Seven Additional Newborn Screening Disorders Coming to NJ: Are You Ready?

DEBRA-LYNN DAY-SALVATORE, MD, PHD, FAAP, FACMG

CHAIR, DEPARTMENT OF MEDICAL GENETICS & GENOMIC MEDICINE

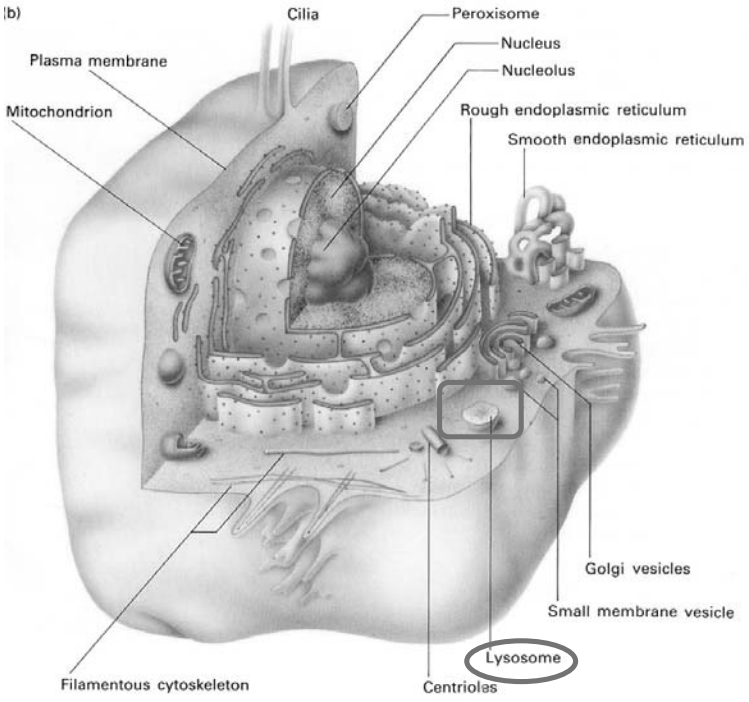
SAINT PETER'S UNIVERSITY HOSPITAL
NEW BRUNSWICK, NJ

DISCLOSURES

- Genzyme, A Sanofi Company
  - Consultant, independent research contractor, member of advisory committees, speaker, clinical trial principal investigator
- NJDOH
  - MCH Block Grant recipient
- Chair, NJ NBS Pediatric Metabolic/Genetic Specialty Group
- Co-Chair, NJ NBS LSD and ALD Working Groups

WHAT ARE LYSOSOMES?

- Membrane-limited cytoplasmic organelles
- Contain cocktail of acid hydrolytic enzymes*
- Digest extracellular lipid, protein, carbohydrate, and nucleic acid macromolecules intracellularly
- Degrade cell membranes and organelles during apoptosis



*Glycosidase, peptidase, sulfatase, lipase, phosphatase, nuclease, peroxidase, reductase, thioesterase, etc.

LYSOSOMAL STORAGE DISORDERS

Disease Category	Diseases
Mucopolysaccharidoses (11)	**MPS I**, **MPS II**, MPS IIIA-D, MPS IV A-B, MPS VI, MPS VII, MPS IX
Glycoproteinoses (6)	Aspartylglucosaminuria, Fucosidosis, α-Mannosidosis, β-Mannosidosis, Sialidosis, N-acetyl-α-glucosaminidase def.
Multiple Enzyme Deficiencies (5)	Mucolipidosis II, Mucolipidosis IIIA, Mucolipidosis IIIB, Multiple Sulfatase def., Galactosialidosis
Sphingolipidoses (incl. Act. Pro. Def.) (17)	Farber, **Fabry**, **Gaucher types 1,2, & 3**, GM_1-gangliosidosis, GM_2-gangliosidosis B, GM_2-gangliosidosis O, GM_2-gangliosidosis AB, **Krabbe**, Metachromatic Leukodystrophy, **Niemann-Pick A**, **Niemann-Pick B**, Wolman, Prosaposin def., Saposin B def., Saposin C def.
Glycogen Storage Disease (1)	**Pompe Disease**
Lysosomal Transport Defects (3)	Cystinosis, Sialic Acid Storage Disease, MMA
Lysosomal/endosomal Trafficking /fusion Defects (5)	N-P type C1, N-P type C2, Mucolipidosis IV, Danon Disease, Chediak-Higashi
Neuronal Ceroid Lipofuscinoses (11)	CLN1-3, CLN4A, CLN4B, CLN5-10

HOW ARE LYSOSOMAL STORAGE DISORDERS INHERITED?

- LSDs are inherited in an autosomal recessive (AR) fashion EXCEPT for Fabry Disease and Hunter Syndrome (MPS II), which are X-linked (XL)
  - Increased incidence with consanguinity (AR)
  - Large family cohorts with Fabry disease (XL)

LYSOSOMAL STORAGE DISORDERS

- Underdiagnosed and misdiagnosed due to:
  - Early demise (included in differential for NIH)
  - Later onset – residual enzyme activity level
  - Non-specific findings (substantial overlap)
- Normal appearance at birth – majority
- Normal development – variable time period
- No acute metabolic crisis
- Chronic, progressive evolution of symptoms in the absence of treatment

LYSOSOMAL STORAGE DISORDERS
Manifestations

Parenchymal (Visceral)

- Pulmonary (apnea, recurrent pneumonia, obstructive airway, pulmonary htn)
- CV (cardiomyopathy, arrhythmias, CHF, vascular occlusion, valvular disease)
- GI (FTT, N/V, episodic diarrhea, bloating)
- HSM (thrombocytopenia), hernias
- Proteinuria, renal failure

CNS

- Myopathy, szs, spasticity, bulbar palsies, ataxia, depression, peripheral neuropathy, intellectual decline

Connective Tissue

- Coarse facial features (macroglossia, gingival hyperplasia)
- Dysostosis multiplex (DM)
- Cutaneous findings (angiokeratomas, ichthyosis, xanthomas)

Sensorineural/mixed HL

Vision

- corneal clouding, cherry red spot, optic atrophy, glaucoma, lens opacities, ophthalmoplegia

GAUCHER DISEASE

Gene/Enzyme	GBA/Acid β-glucosidase (glucocerebrosidase)
Clinical features	Hepatosplenomegaly, anemia, thrombocytopenia, bone crises, Erlenmeyer flask deformities (femoral shaft), avascular necrosis and fracture (femoral/humeral head, vertebral bodies, pelvis), osteopenia, lytic lesions (humeral, tibial, fibular shaft), growth restriction, pulmonary hypertension, interstitial lung disease, cholelithiasis; strabismus, cortical thumbs, neck retroflexion with type 2
Testing	Enzyme level (residual activity not always reliable predictor of severity) and mutation analysis (some genotype/phenotype correlation)
Management	Monitor hematologic and biochemical parameters, skeletal manifestations, organomegaly, quality of life, bisphosphonates
Treatment	Imiglucerase (Cerezyme) [1993], Velaglucerase alfa (VPRIV), Miglustat (Zavesca)*, Taliglucerase alfa (Elelyso), Eliglustat (Cerdelga)*
Other	Avoid splenectomy; risk factor for Parkinson disease; increased incidence in individuals of Ashkenazi Jewish ancestry; continuum (3 major types, 1-3) and 2 subtypes (perinatal lethal & CV)

