Newborn Screening in Texas

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Disclosure
Debra Freedenberg, M.D., Ph.D.
has no relationships with commercial companies to disclose

Learning Objectives
At the end of this presentation the participant will be able:
1. To understand how the Texas Newborn Screening (NBS) Program functions
2. To address considerations of adding newborn screening for new conditions
   • X-Linked Adrenoleukodystrophy (X-ALD), and
   • Spinal Muscular Atrophy (SMA)
3. To address ethical considerations in newborn screening.

Goals of Texas NBS Program
Two screening tests for each baby born in Texas
• 24 – 48 hours of age
• 1 – 2 weeks of age

Infants testing positive receive prompt and appropriate confirmatory testing.

Diagnosed infants are maintained on appropriate medical therapy.
Texas Newborn Screening Program History

- 1963 – Phenylketonuria (PKU) pilot
- 1965 – Mandated PKU screening
- 1978 – Added Galactosemia & Homocystinuria screening
- 1980 – Added Congenital Hypothyroidism screening, Recommended second screen
- 1983 – Discontinued Homocystinuria screening, added Hemoglobinopathy screening, Required second screen
- 1989 – Added Congenital Adrenal Hyperplasia screening
- 1995 – Added second-tier DNA testing for hemoglobinopathies
- 2000 – Added hearing screening
- 2005 – National Newborn Screening and Global Resource Center review – external review of NBS program
- 2005 - House Bill 790 mandated expansion to American College of Medical Genetics recommended core panel of 29 disorders as funding allowed
  - No funding for Cystic Fibrosis provided
  - Required cost effectiveness study
- May 2006 - Cost effectiveness study complete, testing to be performed by DSHS Laboratory
- December 2006 - 1st abnormal Tandem Mass Spectrometry (MS/MS) results reported
  - 19 new disorders
- January 2007 - Added Biotinidase deficiency screening
- 2009 - HB 1672 – added provisions for
  - Disclosure to parents that specimens can be retained & used for research and QA/QC
  - Parents to request specimen destruction
  - Confidentiality of specimens and data
  - Sickle cell trait screening
- December 2009 - Added cystic fibrosis screening
- Spring 2010 - NBS Advisory Committee formed
- 2011 - HB 411 - amended HSC 33.018 related to the confidentiality and changed from an opt-out process for all residual specimen uses to an opt-in process for external research purposes
- December 2012 – Added Severe Combined Immunodeficiency (SCID)
- 2014 – Added Critical congenital heart disease (CCHD)
- 2015 – Added MS/MS secondary targets

Newborn Screening Panel

Currently screen for 53 disorders from dried blood spots
- Congenital Hypothyroidism
- Congenital Adrenal Hyperplasia
- 4 Hemoglobinopathies
- Galactosemia
- Biotinidase Deficiency
- 14 Amino Acid Disorders
- 13 Fatty Acid Oxidation Disorders
- 15 Organic Acid Disorders
- Cystic Fibrosis
- SCID and T-cell related lymphocyte deficiencies
  - Plus 2 Point of Care screening
    - Hearing loss
    - CCHD

The Logistics of Newborn Screening in Texas

- The healthcare provider requests specimen collection forms
- DSHS Laboratory assigns form serial numbers to the healthcare provider and ships the forms
- Healthcare provider collects the specimen and sends it to DSHS
- Specimen is assigned a laboratory ID number in the laboratory data system
- Demographic sheet is separated from the blood spots and sent to Demo Entry team where the information is entered into the database
- Specimen is sent to NBS Laboratory for testing

Types of Kits

- Medicaid / CHIP / Charity
  - Newborn or mother is eligible for Medicaid
  - Newborn is eligible for CHIP
  - Baby doesn’t have insurance or other payment source
  - Kits are free to provider

- Insurance / Self-Pay
  - Payment is due within 90 days of invoice date
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NBS Kit Components

- Parent Information
- Parent Decision Form
- Demographic Form (white and yellow copies)
- Filter Card
- Instructions and Fold Over Flap

Parent Decision Form

- HB411 became law in June 2011 and made major changes to NBS specimen retention and residual use.
- Opt-in for long term storage and possible research uses - effective June 1, 2012 - Use of Parent Decision Form.
- ~53% of NBS have a parent decision form returned.
- ~73% of those returned and valid give permission for longer storage and external public health research uses (39% of all newborns).

