



KNOWLEDGE OPPORTUNITIES

**Anne Marie Comeau, PhD,
Deputy Director**

**New England Newborn Screening
Program**

Professor, Pediatrics

**Beyond the Bloodspot:
Technology Impact on Clinical Care
Washington DC 2013**

Thank You's

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Jaime Hale Jacalyn Thompson

Michele Caggana

Mei Baker

Mike Glass

Susan Tanksley

Jelili Ojodu Elizabeth Jones

Suzanne Cordovado, Marie Earley, Francis Lee

Carla Cuthbert



Newborn Screening is ...

a public health program that
provides an opportunity for early
identification and early treatment
of infants with conditions that
otherwise would go unrecognized
prior to irreversible clinical damage.

**newborn
screening**

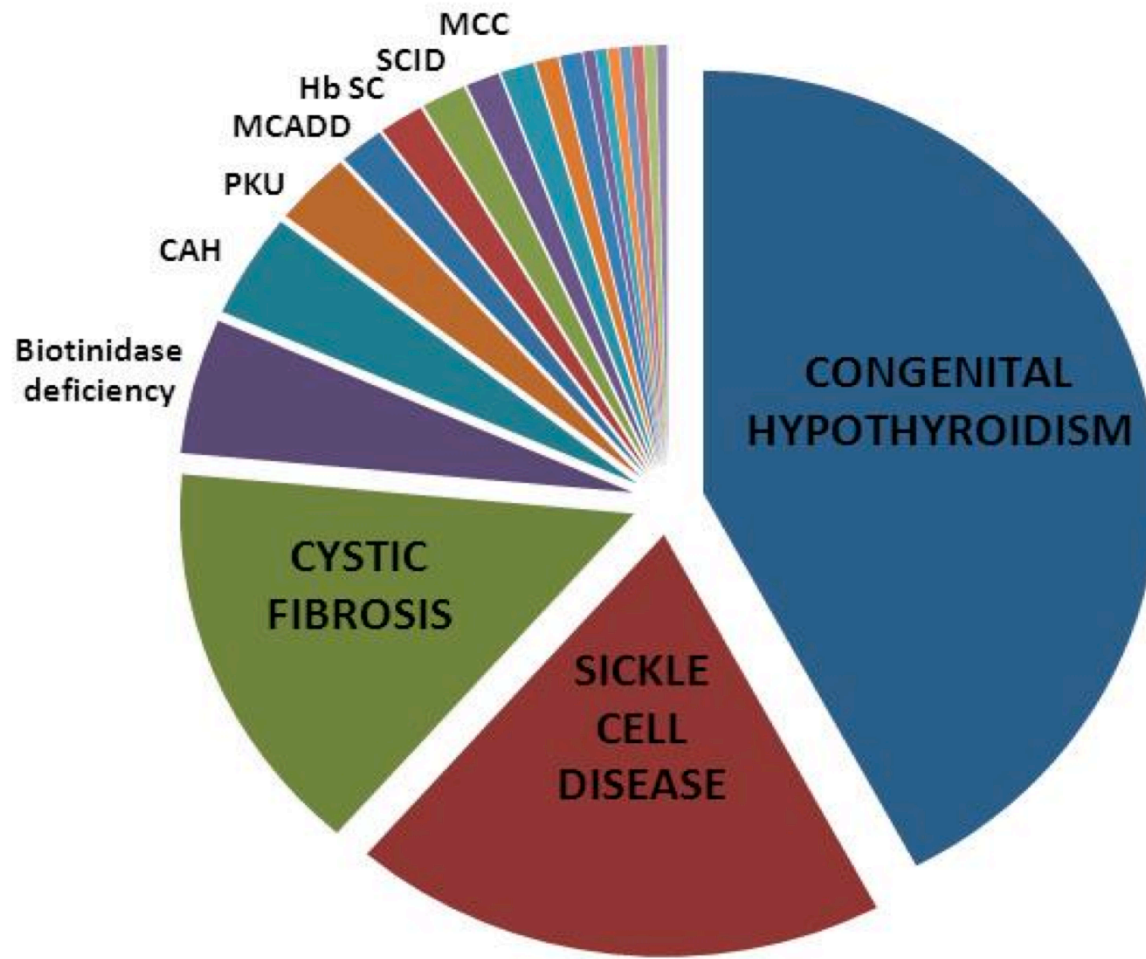
**next-gen
sequencing**

**KNOWLEDGE
OPPORTUNITIES**

**next-gen
sequencing**

**newborn
screening**

Relative Proportions of Infants Identified by Newborn Screening



Texas Newborn Screening Laboratory

8 plates are distributed to
5 areas to test for
29 disorders.



Hemoglobinopathy Screening:

One test is used to identify:

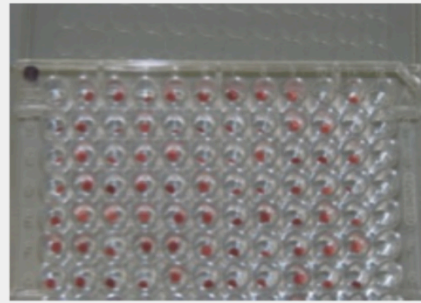
Sickle Cell Anemia
Sickle Hemoglobin C Disease
Sickle/Beta Thalassemia Disease
Other hemoglobinopathy diseases and traits



Endocrine & Cystic Fibrosis Screening:

