Long-Term Follow-Up National Projects

Heartland Genetics and Newborn Screening Collaborative Annual Conference

August 25, 2011

Amy Brower, PhD

Presentation Overview

- Long-Term Follow-Up
- Introduction of Data Set Development
- Data Capture Tool Development
- Emerging Efforts
  - SACHDNC Statements
  - Workgroups Focused on LTFU
  - Research Projects

Screening Across the Life Course


Newborn Screening


Diagnostic


Preconceptual


Presymptomatic


Predispositional

Newborn Screening

- **Comprehensive System**
  - **Screening**
  - **Diagnosis**
  - **Long-Term Follow-Up**
- **All of the conditions are chronic and require medical care and other related services throughout the affected individual's lifetime**

Newborn Screening

- Newborn screening is one of the nation's most successful public health programs.
- Newborn screening programs test babies for disorders that are often not apparent at birth.

What to Screen For?

- **Principles of population screening**
  - **Incidence of condition**
  - **Screening test**
  - **Treatment**
  - **Cost**
- **Newborn screening**
  - **Incidence**
  - **Screening test in newborn period**
  - **Treatment and/or benefit**

The 'liberal gene': An instant guide

Scientists say they have found a gene that pushes some people to the left of the political spectrum. Here's how it works

POSTED ON OCTOBER 29, 2010, AT 2:58 PM

Your political views might not be entirely something you pick up at school or in talks around the dinner table — a new study suggests you might have been born with them. Scientists from the University of California-San Diego and Harvard, in a paper published in *The Journal of Politics*, say they have discovered that some people have a genetic predisposition to liberal thinking. What is this "liberal gene" they found, and does it really decide where a person will end up on the

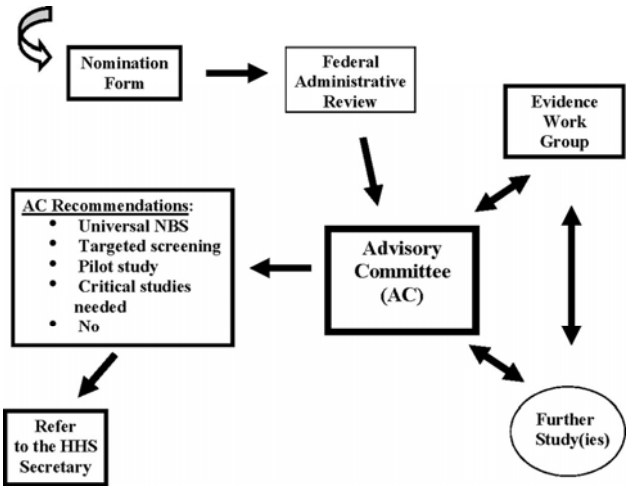
Could this baby have the DRD4 "liberal" gene? *Photo: CC BY: Jared and Corin*

Evolving Standard

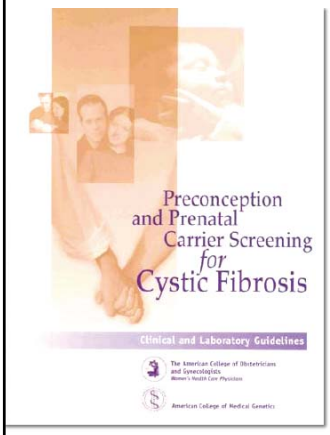
- From 1960 to 2005 the number of conditions screened varied from state to state
- The American College of Medical Genetics (ACMG) recommended a uniform panel of 29core conditions and 28 secondary conditions
- Federal Advisory Committee created nomination and evidence review process to add new conditions to the panel
- Currently 30 core conditions and 29 secondary

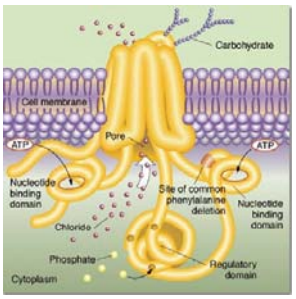
http://www.hrsa.gov/heritabledisorderscommittee/sachdnc.pdf

Nomination and Review Process



Evidence Based Expansion





"Woe to the child which kissed on the forehead tastes salty. He is bewitched and will soon die."