FABRY DISEASE

Gene/Enzyme	GLA/α-Galactosidase A
Clinical features	Acroparesthesias, crises, hypohidrosis, heat/cold intolerance, angiokeratomas, corneal opacities, retinal vascular lesions, episodic diarrhea, bloating, N/V, progressive renal insufficiency, ESRD, LVH, coronary and valvular disease, arrhythmias, cardiomyopathy, TIA, early stroke, depression, tinnitus, hearing loss, fatigue
Testing	Enzyme level (residual activity not always reliable predictor of severity) and mutation analysis
Management	Monitor renal, neurologic, and cardiac function, pain control, pancrelipase, aspirin, ACE inhibitors, valve replacement, dialysis, avoidance of stimuli that precipitate pain, avoidance of smoking
Treatment	Agalsidase beta (Fabrazyme) [2003]
Other	Most commonly reported features in women (heterozygotes) were cardiac (59%) and neurological (77%); treatment criteria and monitoring regimen should be the same in men and women; cardiac, renal, and cerebrovascular variant forms

POMPE DISEASE

Gene/Enzyme	GAA/α-1,4-Glucosidase
Clinical features	Cardiomegaly, hepatomegaly, hypotonia, cardiomyopathy, FTT, macroglossia, cardiorespiratory failure, ptosis, muscle weakness, exercise intolerance, sleep apnea, hearing loss, osteopenia, fx
Testing	Enzyme level (may require fibroblasts and/or muscle) and mutation analysis; mutational analysis may permit determination of CRIM status and whether immunomodulatory protocol is required
Management	Monitor cardiac, pulmonary, GI, nutrition, hearing, neurologic function, and fracture risk
Treatment	Aglucosidase alfa (Myozyme) [2006], (Lumizyme)
Other	Continuum (3 major types – classic infantile-onset, non-classic IO, and late-onset); high surgical/anesthesia risk; avoid certain agents (digoxin, ionotropes, diuretics); pseudodeficiency allele is common in Asian populations

POMPE DISEASE

"Newborn Screening, Diagnosis, and Treatment for Pompe Disease Guidance Supplement"

Kishnani, Priya; Hwu, Wuh-Liang; Atherton, Andrea ; Bodamer, Olaf; Burton, Barbara; Day-Salvatore, Debra; Giugliani, Roberto ; Jones, Simon; Kronn, David; Nakamura, Kimitoshi; Okuyama, Torayuki; Scott, C.; Swoboda, Kathryn

Supplement is scheduled to appear as a print-and-online companion to the July 2017 issue of Pediatrics. All supplements are published in the online edition at www.pediatrics.org and will be released online on the 1st of the publication month.

MPS I

Gene/Enzyme	
Clinical features	Umbilical/inguinal hernias, frequent URIs, facial coarsening, hepatosplenomegaly, macroglossia, hearing loss, corneal clouding, mitral/aortic valve regurgitation, gibbus deformity, joint ROM limitation, recurrent rhinitis, carpal tunnel syndrome, hydrocephalus, ID possible
Testing	Enzyme level (residual activity not always reliable predictor of severity) and mutation analysis (some genotype/phenotype correlation); pseudodeficiency alleles complicate diagnosis
Management	Intervention for developmental delays; hats with visors/sunglasses to reduce glare; cardiac valve replacement prn; physical therapy, orthopedic surgery prn (joint replacement, atlanto-occipital stabilization, early median nerve decompression for carpal tunnel syndrome); shunting for hydrocephalus; tonsillectomy and adenoidectomy for eustachian tube dysfunction and/or upper airway obstruction; tracheostomy for sleep apnea, pulmonary hypertension, right heart failure; PE tubes; surgical intervention for cervical myelopathy.
Treatment	Hematopoietic stem cell transplant (HSCT), ERT (Aldurazyme® [2003]), intrathecal ERT in clinical trials
Other	Continuum (severe to attenuated)

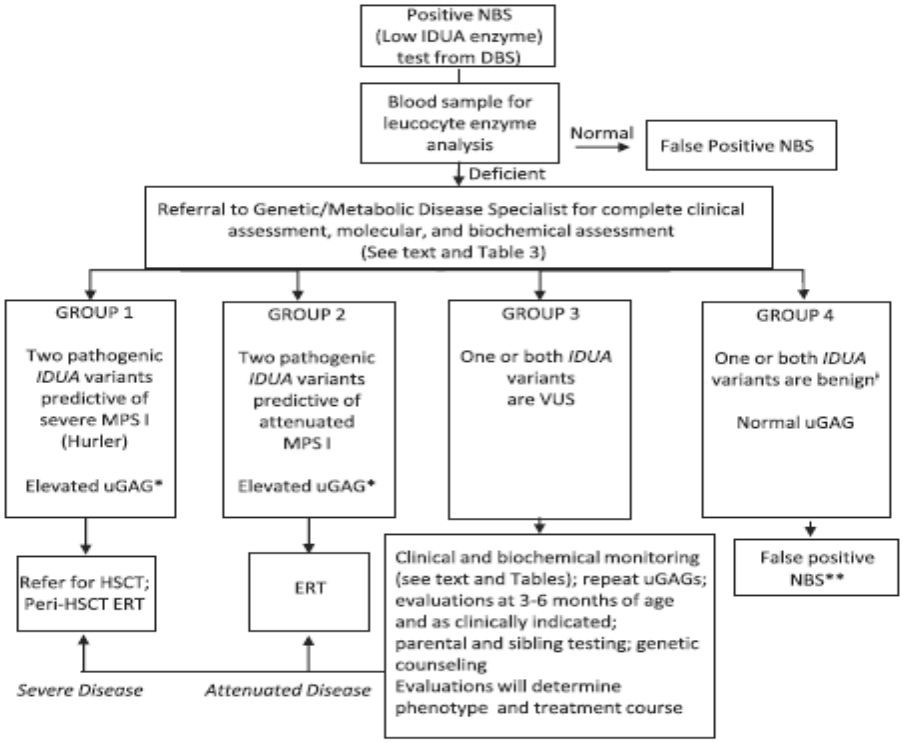
THE JOURNAL OF PEDIATRICS • www.jpeds.com WORKSHOP/SYMPOSIUM SUMMARY

Mucopolysaccharidosis Type I Newborn Screening: Best Practices for Diagnosis and Management