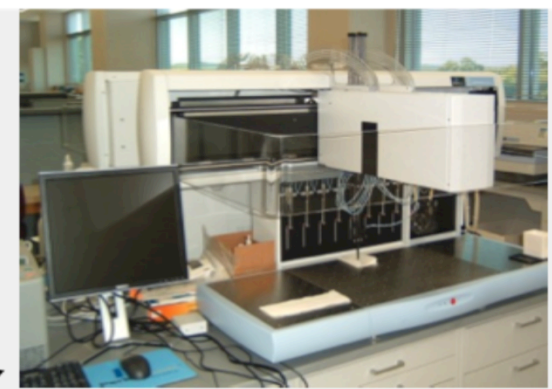
Three tests are used to identify:

Congenital Hypothyroidism
Congenital Adrenal Hyperplasia
Cystic Fibrosis



SCID Screening:

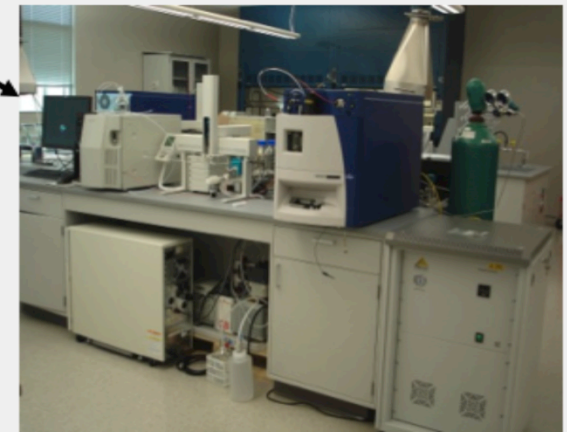
One molecular test is used to identify:
Severe Combined Immunodeficiency



Galactosemia & Biotinidase Screening:

Two tests are used to identify:

Galactosemia
Biotinidase Deficiency



Tandem Mass Spectrometry Screening:

One test is used to identify:

6 amino acid disorders (e.g. PKU)
5 fatty acid disorders (e.g. MCAD)
9 organic acid disorders (e.g. glutaric acidemia type 1)

NEWBORN SCREENING CALLS TO THE FRONTLINE OF DEFENSE



NEWBORN SCREENING CALLS TO THE FRONTLINE OF DEFENSE



EVERY 3
MINUTES:

1 high risk

6 additional
actionable

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?

Current Purposes of DNA in NBS

(data generated prior to full diagnostic evaluation)

- Enhance capacity of screening for conditions not otherwise included...

TREC assay for SCID: molecular in **FIRST TIER**

- Enhance specificity of 1st tier test....

CFTR mutation assay after IRT: molecular in **SECOND TIER**

- Supplemental just-in-time

Increase available information to aid diagnostic evaluation...

GALT mutation assay: molecular in **SECOND TIER**

Current DNA testing:

Regardless of purpose, the DNA target might be

A specific allele

A specific structure

A foreign element

Qualitative or Quantitative

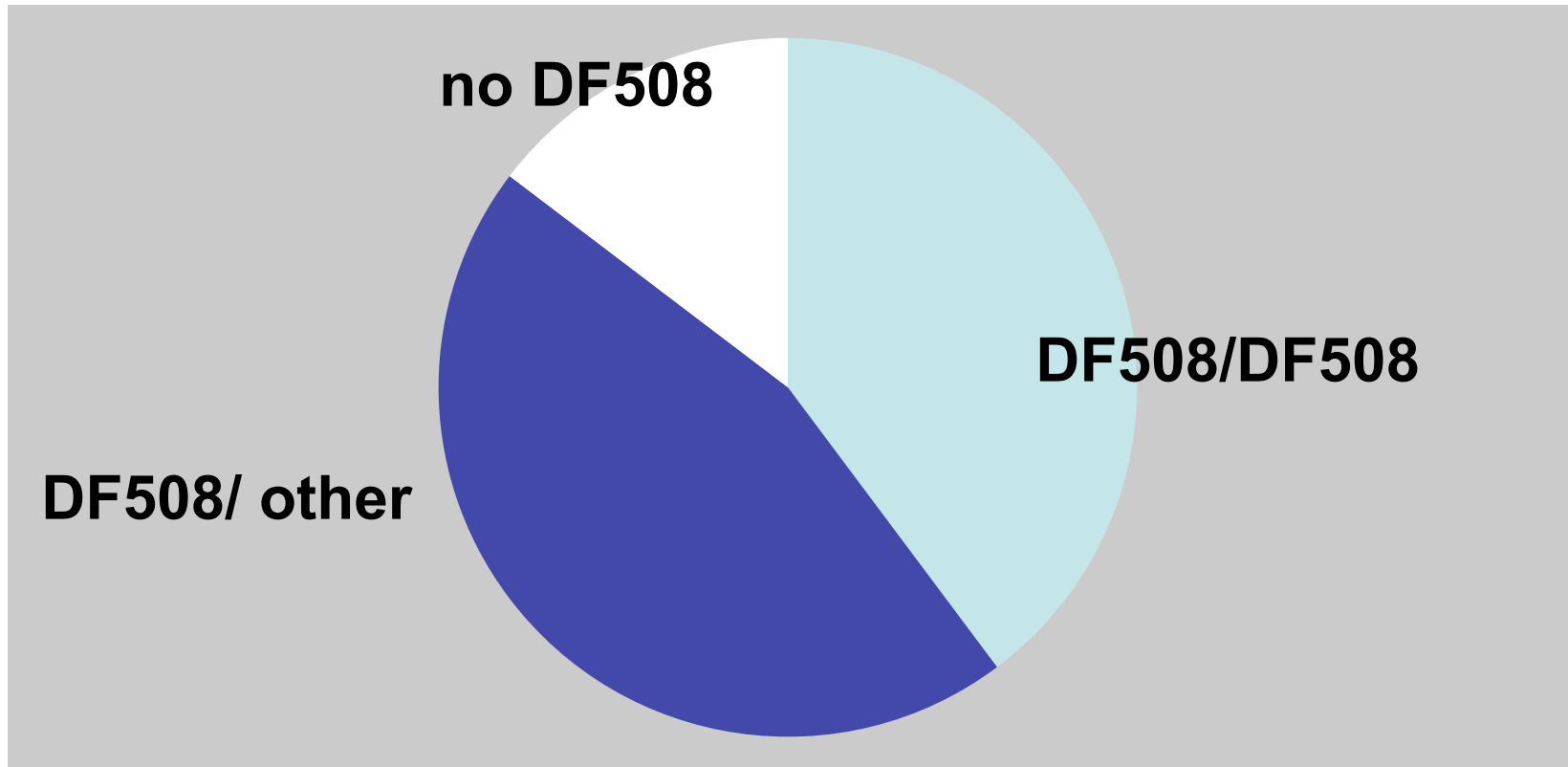
Like other targets, these can be multiplexed.