Northern European Folklore

Long-Term Follow-Up of Newborn Screening Patients

- Selected Milestones
  - HRSA Regional Collaboratives and NCC (2004)
  - Recommended Uniform Screening Panel (2005)
  - Public Law 110-204 Newborn Screening Saves Lives Act (2007)
  - SACHDNC Statement on LTFU (2008)
  - NICHD NBSTRN (2008)
  - NICHD Hunter Kelly Newborn Screening Research Program (2009)
  - HRSA NCC Long-Term Follow-Up Data Collection Workgroup (2008)
  - CDC Surveillance Project (2008 – 2011)
  - Joint Workgroup – HRSA NCC LTFU and NICHD NBSTRN Clinical Centers Workgroup (2009)
  - SACHDNC Statement on LTFU (2011)

SACHDNC Statements on LTFU

- **Key Features**
  - **Assurance and provision of quality chronic disease management**
  - **Condition-specific treatment**
  - **Age-appropriate preventive care throughout the lifespan of affected individuals**
- **Components**
  - **Care coordination through a medical home**
  - **Evidence-based treatment**
  - **Continuous quality improvement**
  - **New Knowledge discovery**

Hunter Kelly Newborn Screening Research Program

Identifying, developing, and testing the most promising new screening technologies, in order to improve already existing screening tests, increase the specificity of newborn screening, and expand the number of conditions for which screening tests are available

Experimental treatments and disease management strategies for additional newborn conditions, and other genetic, metabolic, hormonal and or functional conditions that can be detected through newborn screening for which treatment is not yet available.

Public Law 110-204

Newborn Screening Saves Lives Act of 2007

Work in consultation with the appropriate State departments of health, and focus research on screening technology not currently performed in the States and conditions on the uniform screening panel

Other activities that would improve newborn screening, as identified by the Director.

Health Outcomes

Intake

- Demographics
- SES
- Family History
- Prenatal History
- Neonatal History
- Birth Measurements
- Newborn Screening
- Hearing Screening
- Diagnostic Testing

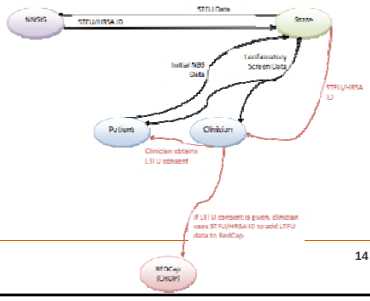
Childhood

- Monitoring Labs
- Diet
- Therapies
- Emergency Management
- Developmental Screening
- Imaging Studies
- Intercurrent Complications

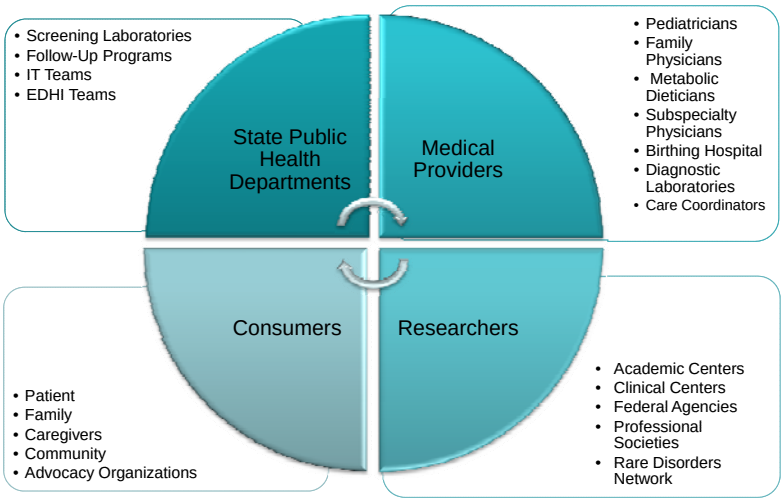
Adulthood

- Monitoring Labs
- Diet
- Therapies
- Emergency Management
- Imaging Studies
- Intercurrent Complications

- Create a uniform dataset for all conditions “80%”
- Create condition-specific datasets



NBS Stakeholders



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Introduction of Long-Term Follow-Up Data Sets

- Joint effort
  - NCC/RC Long-Term Follow-Up Workgroup
    - Heartland - Julie Miller and Stephen Kaler
  - NBSTRN Clinical Centers Workgroup
- Objective
  - Develop minimum data set with accompanying informatics tools to
    - Enhance health services delivery
    - Empower research
    - Facilitate surveillance
- Scope
  - Conditions in current recommended newborn screening panel

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Methodology

- Literature and Key Effort Review
- Stakeholder Engagement
- Expert workgroups
  - Hemoglobinopathies
  - Endocrinopathies
  - Metabolic Disorders
  - CF
  - Hearing Loss
  - SCID
  - LSD
- Standardization and Coding

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Defining a Uniform Data Set

Intake

- Demographics
- SES
- Family History
- Prenatal History
- Neonatal History
- Birth Measurements
- Newborn Screening
- Hearing Screening
- Diagnostic Testing

Childhood

- Monitoring Labs
- Diet
- Therapies
- Emergency Management
- Developmental Screening
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- Intercurrent Complications

