“Newborn screening for identification & prospective follow-up of SMA infants”
SPOT SMA study update

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Why NBS for SMA?

SMA is a severe and common disease

The “most common” lethal recessive genetic disease in childhood (1/10,000 births)

High frequency of severe outcomes in infancy and childhood

SMA is usually an early onset disease

Clinical onset before 18 months in > 80% of patients

Severe infantile variant accounts for > 50%

SMA type I and type II phenotypes comprise the majority affected

SMA has a well known DNA molecular defect

Homozygous SMN1 deletion in 95 to 98% of cases

Robust diagnostic test – wave-melt or quantitative PCR assay

SMN2 dosage correlated with the phenotype: SMN2 dosage < 3 highly predictive for the severe infantile phenotype
Is SMA ready for NBS?

• NBS classically limited to diseases with proven therapy requiring early intervention for best outcomes

• Arguments for NBS in SMA include
  • Avoidance of “diagnostic odyssey”
  • Proactive care in type I is prolonging survival without benefit in motor or respiratory outcomes
  • To facilitate early participation in clinical trials for therapeutics (available trials at present include antisense oligonucleotide therapy for SMA type I infants and AAV-9 SMN gene therapy trial)
Converging support for NBS in SMA

- Rapidly advancing genomic technologies
- Increased support from scientific and medical communities
- Improved knowledge of SMA outcomes and influence of proactive care
- New therapeutics for SMA in phase II/III trials
- Growing evidence for positive impact of early intervention
The SPOT SMA Study
Screening Pilot for SMA in Newborns

Overview of Specific Aims

1. Exploration of consent, regulatory and ethical issues and psychosocial impact of early diagnosis

2. Implementation of multi-state NBS pilot for SMA using wave melt technology to target screening of bloodspots

3. Comprehensive 2 year follow-up
   • prospectively assess a variety of pre-specified outcomes/biomarkers based on CDEs and outcome measures
   • access/opportunity for proactive care interventions using a medical home model
Summary of Timeline

2008: SMA nominated as a potential candidate for NBS by a collaborative group of physicians, scientists and Families of SMA

  Committee requests pilot study

2010: NIH application for pilot study submitted

2011: Project funded by NICHD

  • June 2011: Strategic Planning Meeting with key personnel from University of Utah, Utah DOH and Colorado.
  
  • July 2011: Presentation of project to NBSAC
  
  • September 2011: Meeting regarding consent issues related to dried blood spots in Utah
  
  • December 2011: Focus groups - consensus in both Utah and Colorado that parents were OK with opt-out model
  
  • June-Dec 2011: Meetings with Utah DOH determined that verbal opt-in model would be necessary to conduct the study in Utah
Summary of Timeline: Utah

2012

• January 2012 – began work on educational materials
• January-May 2012 – development of work flow for verbal consent, laboratory procedures, results and notification of the primary care provider and family.
• June – July 2012 – educational materials finalized
• July 2012 – IRB application submitted to University of Utah IRB
• August 2012 – Approval from University of Utah IRB, submission to Utah DOH IRB.

2013

• February 2013- Tacit approval from Utah DOH IRB for verbal opt-in; however, DOH NBS followup personnel had persistent concerns and added burden of time, insufficient funding and requested additional formal written documentation of opt-in
• July 2013 – Resubmission for verbal-opt in with University of Utah IRB; Screening begins at the University of Utah Hospital only
1. The Colorado Department of Health (CDPHE) declined to participate (in spite of prior letter of support)
2. Overall study oversight via Colorado Multiple Institutional Review Board- approved opt-out consent model based on focus group support
3. Individual hospitals approached via large hospital systems
4. Currently, Colorado has 7 participating hospitals, including 2 new hospitals in 9/2014
5. Total annual enrollment ~ 24,000 babies
Colorado

1. In person trainings conducted with all nursing staff for each shift
2. Study notebook and brochures provided
3. Nurses have basic knowledge of study and instructions for receiving more info
4. Parents are given educational brochure and opt-out information
   - Sometimes handed to them directly
   - Sometimes included in NBS packet
Enrollment to date Colorado (4/2013-9/2014)

Number of babies screened 15,069

Opt out of study 41

Insufficient blood for screening 497

EMR sticker not on screening card 56

Positive screens 0
Opt–out summary
Colorado

1. Options provided to opt-out in person, via phone or internet via REDCAP secure site within two weeks of birth
2. Number of opt-out varies by hospital
   • Fewer opt-outs in some hospitals as percentage of those screened
   • Rate of opt-outs has decreased over time
   • May relate to inconsistent education – needs to be further explored

Bloodspots/babies screened ~3900
Opt in rate ~90%
Weekend coverage N/A – our staff performs all verbal consents
Cases identified primarily via NBS 0
Cases enrolled in LPDR 3*
Rate of opt in has been stable
Reasons for opt out: “too much going on right now”, “my husband isn’t here to discuss”, “new mom needs her rest”, “not worried about SMA”

*one randomly submitted to lab - identified appropriately via wave melt assay, all presented to non-screened hospitals in Utah
Education Materials

• **Brochures - Spanish and English required**
  • Ideally available in prenatal offices for all hospital/birthing centers associated with the study
  • Handed to mother or parents sometime prior to heel prick for newborn screening (challenging to get all babies with limited personnel unless use unit personnel/strategies)
  • Could be provided when they arrive in labor and delivery, but this has proved impractical/intrusive

• **Website – English and Spanish versions**
  • Additional details about the study
  • Educational video about the study
  • Links to additional sites of support
Additional Materials

• Nurses and staff are provided a list of talking points to cover basic study information.

• The video posted to the website can be made available for training and education of hospital staff.

• http://spotsmaco.org and http://spotsmaut.org
Utah procedures

Input and partnership from individual birthing centers and programs is necessary to ensure that:

a) All parents of newborns are aware of the study and receive the brochure during either the labor and delivery or their post-delivery hospital stay

b) Ensure they are provided the verbal opportunity to opt-in to the study

c) Ensure if they do opt-in, that the NBS card is marked appropriately, or some other standard procedure is implemented that will document their verbal consent to opt-in or opt-out
Most significant challenges (so far)

1. Ongoing concerns about potential negative impact on standard NBS processes, legal ramifications

2. Ongoing education of staff who represent study ie implementing standardized training modules, limited opportunities for feedback/modification in a timely fashion, need for audits

3. Consistent provision of the opportunity to opt-in or opt-out across birthing centers and hospitals within a given state

4. A consistent means to integrate processes with standard procedures – ie timing in relation to usual screening, separate cards, etc
Additional lessons learned

1. Direct contacts and face to face meetings with individual hospitals and birthing centers is helpful
2. Population based studies performed on a hospital by hospital by birthing center basis will be unlikely to be successful for rare disorders
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