with SCID may or may not have B cells; if present B cells are non-functioning.
- Infants with SCID may or may not have Natural Killer (NK) cells.

Components of the NENSP SCID Newborn Screening Program

The NENSP SCID Newborn Screening Program includes the following components: screening tests, preliminary diagnostic tests, diagnostic evaluation, treatment, and program evaluation. All infants with Out of Range Newborn Screening results need to have a repeat newborn screen. Only some infants will need the additional workups outlined in steps 2, 3, and 4.

1. **Screening Tests performed on the dried blood spot:**
   The principal test is quantification of a marker that indicates presence of autologous T cells, the "T cell Receptor Excision Circle" (TREC). This is a molecular marker detectable by quantitative PCR. Low or absent quantities of TRECs observed in the screen indicate a possible severe defect in the ability to generate T lymphocytes.
   - As with other screening tests, some values will prompt a request for a repeat specimen.
   - As with other screening tests, some values will prompt a preliminary diagnostic test directly.

2. **Preliminary Diagnostic test performed on specially-collected whole blood:**
   The principal test is a Flow Cytometry test to measure specific T cell markers. Laboratories will have to be pre-qualified to perform these measurements. Measurements indicating low to absent T cell markers confirm a T-cell lymphocytopenia that requires a diagnostic evaluation by a specialist.
   Note: The presence of T lymphocytes alone does not rule out SCID; specialized testing to detect newly generated T lymphocytes must be performed.

3. **Diagnostic Evaluation:**
   The diagnostic evaluation is a specialty referral inclusive of physical exam and specialized immune function tests. Infants whose evaluation yields a diagnosis of SCID will require immediate treatment. In many cases this will be Hematopoietic Stem Cell Transplantation (HSCT). Infants may be found to have other immune deficiencies, such as DiGeorge syndrome, which requires different treatment (thymic transplant), other primary immune deficiencies requiring a spectrum of preventative treatments or may be found to be well.

4. **Treatment:**
   SCID infants may be enrolled for HSCT at a pediatric FACT (Foundation for the Accreditation of Cellular Therapy)-accredited center.

5. **Program Evaluation:**
   Predictive values of the screening algorithm, yields of SCID and other Primary Immunodeficiency Diagnoses, compliance with recommendations, and short and long-term treatment outcomes will be analyzed for quality assurance and quality improvement of the program.

UMASS

For Parents and Families

My baby had a positive SCID Newborn Screening Test

What is SCID Newborn Screening? SCID newborn screening helps to find babies who might have Severe Combined Immunodeficiency (SCID) so that they can be treated. SCID babies have very little or no immune system. Babies with SCID who are found early can be treated early.

What does my baby's positive SCID newborn screening test mean? It means that your baby needs a special test to find out if your baby has SCID. The special test is called *flow cytometry*.

Where do I get a flow cytometry test for my baby? Your baby's healthcare provider has a list of laboratories that can perform this test.

How is the flow cytometry test done? Flow cytometry is a special blood test. Your baby's healthcare provider will arrange for some blood to be taken from your baby for the test.

Do I need to do anything to prepare my baby for the flow cytometry test? No

How will I know the results of the flow cytometry test? Your baby's healthcare provider will contact you with the results and will let you know if any more tests are needed.

What do I do while I wait for the test results? There is nothing special that you need to do. Just as you would for any newborn, you will want to keep your newborn from contact with people who are known to have a contagious illness and keep your newborn out of crowded environments.

What do I do if a family member is sick? As with any newborn, if an immediate family member is sick, strict hand washing before touching the baby is key to preventing illness.

When I have the results of my baby's flow cytometry test, will I know if my baby has SCID? You will know if your baby is no longer considered to be at risk, if your baby needs to have additional tests, or if your baby needs to see a special doctor.