Adulthood

- Monitoring Labs
- Diet
- Therapies
- Emergency Management
- Imaging Studies
- Intercurrent Complications

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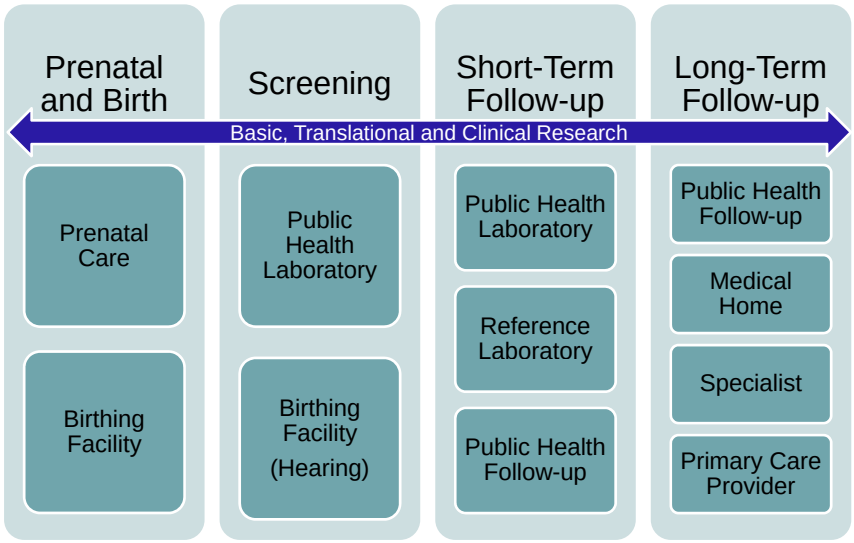
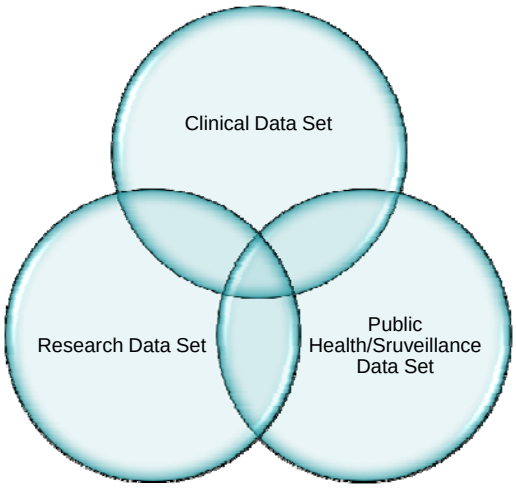
Locations of Information Exchange

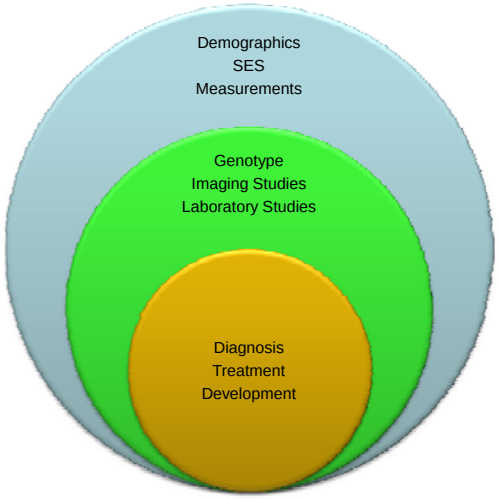


Newborn Screening Translational Research Network 19

Data Sets



Data Sets



Next Steps

- Finish data sets
- Review with Effective Follow-Up Workgroup
- Transfer to National Library of Medicine (NLM)
- Stakeholder buy-in
- Data dictionary & standardized language
- Develop data collection tool
- Summarize, communicate and disseminate
- Pilot

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Emerging Efforts

- PIDTC Data Set
- HRSA Categorical Models
- NYMAC Diagnosis Guide
- Industry Registries
- Disease Group Registries
- NORD Patient Registry