Lorne A. Clarke, MD, CM, FRCPC, FCCMG[1], Andrea M. Atherton, MS, CGC[2,*], Barbara K. Burton, MD, FAAP, FACMG[3], Debra L. Day-Salvatore, MD, PhD, FAAP, FACMG[4], Paige Kaplan, MBBCh, FRCPC, FCCMG, FAAP, FACMG[5], Nancy D. Leslie, MD[6], C. Ronald Scott, MD[7], David W. Stockton, MD, FACMG[8], Janet A. Thomas, MD, FAAP, FACMG[9], and Joseph Muenzer, MD, PhD[10]

Table II. Challenges in predicting disease severity following positive NBS for MPS I

- No biochemical criteria reliably distinguish MPS I subtypes
- Many signs and symptoms that establish an MPS I diagnosis in older patients do not differentiate between attenuated and severe phenotypes, or are not present in newborns
- In the absence of 2 pathogenic *IDUA* variants previously reported to be associated with defined disease severity, genotype/phenotype correlation is complicated by the existence of private (reported only in single individuals with MPS I) missense mutations that can not be used to predict the phenotype
- IDUA enzyme analysis is complicated by pseudo-deficiency because of:
  - Benign variants
  - Reduced in vitro enzyme activity in clinically unaffected individuals
  - Prevalence in African American population



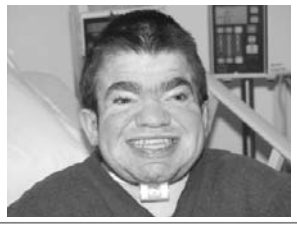
ŧBenign variants are defined as pseudodeficiency alleles
*uGAG levels may not be informative for very young infants due to wide normative uGAG ranges
** Genetic counseling may be considered in these cases

Figure. Proposed decision making algorithm for positive MPS I newborn screen. *VUS*, variant of unknown significance (ie, non-recurrent missense variant).

17.1 Recommended Schedule of Assessments

	Initial Assessments	Every 6 Months	Every 12 Months	Every Other Year
General				
Demographics	X			
Patient Diagnosis[1]	X			
Medical History	X	X		
Physical Examination	X	X		
General Appearance	X	X		
MPS I Disease Clinical Assessments				
Neurologic/CNS				
MRI of Brain	X			X
MRI of Spine	X			X
Median Nerve Conduction Velocity	X			X
Cognitive Testing (DQ/IQ)	X		X	
Ophthalmologic				
Visual Acuity	X		X	
Retinal Examination	X		X	
Corneal Examination	X		X	
Auditory				
Audiometry	X		X	
Cardiac				
Echocardiogram	X			X
ECG	X			X
Respiratory[2]				
FVC/FEV_1	X	X		
Sleep Study	X		X	
Gastrointestinal				
Spleen Volume[3]	X			X[4]
Liver Volume[3]	X			X[4]
Musculoskeletal				
Skeletal Survey by X-ray[5]	X			X
Vitals and Laboratory Tests				
Height/Weight	X	X		
Head Circumference[5]	X	X		
Blood Pressure	X	X		
Enzyme Activity Level	X			
Urinary GAG Level	X	X[4]		
Urinalysis	X	X		
Antibody testing[6]				
Functional Outcome Measurements				
MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life	X	X		

MPS II



Gene/Enzyme	
Clinical features	Short stature, macrocephaly w/wo hydrocephalus, macroglossia, hoarse voice, hearing loss, hepatosplenomegaly, progressive airway disease, spinal stenosis, cardiac (valvular) disease, carpal tunnel syndrome, joint contractures, chronic diarrhea, delayed milestones, cognitive impairment may be severe, normal-near/normal intelligence possible
Testing	Enzyme level (residual activity not always reliable predictor of severity) and mutation analysis (some genotype/phenotype correlation)
Management	Developmental, occupational, and physical therapy; shunting for hydrocephalus; tonsillectomy and adenoidectomy; positive pressure ventilation (CPAP or tracheostomy); carpal tunnel release; cardiac valve replacement; inguinal hernia repair; and hip replacement
Treatment	Elaprase® [2006]

ENZYME REPLACEMENT THERAPY (ERT)

BENEFITS	CHALLENGES
▪ Safe and effective in reversing visceral manifestations ▪ Appears to retard and prevent progression of connective tissue manifestations ▪ No known teratogenicity to date	▪ Does not cross the blood-brain barrier ▪ Does not penetrate well into skeletal muscle ▪ Does not reverse major structural damage (e.g. bone) ▪ Antibody development; infusion-related reactions ▪ Cost; need for regular infusions ▪ When to treat? Optimal dose and frequency

ERT

Infusion-Related

- Seen in 8.5%
- Discomfort, pruritis, burning, swelling at venipuncture site

Hypersensitivity

- Seen in 4.0%
- Pruritis, flushing, angioedema, urticaria, chest discomfort, back spasms, respiratory symptoms, hypotension

Additional Reactions

- Seen in 4.5%
- Nausea, abdominal pain, diarrhea, rash, fatigue, headache, fever, dizziness, chills, tachycardia

NIEMANN-PICK A/B DISEASE

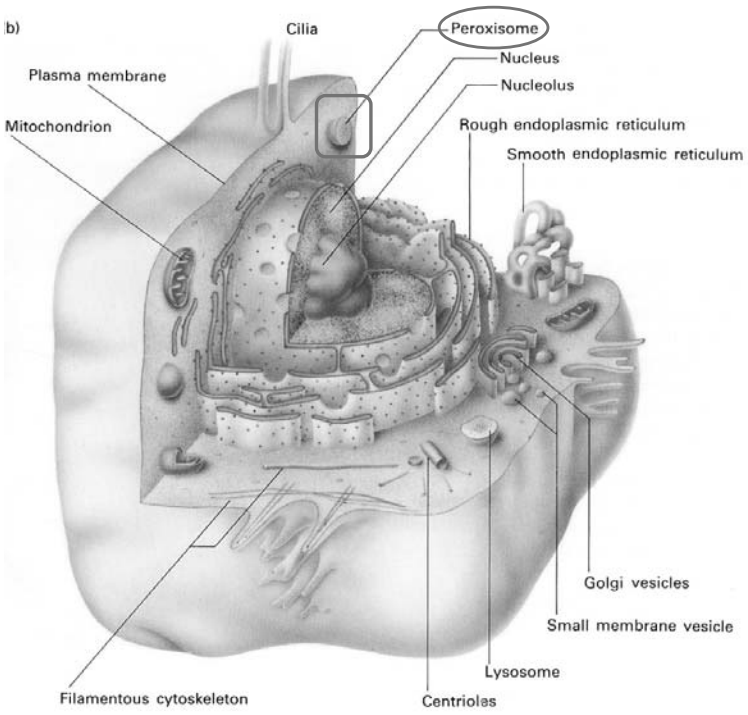
Gene/Enzyme	SMPD1/Acid Sphingomyelinase (A & B)
Clinical features	Jaundice, HSM, FTT, cherry red spot, irritability, sleep disturbance, progressive neurological deterioration
Testing	Enzyme level and mutation analysis
Management	Supportive
Treatment	Hematopoietic stem cell transplant
Other	Increased incidence in individuals of Ashkenazi Jewish ancestry; type B is allelic characterized primarily by visceral involvement and survival into adulthood