Where can I get more information? The best source of information about your baby's results and your baby's condition is your baby's healthcare provider. Information from your baby's healthcare provider will be more helpful to you than general information. There is an NIH website with reliable general information:

http://www.genome.gov/13014325

If you choose to look at this website, please keep in mind that your baby does not yet (and may not ever) carry a diagnosis. Thus the general information may not apply to your baby.

interpretation multiple specimens

ACTION SHEET

for infants with multiple specimens compromising both normal and abnormal SCID NBS results

Infant Name_____

Your patient has a positive (Out of Range) result from SCID NBS. This means that the infant may be at increased risk for Severe Combined Immunodeficiency (SCID).

- **TREC < 252 copies/ul**

  TRECs (T cell Receptor Excision Circles) are the principal marker for SCID newborn screening. This is a molecular marker detectable by quantitative PCR. Low or absent quantities of TRECs observed in the screen indicate a possible severe defect in the ability to generate T lymphocytes.

Note1: Our records show that your patient had an independent specimen with a SCID NBS result that was within normal limits. In this context (and in the absence of no specific clinical concern for SCID) our Program does not recommend further action relative to the SCID NBS results reported with this action sheet.

Note2: Out of Range (Low) TREC results have been observed on specimens from non-SCID infants when the specimens were obtained post-thymectomy (as is often the case post cardiac surgery).

Note3: Some infants who have had cardiac surgery and who also show low TRECs might fall within the spectrum of DiGeorge Syndrome.

We remind clinicians that the SCID NBS algorithm is not a diagnostic test and if you have clinical concerns that could be consistent with SCID, we encourage you to arrange a pediatric immunology consult.

Prompts for Referral to Flow Cytometry

- Undetectable TREC on initial NBS specimen
- Two out of range TREC results (<252 copies/ul) from two independent NBS specimens in the absence of a normal TREC result

  if a subsequent specimen has a normal TREC result prior to flow cytometry being done, then the recommendation for flow cytometry will be withdrawn in the absence of clinical concerns (helpful in NICU)

- Persistent SCID-specific unsatisfactory result due to failed amplification of RNaseP and assurance of good collection

Educational Supplements

Educational Supplements

Manner of reporting

- for primary care providers

  - Provide general description of disease and current knowledge about heredity and mutations

  - Explain where DNA testing falls within NBS algorithm

  - Relate relative risks specific to result.

Educational Supplements

Manner of reporting

For specialty care providers

- Alerts to new mutation panels

For families

- What does this mean
- What do I have to do
- Are there special preparations

Basic Facts about Cystic Fibrosis (CF)

- CF is the most common disorder of autosomal recessive inheritance in Caucasians.
- In general, it occurs in 1/3000 Caucasian, 1/10,000 Hispanic, 1/20,000 African-American, and 1/30,000 Asian-American births.
- Only 15% CF patients have neonatal clinical presentation with bowel obstruction (most commonly meconium ileus). Note that 80-90% infants presenting with meconium ileus have CF.
- Of the remaining 85% of CF patients, 50% would be diagnosed by 14 months without NBS.
- In Massachusetts, 80% of all CF patients would be diagnosed by age 5 years without NBS.
- The most common presenting symptoms are malabsorption diarrhea (due to pancreatic insufficiency) and failure to thrive, recurrent and chronic pulmonary problems, or a combination of both.
- CF pathophysiology is due to Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene mutations (over 1,200 reported). The most common mutation is ΔF508. Abnormal CFTR protein disrupts chloride transport and water movement across secretory epithelial membranes.
- Abnormal secretions in pancreatic ducts, airways, intestines and vas deferens lead to blocked lumens, organ injury and dysfunction.
- Abnormal lung secretions lead to chronic respiratory tract infections with *S. aureus* and *P. aeruginosa*
- High sweat chloride concentration (≥60 mEq/L) results from abnormal epithelial cells in sweat glands. Pilocarpine iontophoresis (Sweat Test) is the gold standard for diagnosis. DNA testing that reveals two CFTR mutations is also diagnostic.