% of Births Screened

- Parents can only refuse to have their child screened if the screening conflicts with a parent's religious tenets or practices.
- In 2014, 409,111 births were registered in TX and 8,241 (2.0%) were not linked to TX newborn screen database.
- 645 were TX residents out of state births.
- 901 deaths occurred within 24 hours after birth.
- ~6,695 (1.6%) newborns not screened.

Courier Services

- First tier - Lone Star Delivery and Processing.
  - Hospitals, Pediatric Clinics
  - 532 NBS submitters
  - 69% of NBS specimens (85% of 1st screens)
  - Pick-up Sun – Fri, deliver Mon - Sat
- Second tier - FedEx
  - 192 NBS submitters
  - 13.8% of specimens (14.5% of 1st screens)
  - Pick-up and deliver Mon - Sat

Pre-analytical Measures

June – September 2017

Day 1: Birth
Day 2: Collection
Day 3: NBS Lab
Day 4: AbN Critical Results
Day 5: All AbN Results
Day 6: Complete testing
Day 7: Complete testing

- 97.0% completion
- 24.3% critical results
Newborn Screening Workload 2017

- Received 743,283 specimens (~380,000 newborns)
- Specimens Assayed and Reported: 737,926
  - Average 2,382 specimens per day
  - 5,357 unsatisfactory specimens (~0.72%)
  - >17,000 (2.4%) specimens reported with presumptive positive results
  - ~830 cases diagnosed
  - Testing & follow-up performed 6 days a week

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Timeline of a specimen in the laboratory...

- Specimen arrives.
- Specimen accessioned.
- Demo entry begins.
- Specimen punched.
- Testing begins for all disorders except Hemoglobinopathy (HB), Biotinidase Def (BIOT) and SCID.
- Remaining time sensitive results released.
- Result report is printed, sent to mailroom, and available online.
- Galactosemia & Cystic Fibrosis DNA results are sent to Clinical Care Coordination.
- Results for most time sensitive disorders are released.
- Clinical care coordination contacts providers for out-of-range results for time critical and time sensitive disorders.
- Hemoglobinopathy and MCAD DNA testing performed in weekly batches.

Result Reporting

- Preliminary panic values are immediately forwarded by fax for some disorders
- Final abnormal results immediately generate a case
- Clinical Care Coordination staff begins follow-up protocols with hospitals, physicians, and parents
- All results reported back to submitting provider via mail, fax, web portal and/or HL7 message

ORDERING AND REPORTING OPTIONS

Test Ordering
- ~130,500 per year (16.7% of NBS)
- Remote Ordering

Reporting
- ~137,000 per year (17.7% of NBS)
- Electronic Reporting Only
Analytical Measures

June – September 2017

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>Collection</td>
<td>NBS Lab</td>
<td>Time Critical Positives</td>
<td>72.1%</td>
<td>Time Sensitive Positives</td>
<td>84.7%</td>
</tr>
</tbody>
</table>

TX Health and Safety Code Section 33.011

• (a-1) Except as provided by this subsection and to the extent funding is available for the screening, the department shall require newborn screening tests to screen for disorders listed as core and secondary conditions in the Recommended Uniform Screening Panel of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children or another report determined by the department to provide more stringent newborn screening guidelines to protect the health and welfare of this state's newborns. The department may exclude from the newborn screening tests required under this subsection screenings for galactose epimerase and galactokinase.