KRABBE DISEASE

Gene/Enzyme	GALC/Galactosylceramidase
Clinical features	Extreme irritability, spasticity, and developmental delay; vision loss, walking difficulties, delayed milestones, regression
Testing	Enzyme activity and mutation analysis
Management	Supportive
Treatment	Hematopoietic stem cell transplant (HSCT) within first 3-4 weeks of life for presymptomatic individuals attenuates clinical course and improves survival, but is not curative
Other	30-Kb deletion associated with infantile form when homozygous; c.857G>A found in late-onset

PEROXISOME

- Organelle present in all human cells except mature erythrocytes
- Metabolic functions include β-oxidation of VLCFA, α-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids
- Two major subgroups of disorders
  - Biogenesis defects (e.g. Zellweger spectrum)
  - Single enzyme/transporter defects (e.g. X-linked adrenoleukodystrophy)



X-LINKED ADRENOLEUKODYSTROPHY

- Affects ~1 in 20,000 males
- At least 20% of heterozygote females are symptomatic
- Affects nervous system white matter and adrenal cortex – 3 main phenotypes in males
  - Childhood cerebral form (35%) manifesting between 4-8 years – ADHD, progressive impairment of cognition, behavior, vision, hearing, & motor function – total disability within 2 years
  - Adrenomyeloneuropathy (AMN) (~45%) – manifests in late 20s as progressive paraparesis, sphincter disturbance, sexual dysfunction, and often impaired adrenocortical function and is progressive
  - Addison only disease (10%) – primary adrenocortical insufficiency (average age of 7 years); AMN may develop later

X-ALD CONFIRMATORY TESTING

- MRI abnormal in males with neurologic symptoms (symmetric enhanced T2 signal in parieto-occipital region)
- 99% of males & ~80% of heterozygote females have elevated plasma VLCFA concentrations (C26:0; C24:0/C22:0; C26:00/C22:0)
- Mutation and deletion/duplication (~6%) analysis of the *ABCD1* gene – 7% *de novo* alterations

X-ALD TREATMENT

- BMT – option for males with evidence of brain involvement by MRI but minimal neurologic or neuropsychologic dysfunction
- Corticosteroid replacement therapy for adrenal insufficiency – no effect on nervous system
- Physical therapy, support, and counseling
- MRI surveillance

NBS for LSDs by MS/MS

Fabry disease – 1/3,860 males (28 referred/9 confirmed)	Fabry disease – 1/13,341 males (34 referred/3 confirmed)
Pompe disease – 1/8,684 (5 referred/4 confirmed)	Pompe disease – 1/4,447 (64 referred/9 confirmed)
Gaucher disease – 1/17,368 (4 referred/2 confirmed)	Gaucher disease – 1/13,341 (17 referred/3 confirmed)
Niemann-Pick A/B – (1 referred/0 confirmed)	Niemann-Pick A/B – 1/20,012 (5 referred/2 confirmed)
Combined prevalence of 3 alone – 1/2,316	Combined prevalence of 4 – 1/2,354
Referred for evaluation – 1/914	Referred for evaluation – 1/333
Mechtler et.al.: 2012 – 34,736 participants in Austria	*Wittmann et.al.: 2012 – 40,024 participants in Hungary*

NBS for LSDs by MS/MS
New Estimated Prevalence

- Fabry disease – 1/7,800 males
- Pompe disease – 1/27,500
- MPS I – 1/35,500
- Combined prevalence of the 3 alone – 1/7,500
  - Combined incidence of all LSDs previously estimated to be 1/6,000
- Estimates based on NBS are 2 to 4 times greater than that estimated by clinical diagnosis

Scott CR, Elliott S, Buroker N, Thomas LI, Keutzer J, Glass M, Gelb MH, Turecek F. J Pediatr. 2013 Aug;163(2):498-503

- Pompe disease – 1/11,300
  - 4 infantile,
  - 41 possible late-onset
  - 47 carriers
  - 29 pseudodeficiency
  - 63% of those tested were unaffected
- X-ALD – 1/11,800
  - 46 mutations (28M:18F)
  - 80% of positive screens confirmed to have pathogenic variant

NY STATE NBS RESULTS AS OF 2/7/2017 (NBSTRN) – 543,00 screens

NJ NBS FOLLOW-UP for LSDs/X-ALD

- All infants with a positive NBS in NJ for a lysosomal or peroxisomal disorder will need to be evaluated by a consultant
- Long-term management and follow-up will be critical
- Detailed prospective data collection needs to be a priority

Newborn Screening
It's more than PKU

Scott Shone, PhD

April 25, 2017

From ALD to Zika: Newborn Screening and Surveillance in NJ

Learning Objectives

- Understand the importance of newborn screening and the impact of early intervention.
- Explain the difference between screening and diagnostic laboratory tests.

Screening Tests vs. Diagnostic Tests

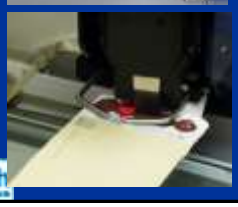
Screening Tests

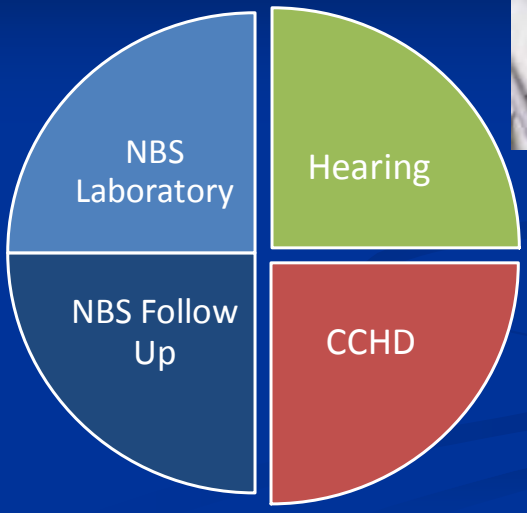
- Detects potential disease indicators
- Testing for large numbers of asymptomatic people
- Less expensive
- Done quickly
- Minimize false negatives [missed cases]