Components of the NENSP CF Newborn Screening Program

The CF newborn screen may include up to three components:
1. ***Level of serum trypsinogen (IRT),*** a pancreatic enzyme that is elevated in the serum of most CF-affected newborns. Samples with values above the 95th percentile will proceed to *DNA assay (part 2).*
2. ***DNA assay,*** for detection of any of 39 common CFTR gene mutations and when appropriate, 4 DNA variants. Detection of one or more of CFTR mutations will result in newborns being referred for *sweat testing* at a CFF Center (*part 3*)
3. ***Sweat Test*** *(Pilocarpine iontophoresis),* for determination of sweat chloride concentration. Sweat chloride concentration ≥ 60 mEq/L suggests a diagnosis of CF. Borderline results (30 - 59 mEq/L) or inadequate sweat quantity for analysis (QNS) may prompt repeat testing.

The NENSP brochure, *Answers to common questions about newborn screening (*available in 9 languages), describes information about all disorders included in newborn screening. This information is also available on the Program's web site (www.umassmed.edu/nbs/).

New England Newborn Screening Program

CYSTIC FIBROSIS NEWBORN SCREENING INFORMATION SHEET

for Primary Care Provider

INTERPRETATION of CF Newborn Screening (CF NBS) result:
*Your patient has a positive **(out of range)** CF newborn screening result.*

This means that the infant is at increased risk for Cystic Fibrosis (CF). The specific risk is dependent on the exact category of positive screen as indicated below.

- **2 Mutations**: IRT >95th percentile and two mutations were detected. The infant most likely has CF.

- **1 Mutation**: IRT >95th percentile and one mutation was detected. The infant has about a 1/30 chance of CF.
  - Infants with "1 Mutation" results who are then shown to have CF have a second mutation that is not included in the screen.
  - Infants with "1 Mutation" results whose diagnostic test shows them to be unaffected are carriers.

RECOMMENDED NEXT STEPS BY PRIMARY CARE PHYSICIAN:

- If you have not already been contacted by the NENSP, call 617-983-6300 and ask for CF follow up. Additional information will be provided to you.
- Contact family. Report positive newborn screening result and refer infant for diagnostic sweat test (with parent genetic counseling if a mutation was detected)
- Contact CF Center. Schedule sweat test; when scheduling, indicate that the referral is because of a positive newborn screening result.

Note: There is no age-specific criteria for sweat testing. Ideally, infants will have attained a weight of 2 kilograms prior to the sweat test. The likelihood that the sweat test result on a young infant will be complete is very good. QNS rates vary by center but in general, more than 90% infants should have valid test results after one visit.

Expected number of referrals and case detections:

(estimates based on 100% participation)

- Each day, 1 screened baby will be referred for sweat testing (250 babies/year)
- Each year, 25 – 40 babies with CF will be identified
- A baby referred with a *POSITIVE screening* result has a 1/11 chance of having CF (risk is category dependent- see below)

Limitations of CF Newborn Screening

CF newborn screening has limitations. Keep in mind that this screening algorithm is **not a diagnostic test.** No screening algorithm is perfect in its ability to detect all affected individuals while also producing no false positive results.

We anticipate that 1 CF affected baby per year may not be detected by this screen (i.e., would have a *FALSE NEGATIVE* CF newborn screening result) and will present later in life with CF symptoms. **A sweat test remains clinically indicated for evaluation of any child with symptoms suspicious for CF.** Clinicians at the NENSP and CF centers will remain available to consult on such clinical scenarios.

For Parents and Families

My baby had a positive CF Newborn Screening Test

What is CF Newborn Screening? CF newborn screening tests help to find babies who might have cystic fibrosis. Most babies with positive newborn screening tests do not have CF. Babies who do have CF and who are found early can be treated early.

What does my baby's positive CF newborn screening test mean? It means that your baby needs a special test so that you can know if your baby has CF. The special test is called a *sweat test*.

Where do I get a sweat test for my baby? We recommend that experts at a CF Center do the sweat testing. At a CF Center, staff members know how to do the test on young babies. In addition, there will be support staff at the Center who may be able to provide you with genetic counseling about your baby's CF newborn screening test or who will be able to help if the sweat test result is not clear.