New Conditions on RUSP but not TX NBS Panel

• Pompe
  • Approved for addition to the Recommended Uniform Screening Panel (RUSP) in March 2015
• Mucopolysaccharidosis Type I (MPS1)
  • Approved for addition to the RUSP in February 2016
• X-linked Adrenoleukodystrophy (X-ALD)
  • Approved for addition to the RUSP in February 2016
  • Appropriation of $1.2 million for implementation planned 9/2019
• Spinal Muscular Atrophy (SMA)
  • Approved for addition to RUSP in July 2018

New Disorders Grant X-ALD Activities Completed

• APHL funded – 2 Year grant (~$135,000)
• Initiate preparation and implementation activities for X-ALD newborn screening and to achieve the three following goals:
  • Develop the ability to perform second-tier sequencing analysis for X-ALD screening
  • Develop follow-up algorithms for abnormal X-ALD screens and establish a clinical referral network
  • Develop or update educational materials for families, providers, and the general public

Current Grants

CDC SCID NextGen Grant

• Development and validation of laboratory procedures using Next Generation sequencing technologies to assess genes causing SCID

CDC Implementation of Statewide Newborn Screening for X-ALD in Texas: Capacity Building and Quality improvement through data harmonization

• Develop test methodology and protocols, train laboratory staff and educate health care providers

Clinical Care Coordination

• Development and validation of laboratory procedures using Next Generation sequencing technologies to assess genes causing SCID

CDC Implementation of Statewide Newborn Screening for X-ALD in Texas: Capacity Building and Quality improvement through data harmonization

• Develop test methodology and protocols, train laboratory staff and educate health care providers
2015-2017 Confirmed Cases

<table>
<thead>
<tr>
<th>Disorder</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotinidase Deficiency</td>
<td>39</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>Congenital Adrenal Hyperplasia</td>
<td>87</td>
<td>92</td>
<td>68</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>66</td>
<td>71</td>
<td>61</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Sickle Cell Anemia</td>
<td>165</td>
<td>189</td>
<td>193</td>
</tr>
<tr>
<td>Various Other Hemoglobinopathies</td>
<td>38</td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>283</td>
<td>292</td>
<td>259</td>
</tr>
<tr>
<td>Metabolic Disorder</td>
<td>123</td>
<td>108</td>
<td>121</td>
</tr>
<tr>
<td>Severe Combined Immune Deficiency</td>
<td>7</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>T-Cell Related Lymphocyte Deficiencies</td>
<td>119</td>
<td>82</td>
<td>70</td>
</tr>
<tr>
<td>Grand Total</td>
<td>934</td>
<td>925</td>
<td>832</td>
</tr>
</tbody>
</table>

**SHORT TERM Follow-up**

**Overview**
- A case is opened for each out-of-range result
- Cases are monitored until an infant is cleared or diagnosis is determined
- Resources are provided for guidance on recommended actions

**URGENT Follow-up**

**POSITIVE SCREEN WITH VERY ELEVATED LEVELS: MEDICAL EMERGENCY**
- Reported immediately to nurses in NBS CCC
- On the same day, CCC Nurse will notify Primary Care Provider (PCP) by phone and fax the laboratory results reports received from the DSHS Lab
- If no PCP is on record for the newborn or cannot be located, the nurse will notify the parents directly

**Finding The Medical Provider**
- Find the Medical Provider responsible for the medical care of the baby
- Determine if the baby is in the hospital
- If a Medical Provider can be located:
  - Provide results
  - Provide guidance for recommended actions

**Finding The Family**
- If a Medical Provider cannot be located:
  - Contact parents to obtain PCP information
  - If a PCP is not identified:
    - Provide results to the family
  - Direct family to an Emergency Department (ED) if necessary
  - CCC Nurse will coordinate with ED staff if family directed to ED
When All Else Fails

If baby cannot be located:

- Utilize DSHS Regional Social Workers to assist with:
  - Locating the baby
  - Connecting baby with health-care providers and services.
- Involve other agencies, including law enforcement and/or CPS if necessary.