Information Source	LTFU Data Set Question/HRSA Topic Area/NYMAC Clinical Note
HRSA Categorical designation diagnosis	Elevated C8 with C6<C8>C10
HRSA Categorical designation diagnosis	Two disease-causing mutations
HRSA Categorical designation diagnosis	Elevated C8:C10
NYMAC_Abnormal Newborn	Elevated C8; Lesser elevation of C6 and C10, C10:1; Mutation detection in some states
NYMAC_Initial Diagnostics	Acylcarnitine profile and urine acylglycines
NYMAC_Additional Tests	Blood glucose
NYMAC_Additional Tests 2	Plasma carnitine, total and free
NYMAC_Additional Tests 3	Urine organic acids
NYMAC_Diagnostic Confirmation	Typical pattern of acylcarnitines is diagnostic - C6<C8>C10; elevated urine hexanoglycine and suberylglycine; mutation analysis in absence of typical metabolite pattern is required
NYMAC_MIM #	201450
NYMAC_SNOMED Code	128596003
NYMAC_ICD-10-CM Code	E71.311
NYMAC_Newborn LOINC	53175-6;45211-0, 45197-1,45198-9
NYMAC_Enzyme Commission #	607008/1.3.99.3
LTFU Data Set Diagnostic	Aclycarnitine Profile
LTFU Data Set Diagnostic	Organic Acids
LTFU Data Set Diagnostic	Acylcarnitine
LTFU Data Set Diagnostic	Carnitine
LTFU Data Set Diagnostic	Fatty acid oxidation probe assay
LTFU Data Set Diagnostic	Western Blot
LTFU Data Set Diagnostic	Fatty acid prorile
LTFU Data Set Diagnostic	C16OH, C16:1-OH,C18-OH, C18:1-OH,C16OH/C16

Public Health Focus - Data Categories Identified

- Subjective Summary – Well or Not
- Continuity of Care
- Patient Tracking
- Physical/Growth Parameters
- Access/Barriers to Care
- Services
- Health Status
- Review of Systems
- Disorder Related Interventions
- Developmental Assessment
- Subjective Summary – Well or Not
- Data Quality

Identified Questions

- Are we preventing or reducing morbidity/mortality without additional harm?
- Is there universal access to the program?
- Are we doing this in the most effective way?
- Are we doing this in the most cost effective way?
- Is the disorder on newborn panel?
- What percent of children with disorders remain in care between the ages of one and five years old?
- What percent become lost to follow-up?
- What percent of parents refuse treatment?

Questions

- What percent died due to problems associated with the disorder?
- What percent were determined not to need ongoing treatment?
- What percent of children (combined or by specific type of disease) had age appropriate developmental status with respect to speech, physical development, mental/cognitive development, gross motor and fine motor development?
- What percent of children were severely delayed with respect to any of the developmental measures and what year of life did the delays become apparent?

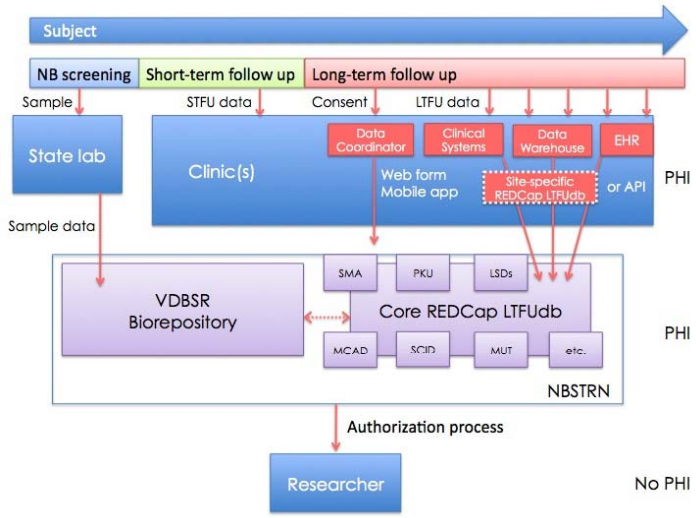
Questions

- What percent of patients experienced symptoms associated with their disorder and at what age did the symptoms become apparent?
- In any given year, what percent of children experienced the loss of skills they had previously acquired?
- What percent of children had no hospitalizations or emergency room visits in the previous year of life?
- What disorders are associated with the greatest number of hospitalizations and emergency room visits due to disorder-related complications?
- What disorders are associated with the highest utilization of metabolic center visits?
- What percent of children are receiving a multidisciplinary team of services, including nutritional counseling, health education and social services counseling?

Next Steps

- **Survey meeting attendees to match public health data categories with LTFU data set elements**
- **Generate public health data set**
- **Disseminate public health data set**
- **Finalize public health data set**
- **Pilot**
- **Develop assessment measures**