I had a negative CF blood test when I was pregnant. Does my baby still need a sweat test? Yes. Any baby whose newborn screening result is positive should have a sweat test.

How is the sweat test done? The sweat test is simple and should not hurt your baby. If you yourself had a sweat test, your skin might feel warm and tingly for about five minutes during the test. Before the test, the technician will apply a chemical that causes sweating to a small area on your baby's arm or leg. Then, an electrode is attached to stimulate a weak electrical current. Your baby's sweat is collected on a piece of filter paper or in a plastic coil. The collected sweat is then sent to the lab and tested. It takes about one hour from start to finish.

Do I need to do anything to prepare my baby for the sweat test? Do not use any lotions or creams on your baby's arms or legs on the day of the test. Any regular medications may be continued and will have no effect on the test results. Because clinic rooms can be chilly, bring an extra blanket or sweater and hat to help keep your baby warm during the test.

How will I know the results of the sweat test? That depends on how the CF Center works. At some Centers, sweat test results are phoned to your baby's doctor at the end of the day and the your baby's doctor will contact you. At other Centers, you may have a genetic counseling appointment before you leave and sometimes the genetic counselor will report the results to you. You can ask ahead of time so that you know what to expect.

When I have the results of my baby's sweat test, will I know if my baby has CF? Most of the time the results of your baby's sweat test will clearly tell you whether your baby has CF or not. Sometimes, the sweat test will have to be repeated.

Educational Supplements

For clinical inquiries

"In Range" results reported to you in a single mailing:

Targeted congenital disorder/Analyte Tested	Results Within Range	Results Out of Range
Cystic Fibrosis/CF Percentile	a % that is ≤ 95	

Interpretation: *No DNA testing was prompted by the immunoreactive trypsinogen (IRT) result; the IRT level was ≤ 95th percentile. This in-range screening result has a negative predictive value of 99.99% for cystic fibrosis. Note that any baby with this result still has at least a 1/50 chance of being a CF carrier.*

"IN RANGE" results reported to you in a second mailing:

First mailing's result:

Targeted congenital disorder/Analyte Tested	Results Within Range	Results Out of Range
Cystic Fibrosis/CF Percentile	**~ PENDING – FINAL REPORT WILL FOLLOW**	

Second mailing's result:

Targeted congenital disorder/Analyte Tested	Results Within Range	Results Out of Range
Cystic Fibrosis Screen	IN RANGE~	

Interpretation: *DNA testing was performed on this specimen and no mutations were detected from our panel of common mutations. In addition, though the immunoreactive trypsinogen (IRT) was > 95th percentile, it did not meet our criteria for recommending a sweat test in the absence of observed mutations. The negative predictive value of this test is very high. However, because we do not screen for all of the >1000 mutations currently reported in the CFTR gene, there remains a very small possibility that this baby carries one or more mutations that are not included in our panel of common CFTR mutations.*

"IN RANGE" results: In range results are considered normal, and our Program recommends no further action. HOWEVER, we remind clinicians that the CF newborn screening algorithm is not a diagnostic test, and will NOT detect all CF-affected infants. IF YOU HAVE PERSISTENT CLINICAL CONCERNS that could be consistent with CF, such as poor weight gain, malabsorption stools, recurrent respiratory tract infections, recurrent respiratory symptoms such as cough or wheezing, or if you have information that both parents are carriers of CF mutations, we encourage you to consider a sweat test, which is still considered the gold standard.

Record Keeping

Record Keeping

- CLSI – store all reports for 4 years
- patient folders at hand for re-faxing to included health care providers

Record Keeping

- Short-term follow up – case or carrier?
- Mid to Long-term follow up
  - concordant with diagnostic testing?
  - completion of genetic counseling? (cc NBS)
  - Consistent with parent testing?
- Surveillance

  Communications with clinical centers for late diagnosis of false negatives