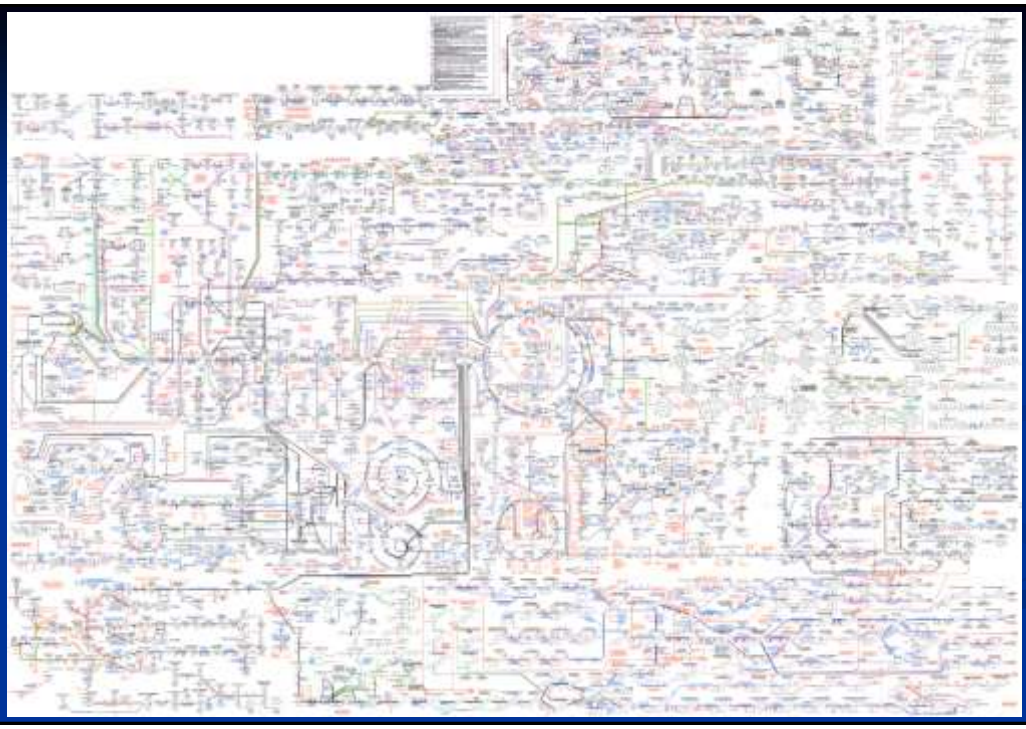
Diagnostic Tests

- Establishes disease presence/absence
- Testing for small numbers of symptomatic people or those with positive screening tests
- More expensive
- Can take longer
- Minimize false positives [unnecessary treatments]

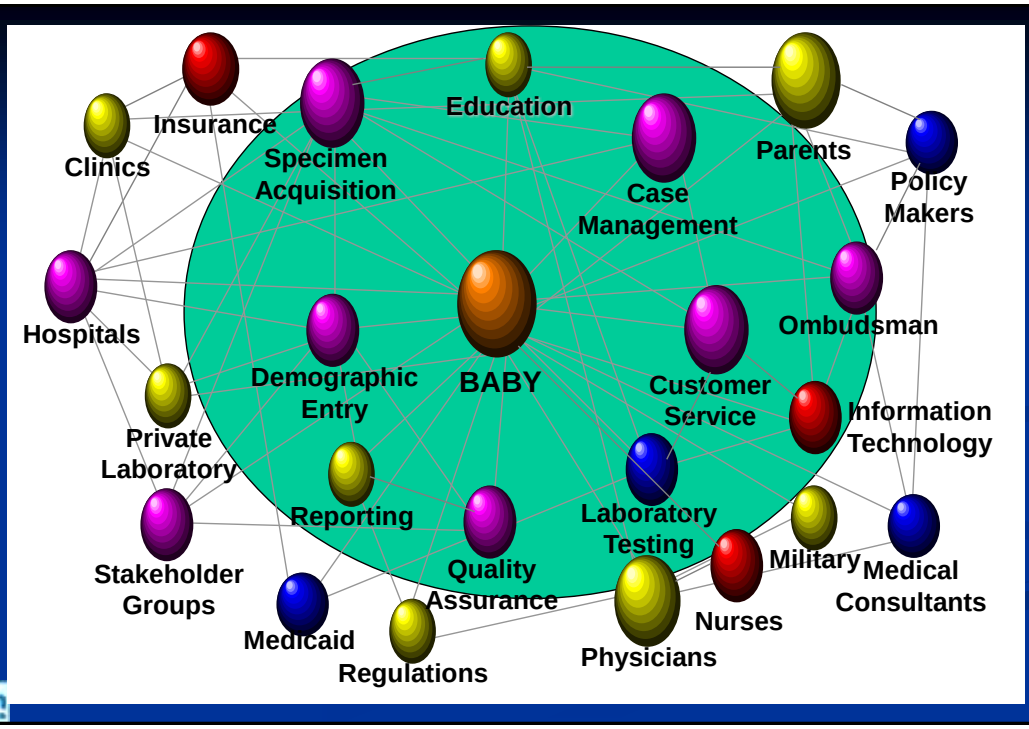
Different Models for Screening Newborns







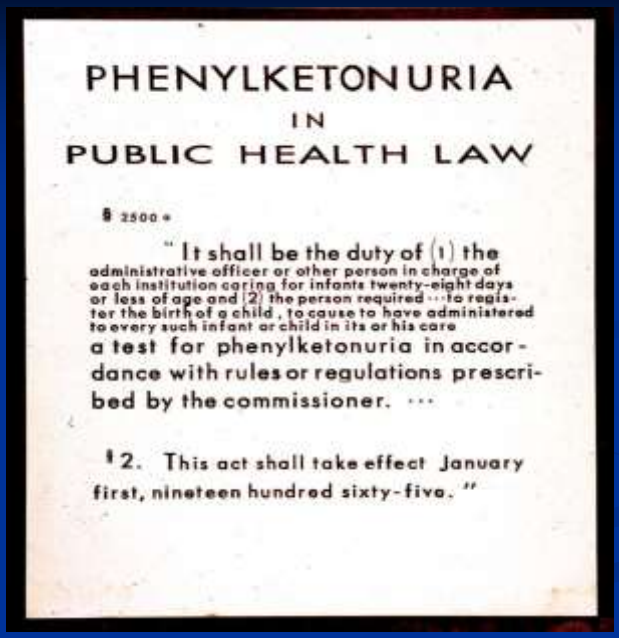
Hematology
Hemoglobinopathies
Pulmonary
Cystic Fibrosis
Genetics
Metabolism
Organic Acidurias
Fatty Acid Oxidation Disorders
Amino Acidopathies
Other Enzyme Deficiences
Endocrine
Congenital Endocrinopathies
Hearing
Congenital Hearing Loss
Immunology
Severe Combined Immunodeficiency
Cardiology
Critical Congenital Heart Disease



In the beginning there was only PKU

Dr. Robert Guthrie

PKU test on blood spots developed in 1961

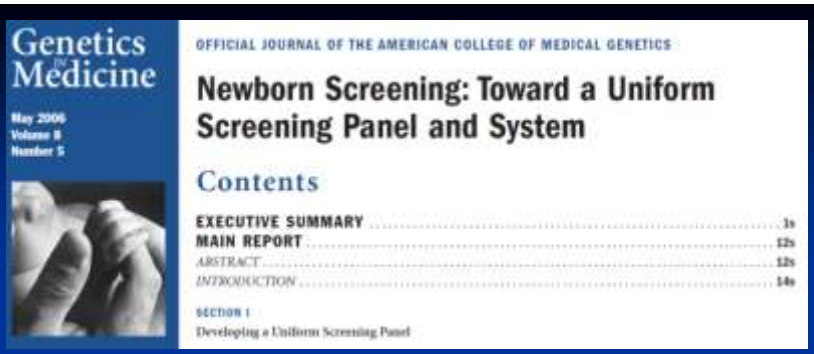


Federal Mandates

Why these disorders?