If baby cannot be located:

- Utilize DSHS Regional Social Workers to assist with:
  - Involve other agencies, including law enforcement and/or CPS if necessary.

Resources Distributed For Out-of-range Newborn Screen Results

Urgent Results — Fax to Medical Provider

- NBS letter with:
  - NBS disorder-specific lab results
  - Contact information for the CCC Nurse responsible for the NBS case
  - Disorder-specific ACT/FACT Sheet.
- List of regional subspecialist consultants.

Out-of-Range NBS — Mail

- Information to parent
- NBS letter
- General NBS Brochures.

Sickle Cell Trait Notification

- Required to screen by law
- Notify parents by certified letter, informational brochure, and list of resources included
- If letter returned, research new address, and resend not certified

Long Term Follow-Up

- Follow all conditions except CCHD and Sickle Trait for long term follow-up
- Long term follow-up elements identified by specialists for condition
- National efforts underway to identify common data elements
- Contact at varying times in first year of life
- Yearly contact after first year of life
- Forms returned by specialist, PCP, or parent

Long Term Follow-Up (continued)

- Girls with Hyperphenylalaninemia receive letter reminding of reproductive risks and importance of diet during pregnancy at 11 years of age
- Database now being redesigned to reflect harmonized common data elements
- Dedicated personnel for long term follow-up

NBS Support Group

- Ombudsman
- Educators (web and external)
- NBS Benefits Program
- Hearing Screening — Texas Early Hearing Detection and Intervention (TEHDI)
Advisory Committees

- NBS Advisory Committee was established in 2010
  - most recent meeting 10/19/2018
- Sickle Cell Advisory Committee
  - (no longer active)
  - was established in 2016 to raise awareness of sickle cell disease and sickle cell trait. Discontinued 2018 (Sunset review)
  - two members from former sickle cell advisory committee were added onto NBS Advisory Committee

System Stakeholders

- Meet yearly with ad hoc specialty groups for technical review/assistance
  - Metabolic
  - Pulmonary
  - Immunology
  - Ad Hoc meetings as needed (Metabolic when implemented secondary conditions, Immunology when SCID implemented)
- Regularly scheduled NBS system stakeholder update conference calls
  - March of Dimes
  - Texas Medical Association
  - Texas Pediatric Society
  - Texas Hospital Association
  - Texas Academy of Family Physicians

Additional DSHS Resources

- Children with Special Health Care Needs (CSHCN) Services Program to distribute parental support resources flyer for those with confirmed conditions identified by NBS
- Regional DSHS social workers to help locate families and assist with linking to public services

NBS Educational Efforts

- Newborn Screening Grand Rounds
- Newborn Screening Journal Club
- Tales from the Crib
- NBS Morbidity and Mortality Conference
- Educational Outreach
  - External Grand Rounds
  - General NBS presentations upon request
  - Webinar General NBS Grand Rounds

NBS/Genetics Educational Efforts

DSHS Sponsors:

- Yearly State of the Art Genetics Conferences-designed for primary care providers
- Baylor Seminars with Genetics-community based genetic seminars (joint with UT Austin Center for Disability Studies)
- Teratogen Information Program
  - University of Texas Health Science Center at Houston
- Clinical genetics medical student summer internships
- Hearing Screening Public Health Interns (Blue Ribbon Program)
Educational Projects for CCHD

• Funded TxPOP1 project
  • Tool Kit developed for CCHD screening
    Completed August, 2013

• Funded TxPOP2 project
  • Addressed NICU and rural CCHD screening
  • Developed general NBS and condition specific brochures
    Completed August, 2014

