Feasibility of a Population Based Newborn Screening Study for Spinal Muscular Atrophy in Colorado
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Abstract

Objective: To determine the feasibility of conducting population based newborn screening pilot studies using the SPOT SMA protocol in Colorado.

Design/Methods: A prospective population based study was implemented with the goal of screening 400,000 babies in Colorado and Utah to detect approximately 40 babies with Spinal Muscular Atrophy (SMA). The Colorado experience is described here. Following extensive negotiations the Colorado Department of Public Health and Environment (CDPHE) declined to participate in the study at the state level. Investigators contacted birthing hospitals and hospital systems to engage personnel and obtain regulatory approval. Participating centers approved a full waiver of consent and HIPAA using an opt-out model that does not require written or verbal consent. Dried blood spots (DBS) are collected for SPOT SMA following state mandated screen. There is a two week window in which mothers can opt-out in person, via the internet, or over the phone.

Results: Seven hospitals in Colorado have been enrolled in the SMA study, with total annual births of approximately 20,000. In the first year of screening, 9,383 screening cards were collected from seven hospitals. Of the samples collected, 242 (2.58%) did not have a DBS due to a lack of blood following mandated screening and 673 (7.2%) had not been shipped due to the pending two-week opt-out period. Of the remaining 8,468 samples, 31 (0.37%) mothers opted-out of the SMA screen. No screen positive samples have been identified.

Conclusions: Low enrollment numbers have resulted from the inability to conduct the pilot through the state newborn screening program. Challenges of establishing initial communication, gaining IRB approval, and obtaining approval from each hospital’s research/grant department affect the expediency of adding participating hospitals. With an incidence of 1 in 10,000, it will be difficult to identify infants with SMA without more hospitals participating. Population based newborn screening studies trying to detect rare genetic disorders may need to be limited to states with more births and those with regulations that support research in newborn screening using dried blood spots. Additional educational programs are under development to ensure parents are aware of their opportunities to opt-out of the study.

Summary

Background and Significance of SMA:  With an incidence of 1 in 10,000 births, spinal muscular atrophy (SMA) is one of the most common lethal recessive genetic diseases (Pearn, 1978; Emery 1991; Hendrickson, 2009; Jedrzejowska, 2010). The condition is medically serious and associated with significant motor disability, respiratory and nutritional compromise, and death in infancy or childhood in more than 50% of affected children (Chung, 2004; Cobben, 2008; Rudnik-Schoneborn, 2009). While there is currently no cure, previous studies have shown the value of early respiratory and nutritional interventions in improving survival and outcomes for children with SMA and have demonstrated that significant neuronal loss occurs within the first six months in infants with SMA type I (Swoboda, 2005; Swoboda, 2007). By the time a diagnosis is made, these infants are often severely nutritionally compromised, resulting in irreversible loss of neurologic function and respiratory reserve. Early diagnosis may provide opportunities to avoid these crises and improve outcomes for affected children.

Newborn Screening and the SPOT SMA Study Design:  Population based newborn screening pilot studies are necessary to assess whether a disorder should be added to the U.S. Secretary of Health and Human Services Recommended Uniform Screening Panel (RUSP). These pilot studies need to gather evidence to evaluate the safety, ethics, feasibility, and benefit of early detection. SMA was proposed as a candidate condition to be added to the RUSP in 2008. The Secretary’s Advisory Committee for Heritable Disorders in Newborns and Children (SACHDNC) recommended that SMA be evaluated through a pilot study to determine whether it should be added to the RUSP.

A prospective population based study was implemented with the goal of screening 400,000 babies in Colorado and Utah to detect approximately 40 babies with SMA. Utah and Colorado executed similar but separate protocols using different consent models (NHLBI R01-HD60045-02). Infants in Colorado were enrolled using an opt-out consent model while Utah implemented an opt-in consent model. Each of these consent models were approved by local institutional review boards. While each state has encountered their own set of barriers and complications in trying to initiate and execute the protocol, this report will focus on Colorado data and the difficulties with implementing a population based newborn screening study using an opt-out model. Following extensive negotiations, the Colorado Department of Public Health and Environment (CDPHE) declined to participate in the study at the state level. State based newborn screening would have allowed the use of the standard dried blood spot to be used for this study, following an opt-out model of consent. An alternative model was adopted, approaching large birthing hospitals and hospital systems independently to engage them in the study protocol and obtain IRB and regulatory approval. Through this model, an additional dried blood spot is collected for the purposes of the study, following the successful collection of the standard dried blood spot.