Data Capture Tool Development



Year 1 Progress

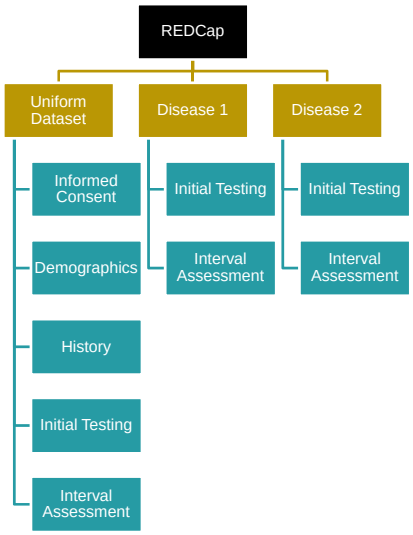
8-5-11 to 10-31-11

- Establish stakeholder relationships ✓
  - NBSTRN NCC (Brower)
  - IBEMC (Berry, Hiner, Bentley, Cameron)
  - Colorado (Thomas, Turtle)
  - NLM (Zuckerman, Goodwin)
  - HRSA (Therrell)
- Gather requirements (IBEMC, Colorado) ✓
- Mock disease eCRF (MCAD) ✓
- Common data element (CDE) standards (Brower, NLM)
- Establish standards ✓
- Validate standards ✓
- Create/obtain CDE data dictionary definitions ✓
- Implement dictionary viewer (see following) ✓
- CDE eCRFs (see following) ✓

Uniform Dataset

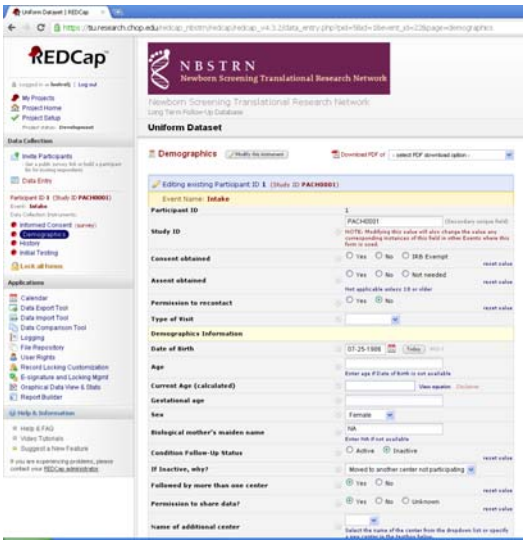
Common Data Elements									
Module	# Intake	# Interval	Total Elements	Initial Discussion	Draft Version	External Review	Changes Made	Final Review	Complete
Care Coordination	3	0	3	x	x				
Demographics	15	10	25	x	x	x	x		
Developmental Assessment	0	7	7	x	x				
Diagnostic Testing	13	0	13	x	x				
Education	0	1	1	x	x				
Emergency Management	1	6	7	x	x				
Family History	8	1	9	x	x				
Home Monitoring	0	1	1	x	x				
Imaging Studies	0	1	1	x	x				
Interval Health History (since last visit)	0	8	8	x	x				
Laboratory Studies	0	8	8	x	x				
Measurements	3	4	7	x	x				
Neonatal History	4	0	4	x	x				
Newborn Hearing Screening	1	0	1	x	x				
Newborn Screening	7	0	7	x	x				
Nutrition	0	3	3	x	x				
Past Health History	4	0	4	x	x				
Pharmacotherapy	0	1	1	x	x				
Prenatal History	6	0	6	x	x				
SES	11	2	13	x	x	x	x		
TOTAL	**76**	**53**	**129**						

REDCap Modules

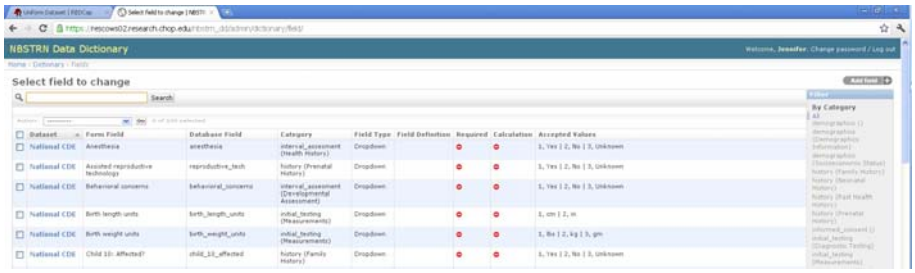


REDCap Data Entry

- All common data elements have been entered
- Validation discussions happening now
- First disease specific set in progress



Data Dictionary



- Data dictionary will track definitions and accepted values for common data elements and each disease specific set of elements

In progress/upcoming

- Select pilot disease (FAO) ✓
- FAO eCRF
  - Create eCRF ✓
  - Add disease-specific definitions ✓
  - Validation 1 (IBEMC) ✓
  - Validation 2 (Colorado) ✓
- Technical requirements ✓
- Compliance/security requirements ✓