Newborn Hearing Screening Grants

CDC – 3 year $150,000/ Year 2
  • TEHDI MIS Enhancements

HRSA – 3 Year $250,000/ Year 2
  • Texas Hands & Voices Contract
  • Parent Support Project with Providers and Families
  • Care Coordinator at DSHS (part-time)
  • TEHDI Regional Learning Community Summits

X-Adrenoleukodystrophy

• Childhood cerebral form
  • ~20% of males with pathogenic variant develop neurodegenerative childhood cerebral form

• Adrenomyeloneuropathy (AMN)
  • ~60–65% of individuals with pathogenic variant – manifests in late twenties with progressive paraparesis, and sphincter disturbances, and often adrenocortical dysfunction

• Adrenocortical insufficiency
  • ~10% of affected individuals

• Adult women carriers
  • ~20% milder later onset progressive paraparesis, sphincter control abnormalities and sensory disturbances. Adrenal function usually normal

• No good genotype-phenotype correlation

X-ALD

• X-ALD leads to the accumulation of very long chain fatty acids in body tissues

• The diagnosis of X-ALD is mainly based on clinical findings, molecular tests and elevated plasma concentration of very long chain fatty acids

• C26:0 lysophosphatidylcholine (C26:0 LPC) is a specific marker for X-ALD and other peroxisomal disorders

• NBS assays target measurement of C26:0 lysophosphatidylcholine (LPC) by tandem mass spectrometry (MS/MS)

Identification of other family members X-ALD

X-linked disorder:
  Identifies other family members at risk
  • ~95% inherited from maternal carrier
  • ~4-5 % new maternal pathogenic variant
  • ~0.9% new de novo pathogenic variant in male

• Clarifies neurologic and endocrine diagnosis in other family members
X-Adrenoleukodystrophy Clinical Care Coordination

At time of out of range result:
- CCC notification to primary care provider by FAX or secure e-mail
- Letter
- NBS screen result
- ACT and FACT sheets
- List of subspecialist consultants (state wide)
- Notification of possible referral to specialty center (metabolic center and/or neurology for X-ALD (X))
- Mail information to parent
- Letter (NBS result and MD information)
- X-ALD NBS Brochures

SMA

- Autosomal Recessive Condition
- Progressive muscle weakness and atrophy resulting from progressive degeneration and loss of lower motor neurons (anterior horn cells)
- Incidence of ~1/10,000
- Etiology is:
  - homozygous deletion/gene conversion of exon 7 in the SMN1 (survival motor neuron gene) located on 5q
    - 95% - 98% of cases
  - compound heterozygotes (point mutations)
    - 2 - 5% of cases
  - 2% of affected individuals de novo deletion

SMA Clinical Variability

- SMN2 gene is located adjacent to the SMN1 gene
- Gene differs from SMN1 by only 5 bases, none of which are predicted to change the amino sequence of the protein
- SMN2 has a single base change intronic to Exon 7 (C to T transition) which disrupts a modulator of splicing leading to exclusion of Exon 7 from 90% of the mRNA transcript
- Clinical severity depends on the copy number of SMN2 genes

SMN2 Copy Number

<table>
<thead>
<tr>
<th>Copy Number</th>
<th>Normal</th>
<th>In SMA I</th>
<th>In SMA III</th>
<th>Total (SMA I + SMA III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14.4%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>32%</td>
<td>7 (13.5%)</td>
<td>0 (0%)</td>
<td>7 (4.9%)</td>
</tr>
<tr>
<td>2</td>
<td>51%</td>
<td>43 (82.7%)</td>
<td>0 (0%)</td>
<td>43 (30.3%)</td>
</tr>
<tr>
<td>3</td>
<td>4%</td>
<td>2 (3.9%)</td>
<td>70 (77.8%)</td>
<td>72 (50.7%)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0%)</td>
<td>20 (22.2%)</td>
<td>20 (14.1%)</td>
<td>40 (28%)</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>90</td>
<td>142</td>
<td></td>
</tr>
</tbody>
</table>