The study was approved by the Colorado Multiple Institutional Review Board (COMIRB). A full HIPAA waiver was also obtained. IRB approval was obtained at each participating hospital or hospital system. Each IRB has approved a full waiver of consent using an opt-out patient consent model in which the parents do not need to give verbal or written consent to participate. Parents may opt out in the hospital.
and a screening card is not completed for that infant. Following discharge, parents may choose to opt out in a two-week period from their baby’s date of birth via phone or internet. If the opt-out occurs after discharge, the sample is destroyed and not shipped to the Associated Regional and University Pathologists (ARUP) laboratory in Utah. Approved patient education includes brochures handed out in post-partum, prenatal clinics, and hospital tours in addition to a study website. Each hospital has adopted a plan for education that is integrated into their typical newborn care.

Eligible infants who screen positive receive confirmatory DNA diagnostic testing through the study, and parents are provided the option to enroll their child in a follow-up study conducted by experienced neuromuscular specialists at the Children’s Hospital of Colorado to observe whether early intervention of current nutritional and physical therapies leads to improved health outcomes.

**Screening Results:** Ten hospitals in Colorado have agreed to participate in the SMA study, with total annual births of approximately 25,000. Five of these ten hospitals are among the largest birthing centers in Colorado. In the first 17 months of screening, 18,156 screening cards were collected from nine hospitals. Of the samples collected, 521 (3.0%) did not have a blood spot due to a lack of blood following the initial heel stick for the state mandated screening and 83 had not been shipped for testing due to the pending two-week opt-out period. Of the remaining 17,552 samples, 43 (0.24%) mothers chose to opt-out of the SMA screen and 738 samples were pending results. All of the 16,736 remaining samples sent to ARUP Labs tested negative for SMA.

**Conclusions:** Enrollment has been slowed by the regulatory approval needed from each birthing facility. Challenges of establishing initial communication, gaining IRB approval, and obtaining approval from each hospital’s research/grant department affect the expediency of adding participating hospitals. Population based newborn screening studies trying to detect rare genetic disorders may need to be limited to higher population density states with public health infrastructure to support research in NBS. The current low opt-out rate may implicate a need to reevaluate the patient education model implemented in hospital-based newborn screening protocols using an opt-out consent model. A broader population based study would have allowed education of parents through other venues (pediatrician offices, birthing classes, etc.). In response to a lower proportion of opt-out requests as the study proceeds, a new policy for re-education of hospital staff at participating hospitals is being developed. More effort may need to be placed in patient education beyond the use of brochures and websites such as educational videos played on televisions in post-partum and face-to-face education. However, these options can be expensive and difficult to implement logistically.

**References:**


Economic Evaluation for SCID Screening: Methods on Cost-effectiveness Analysis and Budget Impact Analysis

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Abstract

Newborns affected with severe combined immunodeficiency (SCID) are prone to infections and can die if left untreated with bone marrow transplantation (BMT). Thus, early detection of SCID followed by prompt BMT treatment is critical for affected babies to live healthy lives. Newborn screening (NBS) for SCID using T-cell receptor excision circle (TREC) test enables early detection of SCID cases. The test has demonstrated high specificity and sensitivity in identifying the affected babies. Although it has been shown to be cost-effective to screen for SCID, many laboratories still have reservations in the implementation due to the unknown projected cost related resources allocation and technology. A budget impact analysis that indicates the resources, human capital, technology, and administrative effort that a facility would undertake could help elucidate these unknown factors, and thus a budget impact analysis could help advocate for the implementation of a newborn screening program for SCID. Thus, this paper aims to distinguish the different economic evaluation tools used to justify for screening (cost-effectiveness analysis and budget impact analysis). A review of the tools will be discussed. We created a calculation model to estimate the costs of SCID screening and treatment, and to compare various cost-scenarios with and without NBS program for SCID. Data were derived from state-level and country-level databases. In brief, in a population of 500,000 (with an incidence of 1/66,000), there would be an upfront cost between $1.2 and 3.2 millions of implementing a SCID screening program; however, from a health care system perspective, there could be cost-savings between $8 million and 32 million due to the reduction of long-term management of care and improved quality of care. These models will be informative to other laboratories considering screening for SCID in the U.S. and internationally.

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Review of Best Practices in Documenting Newborn Screening Refusals for States
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Abstract

Problem: Forty-nine states and the District of Columbia allow parents to refuse participation in newborn screening (NBS) for their children (O’Malley, Brown, Colmers, and Phillips, 2008). Very little is known those who refuse newborn screening, why they refuse screening, or how many conditions have been missed due to refusals. Understanding and documenting refusals can provide important data for improving NBS programs for states.