DNA Testing in the 2nd Tier

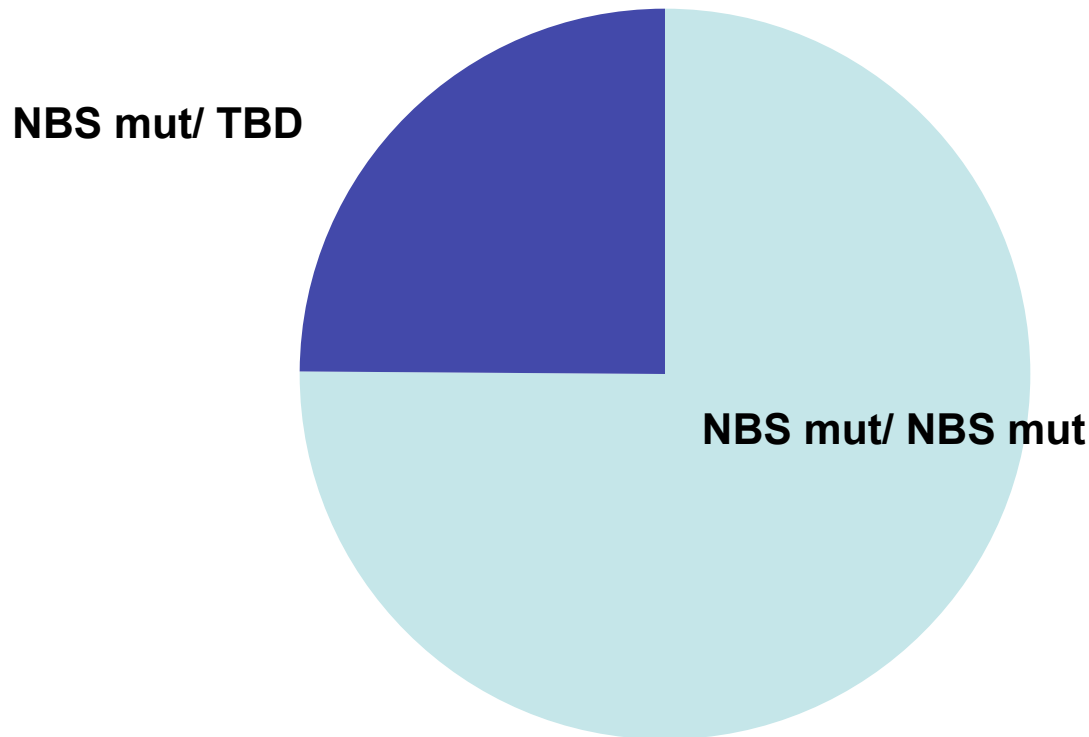
(data generated prior to full diagnostic evaluation)

- Enhance capacity of screening for conditions not otherwise included...
(Conventional genetic)
TREC assay for SCID: molecular in **FIRST TIER**
- Enhance specificity of 1st tier test....
CFTR mutation assay after IRT: molecular in **SECOND TIER**
- Supplemental just-in-time
Increase available information to aid diagnostic evaluation...
GALT mutation assay: molecular in **SECOND TIER**

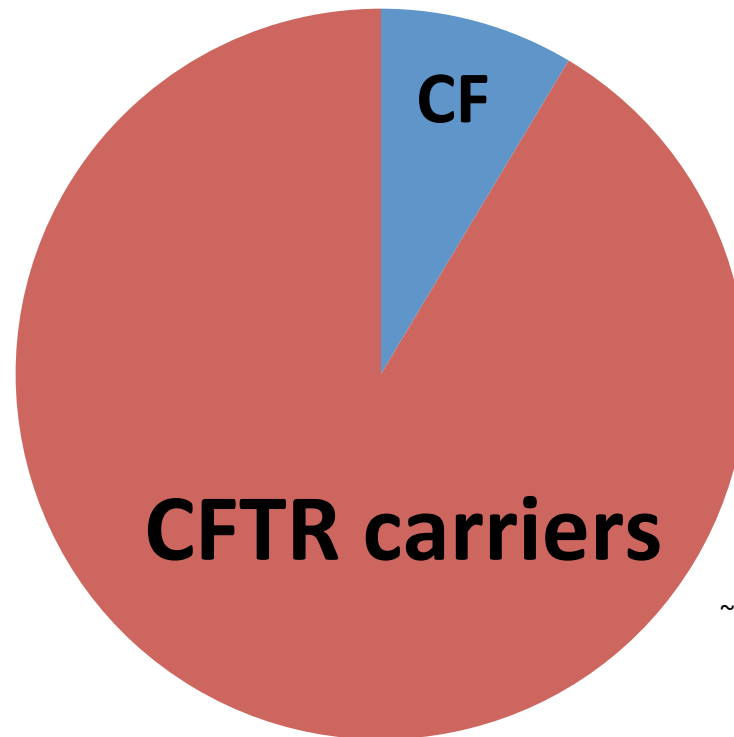
Genotype Distribution Among 450 New England CF infants relative to common allele