HRSA

AMERICAN COLLEGE OF MEDICAL GENETICS



Key Components of Newborn Screening

Education (throughout the process)
Screening, including specimen collection and testing
Follow-up and result reporting
Diagnostic confirmation
Management
Program evaluation and Continuous Quality Improvement

Why these disorders?

HRSA

AMERICAN COLLEGE OF MEDICAL GENETICS

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

NJ NSARC

NJ Health
New Jersey Department of Health

NJ Health

NEWBORN SCREENING

"10" Wilson-Jungner Criteria

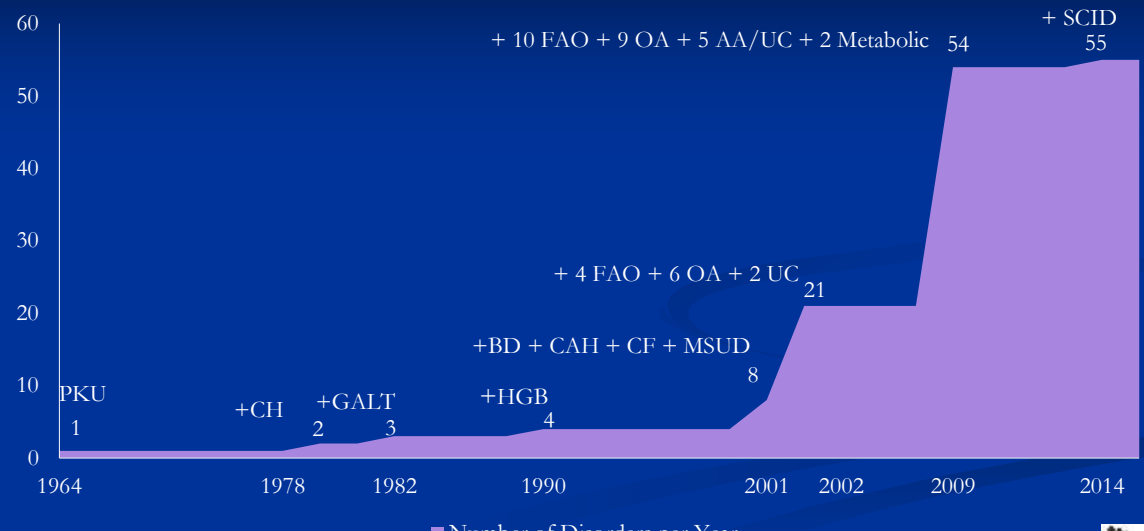
- Important public health concern
- Diagnosis and treatment are available
- Has a latent stage; natural history understood
- Testable in an acceptable way
- Agreed policy on whom to treat
- Economic cost per case "balanced"
- Case finding should be continuous

Wilson JM, Jungner YG. [Principles and practice of mass screening for disease]. *Bol Oficina Sanit Panam* 1968;65:281–393.

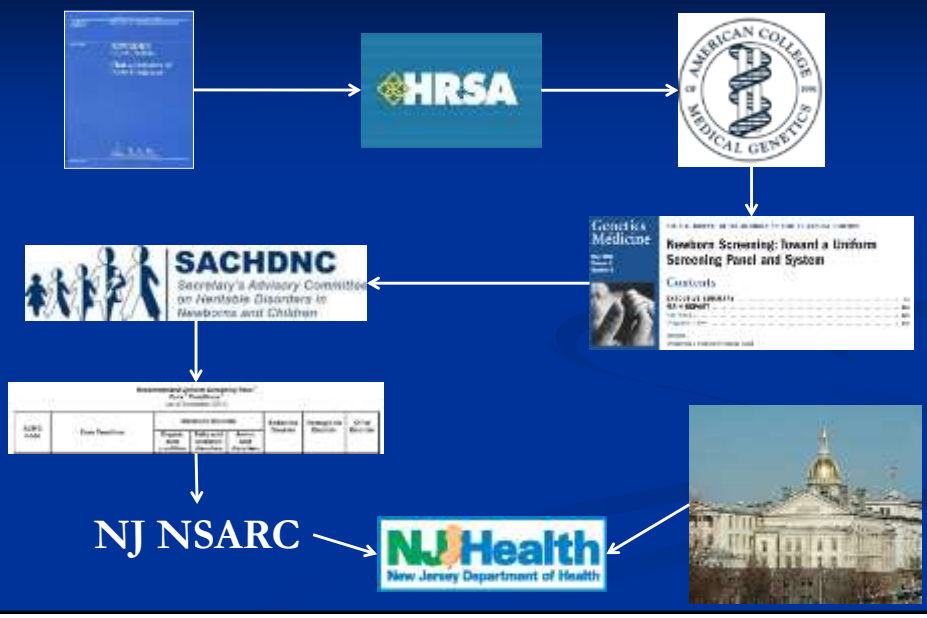
NJ Health

NEWBORN SCREENING

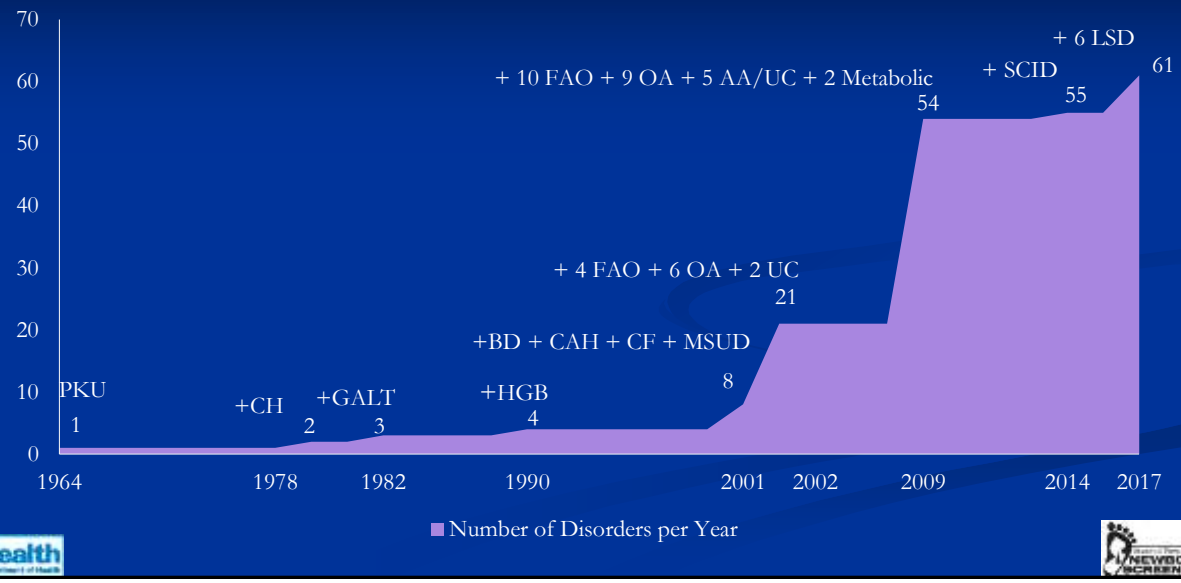
NBS in NJ: Not just PKU anymore!