Yet, there has been little research done on what should be included on refusal forms, the best approaches for collecting data on refusals, and strategies for using those data to inform policy and practice at the state level. The purpose of this project was to identify best practices for documenting newborn screening refusals at the state level by examining refusal forms and state processes for documenting refusals.

Methods: For this study we surveyed state officials responsible for newborn screening (response rate to date is 61%; data collection continues) and did a text analysis on all available refusal forms. Follow-up with in-depth phone interviews will be performed with newborn screening officials in 5 states. Several forms will be reviewed by a panel of parent advocates.

Results: The study is still in progress and will be completed later this month. Preliminary results indicated:

• a wide range of practices in documenting refusals, including use of paper forms that have not been updated for more than 25 years, phone calls, certified letters, or even no state documentation at all.

• a low number of refusals, although many were not sure how many refusals occurred in their state.

• documentation of refusals was a low priority for many states, perhaps due to a low number of refusals.

• most states did not report any specific way data on refusals was used to improve screening practices.

Conclusions and Implications: We will highlight the strengths and weaknesses of a range of refusal documentation practices. Documentation of newborn screening refusals appears to be an underutilized part of program evaluation and may be a missed opportunity to engage with those who are most antagonistic toward newborn screening. As screening programs expand, the ability to understand why parents refuse screening and to use that information to improve programs will continue to increase in importance.

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Summary

Newborn screening saves or improves the lives of more than 12,000 babies each year (1) and is an important part of the Ten Great Public Health Achievements (2) from 2001-2010. However, every year a small number of babies are not screened because their parents refuse screening, putting them at risk for disability or death. Forty-eight states, including the District of Columbia, allow parents to refuse

newborn screening (33 allow refusals for religious reasons and 15 allow refusals for any reason). However, only 34 of these states make an effort to track and document refusals at the state level (19 have a required refusal form, 11 have an optional form, and 4 do not have a form but use other methods to try to track refusals), leaving 14 states – covering 39% of the U.S. births per year (3) – that allow refusals but do not track them at the state level. Documentation of newborn screening refusals is considered an element of good practice in evaluating newborn screening programs (4) and, when done well, can serve the goals of newborn screening programs by facilitating communication, by identifying potential areas for improvement, and by providing information to policymakers.

Unfortunately, there is little information available to states about how to effectively document refusals. The purpose of this project was to identify best practices in documenting newborn screening refusals and to develop recommendations for practice that can be adopted by newborn screening programs.

**Methods:** State newborn screening coordinators were identified through a web search. Coordinators were sent a paper letter informing them of the study and asking them to notify the researchers if they no longer served in this capacity. Coordinators were then contacted through email and asked to participate in a web survey that asked questions about documentation of newborn screening refusals in their state. Coordinators received up to three follow-up emails. Coordinators who did not respond and did not decline were called by the researchers to see if the survey had been sent to the correct place or if they had any questions or concerns about the project. A $5 incentive gift card was offered for completing the survey although only ten participants (24%) accepted the gift card. The final response rate was 82%. We gathered 93% of the newborn screening refusal forms for states that had a required or optional form. If the form was not available on the internet, we requested a copy from the coordinator. Refusal forms were analyzed by key characteristics. We shared three refusal forms, representing a range of characteristics, with a focus group of six parent advocates for discussion. Five states were selected to participate in hour-long in-depth interviews over the phone. The participants for the in-depth interviews were selected because there was some aspect of the refusal documentation process identified in the survey that was unusual or intriguing and because they were willing to participate in the interview. Participants in the phone interviews received a $10 gift card. Finally, information on refusal documentation practices was gathered from states that did not complete the survey by examining those states’ policies and administrative rules.

**Identified Best Practices**

**State processes for documenting refusals**

1. Have a state-level process to document newborn screening refusals. States that do not have a provision for refusals should have a set of procedures in place to use when refusals occur. Although most states believe the number of refusals is small, there are benefits beyond liability protection for documenting newborn screening at the state level, including:
   - Providing clear and consistent information to parents and providers.
   - Allowing state newborn screening programs to follow-up with parents, birth providers, physicians who provide well-child care, hospitals, and policymakers, and to develop targeted educational programs.
   - States that followed-up with parents and physicians who provide well-child care reported some conversions of refusals (15% or more in one state).
   - Verifying all babies born in the state were screened or refused and were not missed or lost.
2. View documentation of refusals as the beginning of a communication process, not the end. As shown in Figure 1, a basic refusal documentation process focuses on counting refusals, protecting the state and providers from liability, and keeping records.