Proportion of New England CF Infants shown to carry one or two mutations by newborn screening

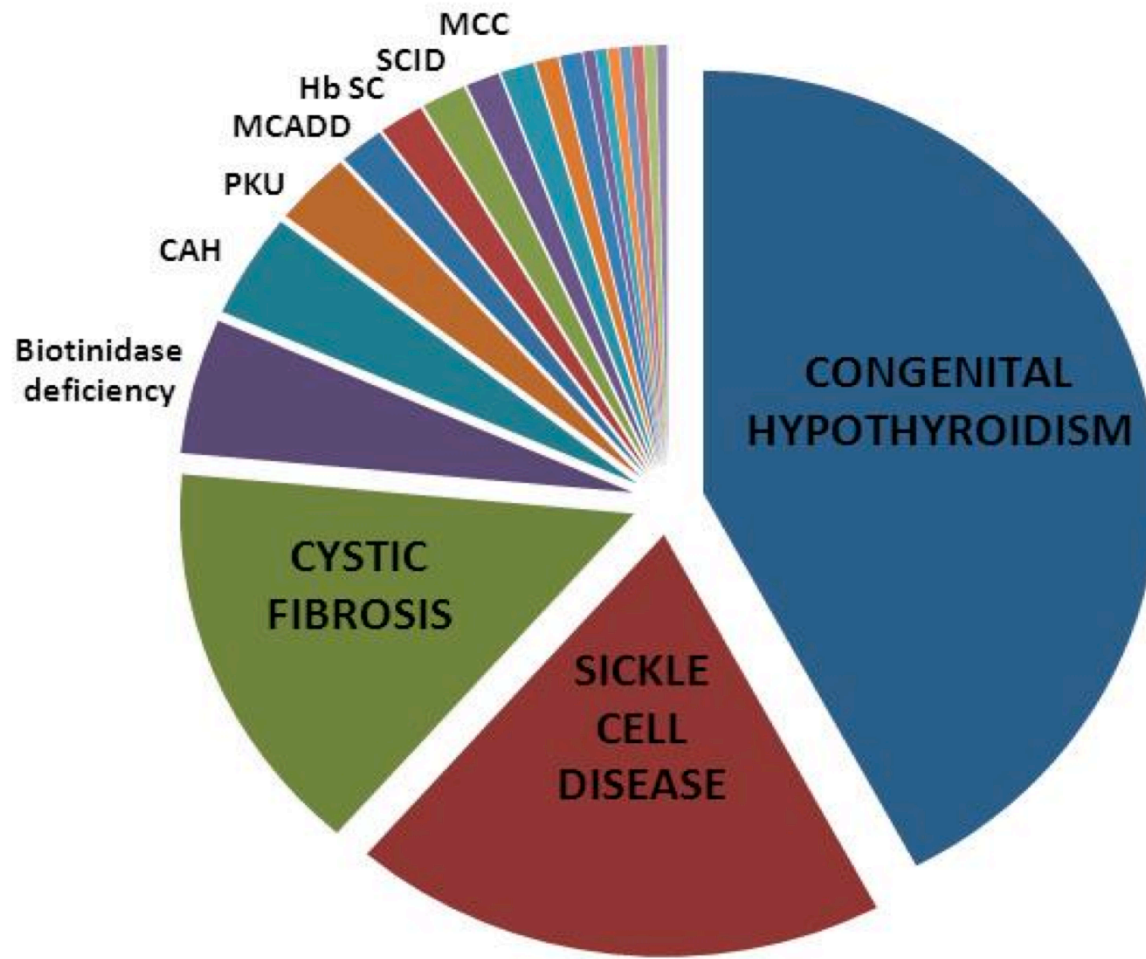


Carriers identified after diagnostic testing in order to find CF



~5% will have two carrier parents

Relative Proportions of Infants Identified by Newborn Screening



Nucleic Acid Testing		Examples	
Applications		Genetic mutations, viral load, clinical diagnosis, forensic analysis	
Multiple	Nucleic Acid Testing		Examples
			Accuracy, precision, sensitivity, specificity
	Nucleic Acid Testing		Examples
			Traditional PCR followed by post-amplification analysis. Detection of
Different			
Varying C	Lumi	Advantages of Real-Time Q PCR	
		Disadvantages	
	Quantit	Quantitative results in real-time	Limited multiplexing capability
		Closed tube, reduced risk of contamination	Can be complex to set up, particularly for multiplexed reactions
		Rapid cycling time (30 minutes to 2 hours)	
		Highly sequence specific	Intra- and inter-assay variation, hence the need for an internal monitoring control

Next Gen Seq?



To be determined:

Analytic validity

- Promising –
- known issues with large deletions, rearrangements, copy number variants

Analytic validity in high throughput

- Promising –
- Scan or target...

Clinical validity

- Ongoing learning...complex traits...