Why these disorders?



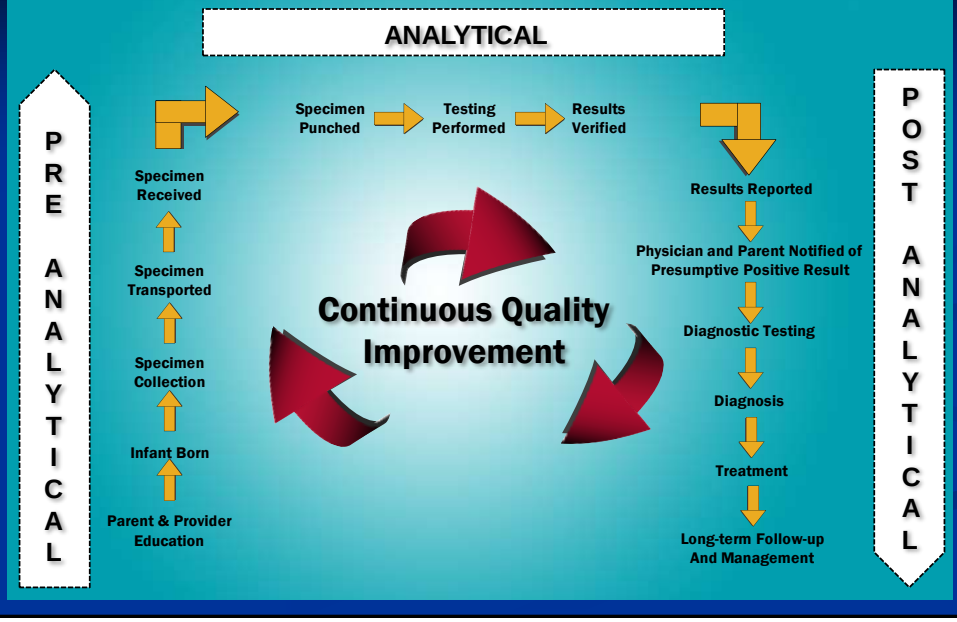
NBS in NJ: Not just PKU anymore!

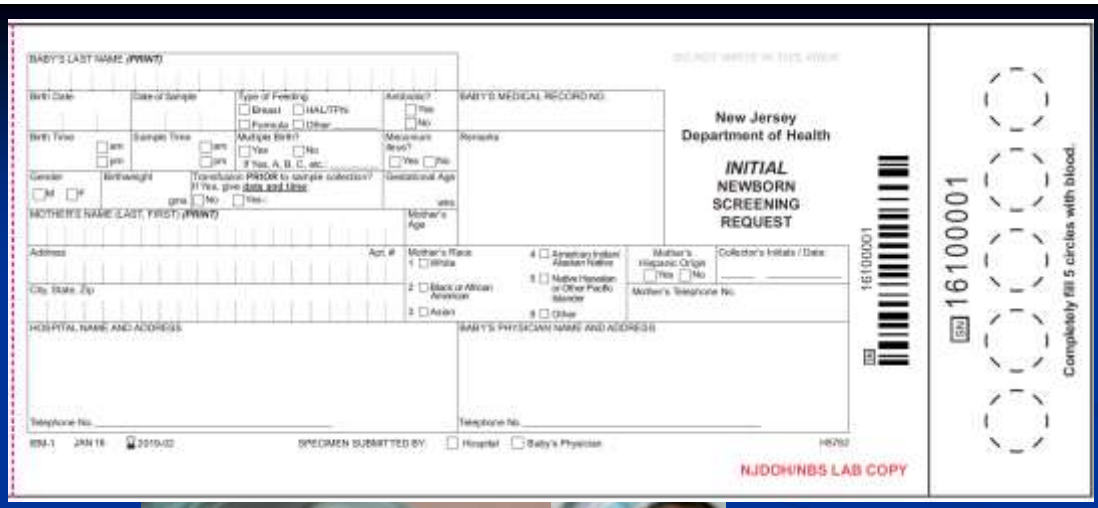


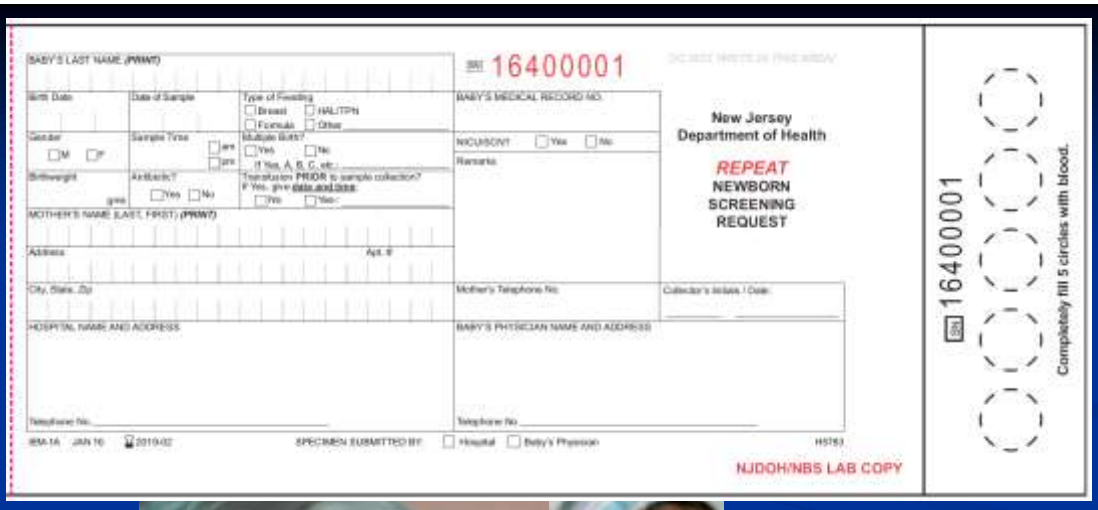
NJ Newborn Screening Program

- Single screen collected at 24 to 48 hrs of age
- ~99,500 births
  - ~118,000 specimens
- 55 disorders
  - SCID – 6/30/2014
- $150 / initial specimen