NBS for SMA

- New York State Pilot
  - Real time qPCR to detect homozygous SMN1 exon 7 deletion
  - Second tier to detect SMN2 copy number by targetedangen SMN1 gene or digital droplet PCR
- Perkin Elmer (in Development)
  - Multiplexed single tier assay with SCID combines detection of SMN1 exon 7 deletion, SMN2 copy number, HEC/SCID and KREC (XLA)
- Taiwan Pilot
  - Real Time PCR
  - Digital droplet PCR for SMN2 copy number and false +
Mechanism of Action

SMA6A binds to a specific sequence in the SMN2 transcript of exons 7 of the SMN2 transcript.

Treatment of SMA

- Anti-sense oligonucleotide that binds to C>T in SMN2 (Spinraza-nusinersen)
- Allows increased production of full length SMN 2 gene product to increase SMN protein
- Approved by the FDA 12/23/2016
- Intrathecal administration
- Cost estimates:
  - $750,000 for first year
  - $350,000 subsequent years
- Gene therapy in development

How to determine which conditions to screen for and how to add them?

- Recommended Uniform Screening Panel (RUSP) established 2006 core and secondary conditions
- Nomination of a condition to the HHS Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC)
- ACHDNC makes recommendation to HHS Secretary after evidence review and committee approval
- HHS Secretary approves ACHDNC recommendation and condition added to RUSP
- Each state decides on conditions their state screens for

Possible Candidate Conditions for NBS

- Fragile X
- Duchenne’s Muscular Dystrophy
- CLN2 (Batten’s) – New ERT
- CMV (Cytomegalovirus)
- GAMT (Guanidinoacetate N-methyltransferase)

Genetic Testing Results

- Genetic information can predict a person’s future
- Genetic tests divulge information about family members
- Genetic information can be used to discriminate/stigmatize
- Genetic testing can cause psychological harm

New Technologies NBS – Ethical concerns

- DNA confirmatory testing for out of range primary analyte
- Pathogenic variants gene panels (MCAD, Galactosemia, Cystic Fibrosis)
- Sequencing (VLCAD)
- Next Gen sequencing
  - Whole exome sequencing (WES)
  - Whole genome sequencing (WGS)
**Framework for Moral Norms**

- Respect for autonomy
- Non-maleficence
- Beneficence
- Justice

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**Wilson and Jungner Classic Screening Criteria**

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.

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**Exome Sequencing Is Not An Infallible Test**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>85% of Mendelian disorders are caused by mutations in coding DNA</td>
<td>Exome is 1% of the genome → no ncRNAs, regulatory regions, or epigenetic changes</td>
</tr>
<tr>
<td>Detects single nucleotide changes, small indels and copy number variation</td>
<td>Cannot detect trinucleotide repeat expansions, large indels, inversions or aneuploidy</td>
</tr>
<tr>
<td>Detects balanced rearrangements</td>
<td>Difficult to interpret</td>
</tr>
<tr>
<td>High diagnosis rate (8-48%)</td>
<td>Incidental findings</td>
</tr>
</tbody>
</table>

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**Ethical, Legal, Economic, and Social Issues-NSIGHT**

- Differences in perceptions of benefits and risks of sequencing between symptomatic and asymptomatic populations
- Parent willingness to accept sequencing and factors associated with parents’ decisions
- Extent to which parents are willing to accept uncertainties inherent in test interpretation
- How key stakeholders make decisions about whom to test, how to share results, under what circumstances, and with what goals
- Public policy regarding use of genome sequencing as part of mandated screening programs

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**NSIGHT Projects**

**Newborn Sequencing in Genomic Medicine and Public Health**

- For disorders currently screened in newborns, how can genomic sequencing replicate or augment known NBS results? Can sequencing replace current screening modalities?
- What knowledge could genomic sequencing provide about conditions not currently screened for in newborns?
- What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?

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**Newborn Screening**

*It takes a village*

Thank you for being part of our village!