To be determined:

Bioinformatics

- Selected targets for first tier screening
- Selected targets for clinical inquiries
- Updating
- Record keeping

Current Reporting

Routine outgoing reports and Responses to clinical inquiries

Same technical report, includes laboratory values

Same result interpretation

Different consultation

Different fact sheets

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

Galactosemia

Supplemental just-in-time

NEW ENGLAND NEWBORN SCREENING PROGRAM

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

Print Date: 8/15/2013

Baby's Name : [REDACTED]

Mother's Name : [REDACTED]

Physician's Name : DR. [REDACTED]

Baby's Sex : MALE

Birth Date : [REDACTED] 09:09 (military time)

Specimen Date : [REDACTED] 03:15 (military time)

Hospital : [REDACTED]

DR. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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		<50 ng/mL(weight dependent)
*Biotinidase Deficiency / Biotinidase	>=30%		>=30%
*Cystic Fibrosis_SCREEN	IN RANGE ~		IN RANGE
Galactosemia / Galactose,Total		>50.0 mg/dL	<14 mg/dL
Galactosemia / Uridyltransferase		No Enzyme Present	Enzyme Present
Hemoglobinopathies / Hemoglobin Isoelectric Focusing	FA		FA, AF, or A
Homocystinuria / Methionine	<1.5 mg/dL		< 1.5 mg/dL
Hypothyroidism (CH) / Thyroxine	16.3 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
*Toxoplasma Infection / Toxoplasma IgG		NOT APPLICABLE	<0.1 OD
*Toxoplasma Infection / Toxoplasma IgM	0.050 O.D.		<0.1 OD
^Metabolic / Additional Metabolic Panel		Out of Range	All in Range
Metabolic / C3		8.91 uM	<8.0 uM

It has been determined that a further specimen is not required, because testing is being performed by an outside lab

^Additional Metabolic Panel:

Amino Acid- Tyrosinemia Type I and II

Urea Cycle- Argininemia, Arginosuccinic Aciduria, Citrullinemia, HHH Syndrome

FAOD- CPT II, Glutaric Acidemia Type II, LCHAD, SCAD, VLCAD

Organic Acid- B-KT, Glutaric Acidemia Type I, HMG, IVA, MCC, Methylmalonic Acidemia, Propionic Acidemia

~ IRT <99.9% and None of Tag-It 39+4 mutations detected.

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Specimen Date : [REDACTED] 03:15 (military time)

Hospital : [REDACTED] H/CPT/STAT

DR. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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~ IRT <99.9% and None of Tag-It 39+4 mutations detected.

**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		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 intrans; 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.

**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		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

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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		Result
GALACTOSEMIA		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.

**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		Result
GALACTOSEMIA		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.

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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"

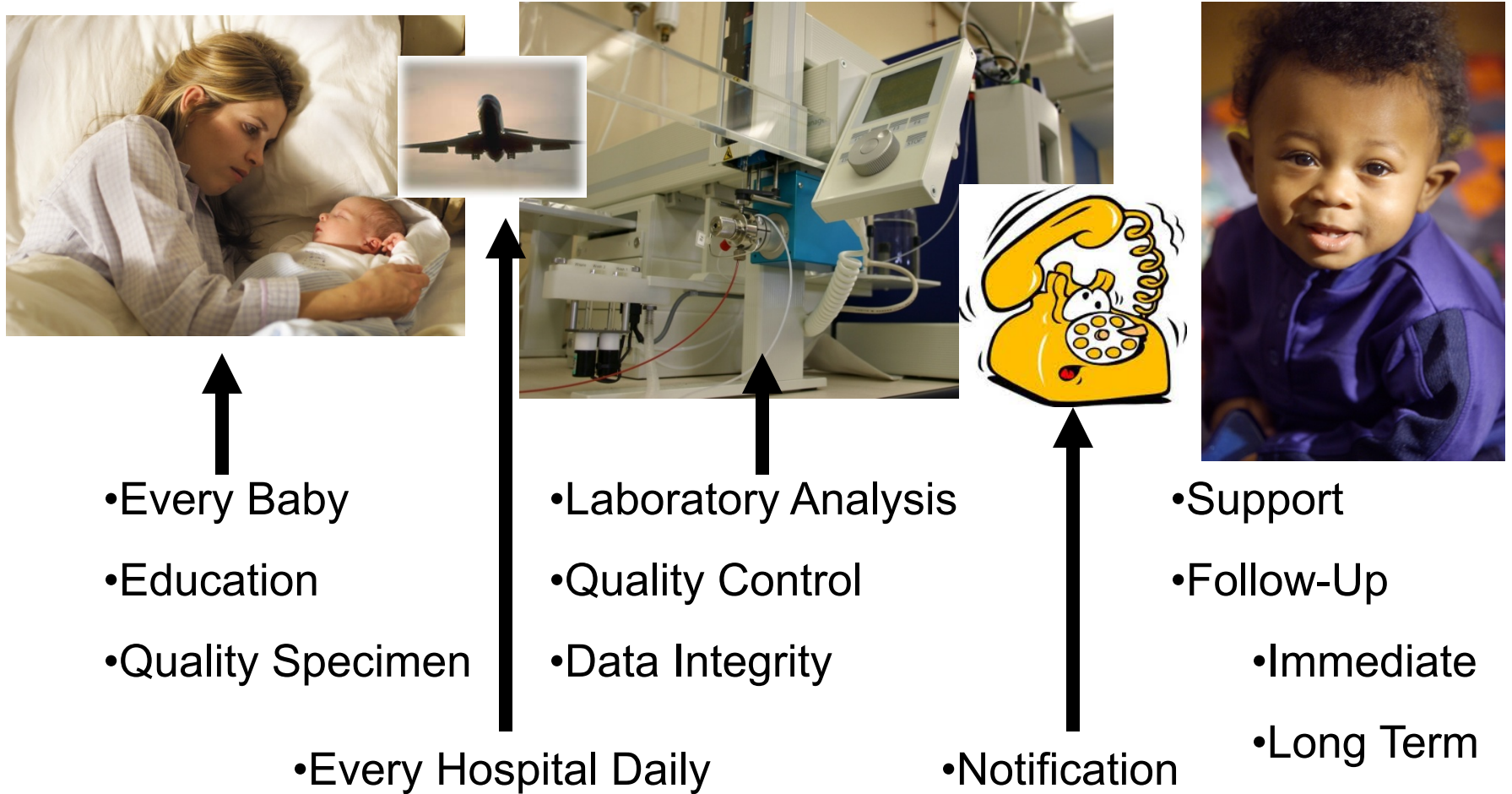
DNA findings do not alter interpretation of biochemical results

- 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.