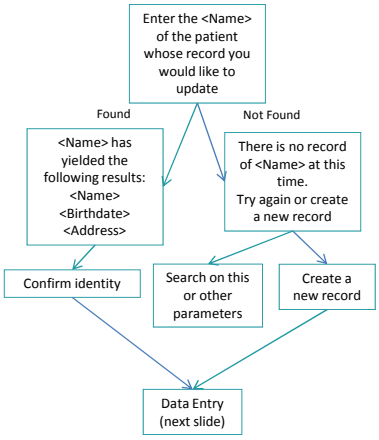
Security Considerations

	Pros	Cons
With PHI	• Identity confirmation after search results • Identity confirmation during data entry • Downstream ability to link to VRDBS/DBS/Other • No additional knowledge needed by providers, better enabling point-of-service data entry by any approved provider	• Substantially more development and maintenance effort/cost • Likely will delay timelines for production system launches • Other privacy issues
Without PHI	• Less development and maintenance effort/cost	• Ability to initially and persistently confirm identity is lost to the provider • Reduced ability to update patient record based on knowledge at time of service

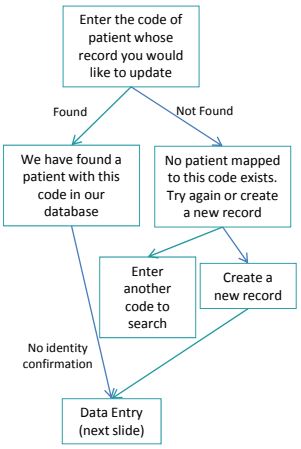
FISMA

FISMA Low Risks:
Record Finding

- **"FISMA low" solution introduces substantial risk to data integrity in some situations**
- **No mechanism for confirming patient identity during lookup transaction**
- **No mechanism for constant confirmation of patient identity on data entry screens (next slide)**
- **Risk is slightly mitigated by using highly variable codes for patients**



With PHI



Without PHI

NNSGRC – Consent for LTFU

Tabulation of State Newborn Screening Program Information – Consent for Storage of Long Term Follow-up Information (July 20, 2011)

	State	If your NBS program is collecting long term follow-up data, is there a consent process in place? yes	no	Are your clinics that collect long term data utilizing a consent process?	Comments	Responder
1	Alabama	No Long Term Follow-up				Ashley
2	Alaska	No Long Term Follow-up				Wood
3	Arizona	No Long Term Follow-up				Jacox
4	Arkansas		X	See Comments	In the Child & Adolescent Health Dept. of the Arkansas Department of Health, Long-Term Follow-up is done yearly, until the child is five years of age. This data is collected without consent and is not shared with any other agency. Long-Term Follow-up information is collected from either Arkansas Children's Hospital clinics or through the PCP. Long-Term Follow-up information is primarily obtained to assure that these children are followed for their condition. At this point, we are not seeking information about health/developmental outcomes, connections with medical homes, quality of life, etc.	Whitfield
5	California		X	See comments	We do not currently use a consent form and conside these data program development and evaluation, which we are permitted to collect by state law without consent. However, we are discussing whether collection beyond our current 5 year limit, which we plan to do, would fall outside those bounds and we may need consent to continue beyond 5 years. We are consulting legal on this issue. Clinic data are collected via vendor agreements with the metabolic or other specialty centers and they enter the LTFU data via online access to our web based system. I'm not aware that they request consents from their patients, although either they or we require consents for new blood samples or unusual studies outside of regular NBS and past one year. As with everything else, there are restrictions on data use. The rules are the same for requesting other data or specimens, to this point we have never released PHI to outside researchers. They are permitted if both the state IRB and our internal review team allow it, but no one has ever requested this to date.	Lorey
6	Colorado		X	See comments	Colorado doesn't perform any state health department-based long-term follow-up. We contract with the Sickle Cell Clinic at the University of Colorado and the Inherited Metabolic Diseases Clinic at Children's Hospital to provide follow-up for abnormal newborn screens for hemoglobinopathies and inborn errors of metabolism respectively. Because these clinics provide ongoing care, by definition they measure long-term follow-up parameters over time. We do not contract with the CF Center at Children's Hospital, but they do care for all children diagnosed with CF through the NBS program, so by definition, again, they are collecting data items related to long-term follow-up. They have their own in-house consent procedures, obviously. But they do not report these long-term follow-up data to the NBS program, so consent for long-term follow-up is not an issue in Colorado.	Taylor
7	Connecticut	No Long Term Follow-up				

SACHDNC Statements

Long-term follow-up after diagnosis resulting from newborn screening: Statement of the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

Alex R. Kemper, MD, MPH[1], Coleen A. Boyle, PhD[2], Javier Aceves, MD[3], Denise Dougherty, PhD[4], James Figge, MD, MBA[5], Jill L. Fisch[6], Alan R. Hinman, MD, MPH[7], Carol L. Greene, MD[8], Christopher A. Kus, MD, MPH[9], Julie Miller, BS[10], Derek Robertson, MBA, JD[11], Brad Therrell, PhD[12], Michele Lloyd-Puryear, MD, PhD[13], Peter C. van Dyck, MD, MPH[13], and R. Rodney Howell, MD[14]