NBS System Process

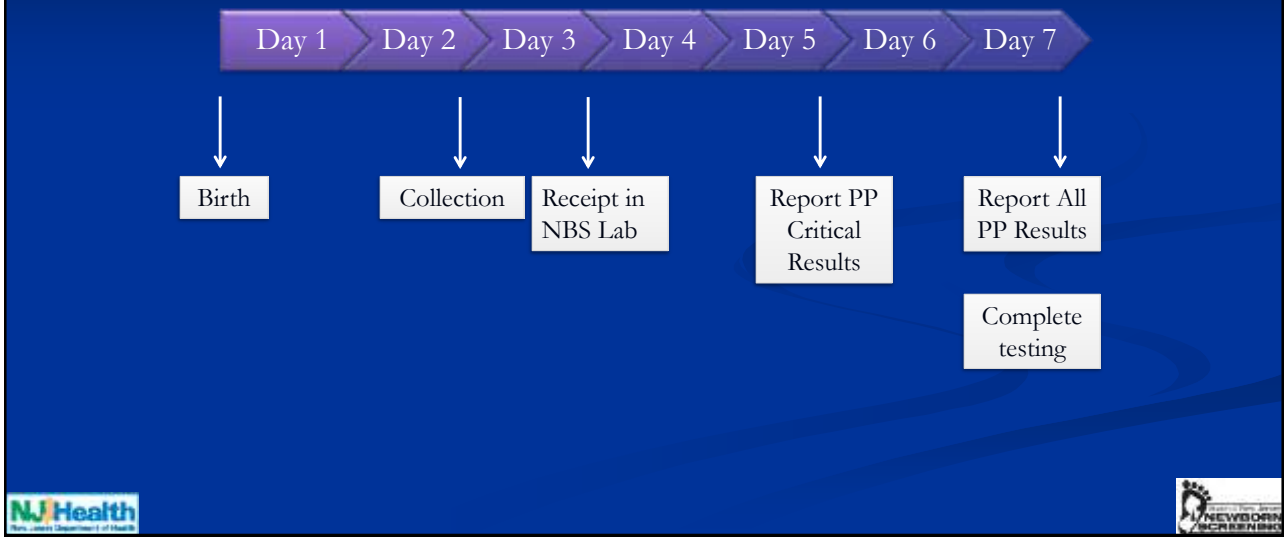





BABY'S LAST NAME (PRINT)
16400001
Birth Date
Date of Sample
Type of Feeding
Breast
HALTTPN
Formula
Other
BABY'S MEDICAL RECORD NO.
Gender
M
F
Sample Time
am
pm
Multiple Birth?
Yes
No
If Yes, A, B, C, etc.:
NICU/SCNT
Yes
No
Birthweight
grams
Antibiotic?
Yes
No
Transfusion PRIOR to sample collection?
If Yes, give date and time:
Yes
Yes:
Remarks
MOTHER'S NAME (LAST, FIRST) (PRINT)
Address
Apt. #
City, State, Zip
Mother's Telephone No.
Collector's Initials / Date
HOSPITAL NAME AND ADDRESS
BABY'S PHYSICIAN NAME AND ADDRESS
Telephone No.
Telephone No.
NBS-1A JAN 10
2010-02
SPECIMEN SUBMITTED BY:
Hospital
Baby's Physician
HS763
NJDOH/NBS LAB COPY
New Jersey
Department of Health
REPEAT
NEWBORN
SCREENING
REQUEST
16400001
Completely fill 5 circles with blood.

ups
Express Envelope

Recommended Timeline



What happens to the results?

- Normal Results
- Abnormal Results
  - Borderline
    - Repeat in 2 days
  - Presumptive
    - Fax results to Follow-up
    - Call results to Follow-up
    - Immediate referral to appropriate consultant
- Unsatisfactory Specimens
  - Call submitter to submit repeat
- Initial Normal Results
  - Submitter
- All Abnormal Results
  - Submitter
  - Doctor of Record
- All Repeat Results
  - Submitter
  - Doctor of Record

How to get results

1. Voice Response System
2. Call NBS Laboratory

How to get results

1. Voice Response System
2. Call NBS Laboratory
3. Fax Release Form

State of New Jersey
DEPARTMENT OF HEALTH

NEWBORN SCREENING RECORDS RELEASE AUTHORIZATION

I, _____ hereby authorize the New Jersey Department of Health's Newborn Screening Laboratory to release the newborn screening laboratory results for _____ to

_____
(Physician Name)

_____
(Address)

_____
(City, State and Zip code)

_____
(Phone Number)

_____
(Fax Number)

Hospital of Birth: _____

Date of Birth: _____

Gender: ☐ MALE ☐ FEMALE

Mother's Last Name at Birth: _____

Parent/Guardian signature _____ Date _____

Please fax completed form to 609-530-6373

JOURNAL SENTINEL

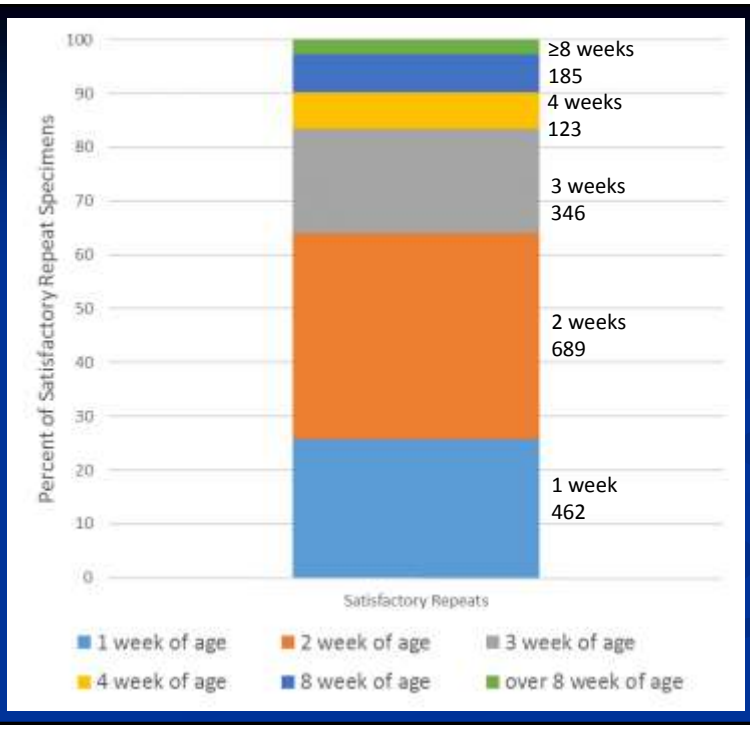
Deadly Delays

Delays at hospitals across country undermine newborn screening programs

Interactive: See how states compare and search for problem hospitals

Colton Hidde: Testing delay puts newborn's life in jeopardy

Lack of weekend lab hours adds to delay, putting babies at risk



New Jersey NBS Program

- 1964 through 2016
- 4,016 confirmed classic cases
  - From 45 of the 55 disorders on our panel
- 3,250 cases of variant forms and carriers

Illness, irreversible damage, death

Early intervention, no/reduced damage, longer and healthier life