*ASR: Analyte Specific Reagent that includes assays for detection of Q188R, N314D, S135L, K285N, L195P, Y209C, F171S, T138M and IVS2-2A>G. 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.

Newborn Screening is a System



Risk Assessment Process

4,000,000

Screen
Negative



Results
mailed to
HOB



No
follow-up
needed

166,451

Unsuitable for
Testing or DOB
(request repeat)



Letter sent to
HOB



NBS follow-up

299,953

Presumptive
Positive
(request repeat)



Letter sent to
HOB and physician
of record



NBS follow-up

51,529

Referral
(very abnormal)



Phone call to
treatment
center and
physician of
record



NBS follow-up

13,711 confirmed cases or 1/290 newborns have a NBS condition

Preparations for the future

- Technical Capacities
- Clinical Utilities
- Reporting and Data Management Policies

Hi Throughput – Large Menus

New York NBS:

30	Conditions
29,299	Daily Tests
782	Confirmed Cases
242,208	Newborns Tested

New England NBS:

30	Conditions
12,602	Daily Tests
301	Confirmed Cases
116,236	Newborns Tested

Wisconsin NBS:

30	Conditions
7,099	Daily Tests
143	Confirmed Cases
67,057	Newborns Tested

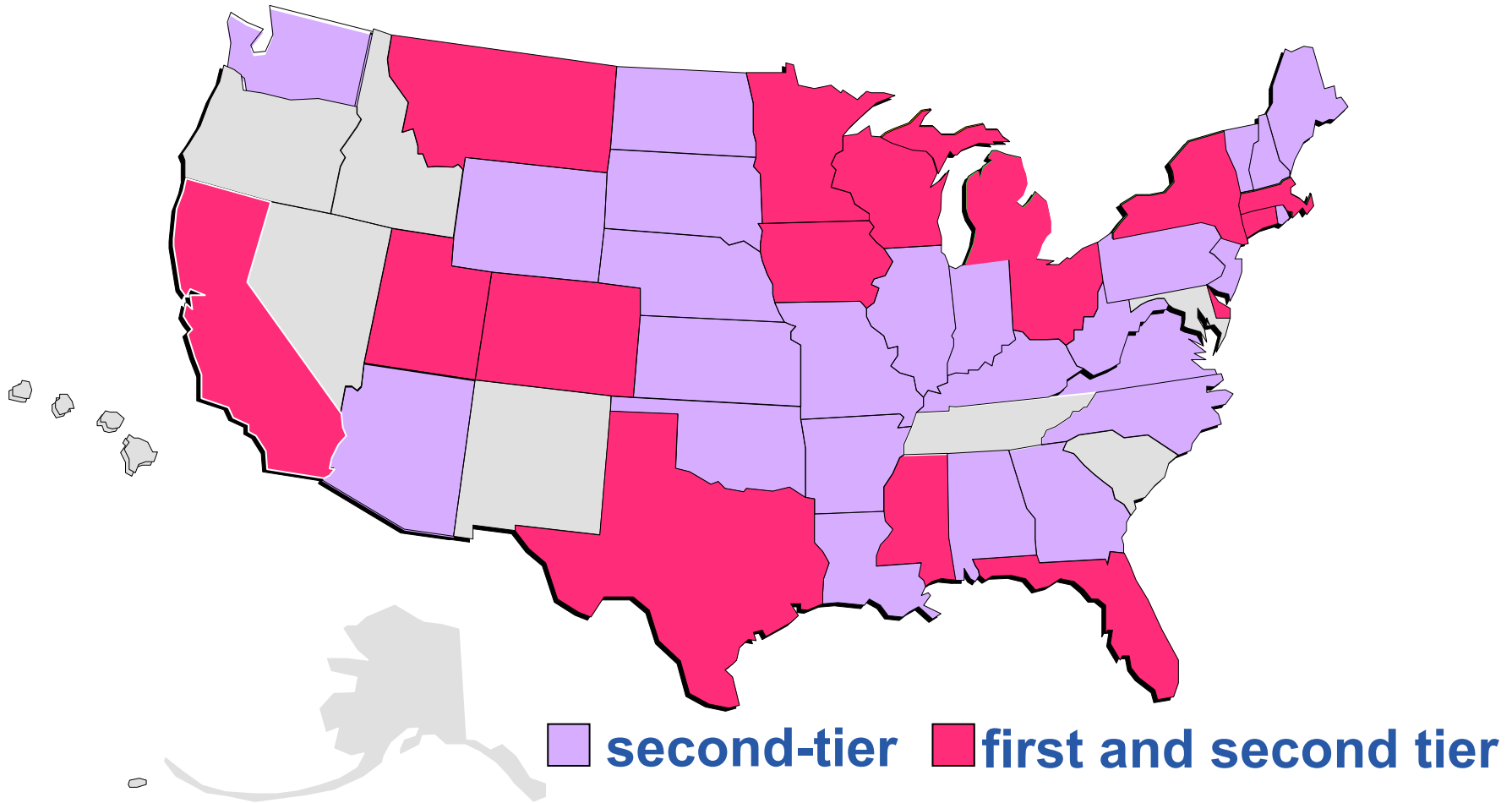
Minnesota NBS:

30	Conditions
6,780	Daily Tests
155	Confirmed Cases
67,780	Newborns Tested

TXNBSP:

29*	Conditions
71,740	Daily Tests
743	Confirmed Cases
379,255	Newborns Tested

Molecular Assays in Use in Newborn Screening 2013



Courtesy, CDC

Examples of pediatric onset actionable conditions for consideration in expansion

Disorder	Age of Onset	Gene/s	Inheritance	Clinical Features	Management (In addition to treatment of manifestations)	Prevention of Manifestations (Primary or Secondary)	Comments	Prevalence
AASE (also Diamond Blackfan Anemia)	Infancy >	RPL5, RPL13	AD	Anemia, increased risk (MDS, AML, ...)	Surveillance/Supportive	—	—	1:200,000
Abetalipoproteinemia	Infancy >	MTPP	AR	FTT, diarrhea, acanthocytosis; ataxia	Surveillance	2 Primary Vit E supplementation	—	Rare
Acanthoplasminemia	Young adults	CP	AR	Retinal degeneration, DM, anemia & ...	Surveillance	Primary/Secondary - Iron Chelators	—	—
Adenomatosis	Neonatal/Inf	CNGA3, CNGB3	AR	Reduced visual acuity, photophobia, ...	Surveillance	Primary BMT/SCIT & EE Spectrum includes SCID	—	1:40,000-1:100,000
ADA Deficiency	Neonatal >	ADA	AR	Disorder of lymphocyte development	Surveillance	Primary: Allopurinol, Dietary modification	—	—
Adenosine phosphoribosyltransferase deficiency	Childhood >	APRT	AR	Kidney stones & chronic kidney disease	Surveillance	—	—	—
ADP-related isolated familial pituitary adenoma	Childhood >	ADP	AD	Familial Pituitary Adenoma	Surveillance	—	—	—
Adrenoleukodystrophy	Infancy >	ABCD5	AR	Adrenoleukodystrophy, Addison disease, ...	Surveillance/Supportive	—	—	Rare
Alagille syndrome	Neonatal >	JAG1	AD	Bile duct paucity, liver disease, card	Supportive/Supportive	—	Variable penetr	1:70,000
ALK-related neuroblastoma	Neonatal >	ALK	AD	Neuroblastoma susceptibility	Surveillance	—	—	—
Alpha1-antitrypsin deficiency	Neonatal/Ad	SERPINA1	AR	COPD (adulthood); liver disease (ne	Surveillance/Support	Primary/Secondary - avoidance of smoke	—	1:500-3500 (Europe)
Alpha-Mannosidosis (lysosomal)	Neonatal >	MAN2B1	AR	Progressive CNS involvement, impair	Supportive	Primary BMT/SCIT (Experimental)	—	—
Alström syndrome	Neonatal/Inf	ALMS1	AR	Progressive hearing & vision loss, ca	Surveillance/Support	Primary/Secondary - lifestyle modification	—	—
Alström syndrome	Neonatal/Inf	ALMS1	AR	Progressive hearing & vision loss, ca	Surveillance/Support	Primary/Secondary - lifestyle modification	—	—
Andersen-Tawil syndrome	Childhood >	KCNK2	AD	Muscle weakness, prolonged QT int	Surveillance/Supportive	—	—	—
Androgen insensitivity syndrome	Infancy >	AR	X-linked	46XY, Ambiguous genitalia, abnormal	Surveillance	—	—	—
APC-associated polyposis	Infancy >	APC	AD	Colonic polyps, colon cancer predispo	Surveillance	Secondary Colonic resection	—	—
Argininosuccinate aminotransferase deficiency	Infancy >	GATM	AR	FTT, developmental delays, autistic	—	2 Primary Creatine supplementation	—	Rare
Arrhythmogenic right ventricular dysplasia/cardiomyopathy (A)	Childhood >	TGFBR3, RYR2	AD	Ventricular tachycardia	Surveillance	Primary antiarrhythmic/Additional gene	—	1:3000 to 1:3250
Asylgalactase A deficiency (metachromatic leukodystrophy)	Infancy >	ARSA	AR	Progressive neurologic dysfunction	Supportive	Primary BMT/SCIT (Experimental)	—	1:40,000-1:160,000
Ataxia with Vitamin E Deficiency	Childhood >	TTPA	AR	Progressive ataxia, loss of proprio	Surveillance	Primary Vit E supplementation	—	2:1:333,000
ATP7A-Related Copper Transport Disorders	Menkes/ORS	ATP7A	X-linked	Menkes-Neurological regression, hy	Supportive	Primary Rx with copper shows promise	—	—
Autoimmune lymphoproliferative syndrome (ALPS)	Childhood >	FAS	AR	Autoimmune disorders, increased ri	Surveillance	—	—	Rare
Autoimmune polyendocrine syndrome, Type 1	Infancy >	AIRE	AR	Mucocutaneous candidiasis, hypop	Surveillance	—	—	Rare
Autosomal dominant lateral temporal lobe epilepsy (ADLTLE)	Infancy >	IGIL	AD	Focal generalized seizures, auditory	Surveillance	Secondary Phenytoin Rx for seizures	—	—
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	Infancy >	CHRNA4, CH	AD	Nocturnal motor seizures	Surveillance	Secondary Phenytoin Rx for seizures	—	—