The US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children provides guidance to reduce the morbidity and mortality associated with heritable disorders, with a special emphasis on those conditions detectable through newborn screening. Although long-term follow-up is necessary to maximize the benefit of diagnosis through newborn screening, such care is variable and inconsistent. To begin to improve long-term follow-up, the Advisory Committee has identified its key features including the assurance and provision of quality chronic disease managem age-appropriate preventive care throughout the lifespan of affected individu to achieving long-term follow-up: care coordination through a medical home, quality improvement, and new knowledge discovery. *Genet Med* 2008:10(

What questions should newborn screening long-term follow-up be able to answer? A statement of the US Secretary for Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children

Cynthia F. Hinton, PhD, MPH[1], Lisa Feuchtbaum, DrPH, MPH[2], Christopher A. Kus, MD, MPH[3], Alex R. Kemper, MD, MPH[4], Susan A. Berry, MD[5], Jill Levy-Fisch, BA[6], Julie Luedtke, BS[7], Celia Kaye, MD, PhD[8], and Coleen A. Boyle, PhD, MS[2]

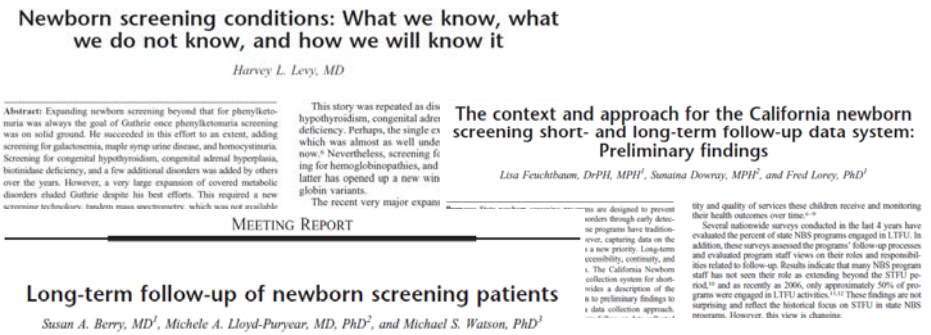
Abstract: The US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children provides guidance on reducing the morbidity and mortality associated with heritable disorders detectable through newborn screening. Efforts to systematically evaluate health outcomes, beyond long-term survival, with a few exceptions, are just beginning. To facilitate these nascent efforts, the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children initiated a project to define the major overarching questions to be answered to assure that newborn screening is meeting its goal of achieving the best quality outcome for the affected children and their families. The questions identified follow the central components of lona-term follow-up—nated effort to improve tracking and monitoring of healthcare delivery (e.g., services used, clinical care received, and health-related outcomes). Efforts to systematically evaluate health outcomes, beyond long-term survival, with a few exceptions, are just beginning. To facilitate these nascent efforts, the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) initiated a project to define the major overarching questions to be answered to assure that NBS is meeting its goal of achieving the best quality outcome for the affected children and their families. Long-term follow-up (LTFU) begins after a newborn with an out of range screening result has diagnostic confirma-

Newborn Screening Translational Research Network

Requests From the SACHDNC Sub-Committees

- **Laboratory Sub-committee**
  - **Need for expansion of vocabulary and coding guidance to include confirmatory testing**
- **Treatment and Follow-up Sub-committee**
  - **Need for a standard messaging and coding approach to capturing common and condition specific follow-up datasets**
- **Education Sub-committee**
  - **Need for education of primary care physicians about the value of HL7 NBS messages and including NBS in a lifetime medical record**

HRSA NCC LTFU Data Workgroup



Newborn screening conditions: What we know, what we do not know, and how we will know it

Harvey L. Levy, MD

Abstract: Expanding newborn screening beyond that for phenylketonuria was always the goal of Guthrie once phenylketonuria screening was on solid ground. He succeeded in this effort to an extent, adding screening for galactosemia, maple syrup urine disease, and homocystinuria. Screening for congenital hypothyroidism, congenital adrenal hyperplasia, biotinidase deficiency, and a few additional disorders was added by others over the years. However, a very large expansion of covered metabolic disorders eluded Guthrie despite his best efforts. This required a new

This story was repeated as dis
hypothyroidism, congenital adre
deficiency. Perhaps, the single ex
which was almost as well unde
now.[6] Nevertheless, screening fo
ing for hemoglobinopathies, and
latter has opened up a new win
globin variants.
The recent very major expans

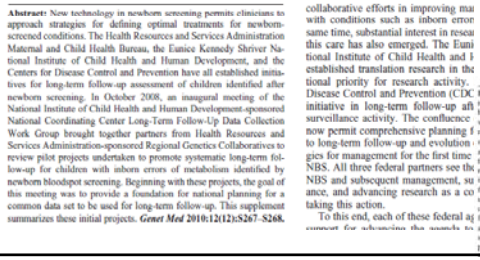
The context and approach for the California newborn screening short- and long-term follow-up data system: Preliminary findings

Lisa Feuchtbaum, DrPH, MPH[1], Sunaina Downey, MPH[2], and Fred Lorey, PhD[1]

MEETING REPORT

Long-term follow-up of newborn screening patients

Susan A. Berry, MD[1], Michele A. Lloyd-Puryear, MD, PhD[2], and Michael S. Watson, PhD[3]



Abstract: New technology in newborn screening permits clinicians to approach strategies for defining optimal treatments for newborn-screened conditions. The Health Resources and Services Administration Maternal and Child Health Bureau, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the Centers for Disease Control and Prevention have all established initiatives for long-term follow-up assessment of children identified after newborn screening. In October 2008, an inaugural meeting of the National Institute of Child Health and Human Development-sponsored National Coordinating Center Long-Term Follow-Up Data Collection Work Group brought together partners from Health Resources and Services Administration-sponsored Regional Genetics Collaboratives to review pilot projects undertaken to promote systematic long-term follow-up for children with inborn errors of metabolism identified by newborn bloodspot screening. Beginning with these projects, the goal of this meeting was to provide a foundation for national planning for a common data set to be used for long-term follow-up. This supplement summarizes these initial projects. *Genet Med* 2010;12(12):S267–S268.

collaborative efforts in improving ma
with conditions such as inborn error
same time, substantial interest in resea
this care has also emerged. The Euni
tional Institute of Child Health and H
established translation research in the
tional priority for research activity.
Disease Control and Prevention (CDC
initiative in long-term follow-up aft
surveillance activity. The confluence
now permit comprehensive planning f
to long-term follow-up and evolution
gies for management for the first time
NBS. All three federal partners see th
NBS and subsequent management, su
ance, and advancing research as a co
taking this action.
To this end, each of these federal ag

Long-term follow-up in newborn screening: A systems approach for improving health outcomes

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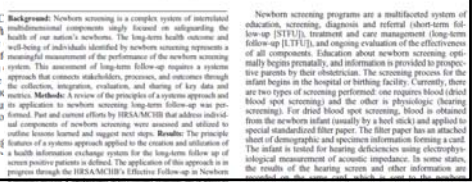

Background: Newborn screening is a complex system of interrelated multidimensional components singly focused on safeguarding the health of our nation's newborns. The long-term health outcome and well-being of individuals identified by newborn screening represents a meaningful measurement of the performance of the newborn screening system. This assessment of long-term follow-up requires a systems approach that connects stakeholders, processes, and outcomes through the collection, integration, evaluation, and sharing of key data and metrics. **Methods:** A review of the principles of a systems approach and its application to newborn screening long-term follow-up was performed. Past and current efforts by HRSA/MCHB that address individual components of newborn screening were assessed and utilized to outline lessons learned and suggest next steps. **Results:** The principle features of a systems approach applied to the creation and utilization of a health information exchange system for the long-term follow up of screen positive patients is defined. The application of this approach is in progress through the HRSA/MCHB's Effective Follow-up in Newborn

Newborn screening programs are a multifaceted system of education, screening, diagnosis and referral (short-term follow-up [STFU]), treatment and care management (long-term follow-up [LTFU]), and ongoing evaluation of the effectiveness of all components. Education about newborn screening optimally begins prenatally, and information is provided to prospective parents by their obstetrician. The screening process for the infant begins in the hospital or birthing facility. Currently, there are two types of screening performed: one requires blood (dried blood spot screening) and the other is physiologic (hearing screening). For dried blood spot screening, blood is obtained from the newborn infant (usually by a heel stick) and applied to special standardized filter paper. The filter paper has an attached sheet of demographic and specimen information forming a card. The infant is tested for hearing deficiencies using electrophysiological measurement of acoustic impedance. In some states, the results of the hearing screen and other information are

Research Projects

- Pilot Newborn Screening Project for Identification and Prospective Follow-up of Infants with Spinal Muscular Atrophy
  - Kathy Swoboda – University of Utah
- Inborn Errors of Metabolism Collaborative: Defining the Natural History of Inborn Errors of Metabolism
  - Cynthia Cameron – Michigan Public Health Institute

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