Auerfeld-Rieger syndrome	Infancy >	PITX2, FOXC	AD	Abnormalities of anterior segment, ...	Surveillance	—	—	1:1,000,000
Bartter syndrome	Infancy >	SLC12A1, KC	AR	FTT, dehydration, polyuria, hypokale	Surveillance	—	—	1:1,000,000
Biliary atresia	Infancy >	RYR2 and CASQ2	AD	Ventricular tachycardia	Surveillance	—	—	1:30,000
Catecholaminergic polymorphic ventricular tachycardia	Infancy >	CYBA, CYBB	AR/X-linked	Recurrent infections	Surveillance/Supportive	—	—	1:20,000
Chronic granulomatous disease	Infancy >	CE3	AR	Infections, autoimmune disorders	Surveillance	—	—	Rare
Complement factor 1 deficiency	Infancy >	CF3	AR	Infections, autoimmune disorders	Surveillance/Supportive	—	—	Rare
Congenital central hypostimulation syndrome (CCHS)	Neonatal >	PHOX2B	AD	Hypoventilation, SIDS	—	—	—	—
Creatine transporter defect	Infancy >	RASA3	AD	AV malformations	Surveillance	—	—	1:1,000,000
CV-ANM	Childhood >	GJA	X-linked	Aortic aneurysms, angiodysplasias, ...	Surveillance	—	—	1:40,000
Familial Atrial Fibrillation	Childhood >	KCNJ2, KCN	AD	Atrial fibrillation	Surveillance/Supportive	—	—	Common
Familial acute myeloid leukemia with mutated CEBPA	Childhood >	CEBPA	AD	AML	Surveillance/Supportive	—	—	1:50,000
Familial Hypoparathyroidism	Infancy >	UPL	AR	Pancreatitis, hepatosplenomegaly	Surveillance/Support	2 Primary Dietary modifications	—	1:1,000,000
Glycogen storage disease type III	Infancy >	AGL	AR	FTT, hypoglycemia, hepatosplenome	Supportive	2 Primary Dietary	—	1:300,000-1:500,000
Gortlin syndrome	Infancy >	PITC1	AD	Nevoid basal cell carcinomas, other	Surveillance/Supportive	—	—	1:30,000
Guanosine diphosphate methyltransferase deficiency	Infancy >	PRF1, UHRF1	AR	Acute illness with prolonged fever;	Surveillance/Supportive	2 Primary BMT	—	1:50,000 births
Hemophagocytic lymphohistiocytosis, Familial	Infancy >	SERPINC1, E	AD	Recurrent angioedema	Surveillance	—	—	1:50,000
Hereditary angioedema	Infancy >	ALDOX3	AD	Hypoglycemia, hepatic and renal dy	Surveillance	—	—	1:40,000
Hereditary fructose intolerance	Infancy >	CHGA	AR	Periodic paralysis	Surveillance	2 Primary Dietary	—	1:20,000
Hemifacial spastic paralysis	Infancy >	KCNJ2, KCN	AD	Arrhythmias, hearing loss	Surveillance/Supportive	—	—	1:20,000
Jewell and Lange-Nielsen syndrome	Infancy >	STAT3	AD	Immune disorders, high lig	Surveillance/Supportive	—	—	Rare
Sub syndrome	Childhood, ad	CACNA1C, CLCN2, SERCA, GABRA1, GABRB2, GABRG1, GABRG2	Variable	Epileptic seizures, tonic-clonic seiz	Surveillance	—	—	1:1,000
Maternally inherited diabetes and deafness	Childhood >	MT-ND1, MT	Mitochondrial	DM, Deafness	Surveillance	—	—	Common (1% of D)
Methylene tetrahydrofolate deficiency (MTHFR Severe)	Infancy >	MTHFR	AR	Microcephaly, seizures	Surveillance	Primary "SMITH"	—	1:1,000,000
Mucopolysaccharidosis type I	Infancy >	IDUA	AR	Storage disorder, hepatosplenomeg	Surveillance	2 Primary ERT	—	1:30,000
Multiple endocrine neoplasia - Type 1	Infancy >	RBX1	AD	Tumors of parathyroid gland, pituita	Surveillance	—	—	1:30,000
Multiple endocrine neoplasia - Type 2	Infancy >	RIT	AD	Medullary thyroid carcinomas, parath	Surveillance	—	—	1:30,000
Myotonic dystrophy type 1 (DM1)	Neonatal >	CX36A3, CO	AD/AR	Heart block, hearing loss	Surveillance/Supportive	—	—	4-5:100,000
Myotonic dystrophy type 2 (DM2)	Neonatal >	MDG17A3	AD	Epilepsy, hepatosplenomegaly, hyp	Supportive	Primary: Medications.	—	1:300,000
Wilson disease	Neonatal >	WAS	X-linked	Neuropsychiatric disorders, liver dy	—	Primary: Medications.	—	1:3,000,000
Wilson-Adams syndrome	Infancy/Child	NR0B1	X-linked	Adrenal insufficiency, hypoparathyro	Surveillance	—	—	1:2,500
X-linked adrenoleukodystrophy	Infancy/Child	NR0B1	X-linked	Adrenal insufficiency, hypoparathyro	Surveillance	—	—	1:12,500
X-linked adrenomyeloneuropathy	Childhood >	NR0B1	X-linked	2 forms: Childhood cerebral, adole	Surveillance	Primary BMT	—	1:20,000
X-linked agammaglobulinemia	Infancy >	BTX	X-linked	Recurrent infections	Surveillance	Prevention of infections	—	—

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