Many states, particularly those with required refusal documentation forms, went well beyond the basic model with one or more enhanced uses of the data from the documentation of refusals. An idealized conceptual model, utilizing enhancements from several different states, is shown in Figure 2. The key difference for these states is recognizing that the most important purpose for documenting newborn screening refusals is to facilitate communication between the many stakeholders while record-keeping, liability protection, and counting serve a secondary role.

*What to include on the form*

3. Include clear contact information for parents and the primary care provider who will be providing the well-baby checks. Inclusion of a medical record number, or other unique identifier for the baby, is also recommended.

4. Make the form available in multiple languages. Non-English speakers may be at a higher risk for not understanding newborn screening.

5. Ask for the reason for refusal. This is most helpful for states that allow refusals for any reason as states that allow refusals only for religious reasons reported seeing “religion” listed. This can also be done through a follow-up phone call or a survey sent with a follow-up letter. Knowing the reason for refusal may allow the screening program to provide a remedy, if possible.

6. Educate about screening, including a summary of conditions screened. Don’t assume parents received your state’s educational materials. Summarizing conditions screened allows the state to add new conditions without having to update the refusal form and was preferred by our focus group.

7. If needed in your state, separate refusal of newborn screening from refusal of bloodspot storage and refusal for research using the bloodspots. Separating screening, storage, and research allows screening to occur for families who are concerned about storage and research issues.

8. Include a website and a phone number that provides additional information about screening. The refusal form might be the only thing some parents see.

9. Include clear instructions on the form, particularly regarding where the form should be sent and who should sign. This will improve accurate form completion.
10. Have separate options for metabolic / genetic, CCHD, and hearing screening refusals. Some parents may object to the drawing of blood but may have no concerns about critical congenital heart defect or hearing screening.

11. Use a paper form or require a portion of the web form be printed and given to the parent. Web-based forms provide some convenience, particularly for data entry. However, they increase the risk that they could be completed by a birth provider and never read or viewed by the parent (this may also be true for paper forms for parents who cannot read English). In addition, parents will have more time to read and understand the form after they return home and if they change their minds they will need the paper form to be able to make contact with the newborn screening program. If a web-based form is to be used it should include a requirement that parents receive a paper copy of the form. Scannable paper forms may also be an option.

12. Do not rely on the bloodspot card as the refusal document as it is sent to a different place and does not have much space for additional information. Instead, consider sending a blank bloodspot card with a checkbox that screening was refused in addition to a separate refusal form. Using a tear-off section on the bloodspot card (at least one state is experimenting with this) might be another way to do this.

**Linking records**

13. Ideally, states should link laboratory records, birth certificate records, and refusals to ensure all babies are accounted for. Integrated electronic data systems are best, but some smaller states do this work by hand.

**Conclusion:** Documenting newborn screening refusals is a critical aspect of the evaluation of newborn screening programs and supports the goals of newborn screening programs by reducing the number of refusals, by allowing follow-up and conversion after a refusal, and by providing information that can inform policy and program improvement efforts. More research is needed to better understand the best approaches for educating providers and hospitals, following-up with parents who refuse screening, and using information about refusals to inform policy decisions.

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**References**


Impact of Lawsuit Settlement and Recent Legislation to the Minnesota Newborn Screening Program

Abstract

The Minnesota Department of Health (MDH) has settled a lawsuit over the storage and use of newborn screening residual dried blood spots and test results. As a result, the district court order to preserve these blood spots and test results was lifted and in accordance with Minnesota Statutes and the 2011 Minnesota Supreme Court ruling, the Department destroyed approximately 1.1 million archived blood spots and over 2 million test results at the beginning of 2014.

In response to the 2011 Minnesota Supreme Court ruling, the 2012 Minnesota Legislature changed the newborn screening statutes to specifically authorize storage and use of blood spots and test results for program operations. Under the 2012 legislative changes, unless a parent or guardian provides written informed consent for extended storage and use of blood samples and test results, the MDH Newborn Screening Program destroys newborn screening test results and leftover blood spots according to the following timelines:

- Blood spots with negative test results at 71 days.
- Blood spots with positive test results at 24 months.
- All test results 24 months after they are reported.

The changes to the Newborn Screening Program allow daily program operations to resume, but have also created challenges such as:

- Monitoring false positives and negatives for rare disorders is difficult with only 2 years of data
- Long term trend data for disorders on the panel no longer exist
- Refinement of cut-off values is limited to a small 2 year data set
- Parents frequently do not have enough time to consent for extended storage and use
- Cost and staff time to carry out destruction and consent processes

These changes have provided benefits to the Newborn Screening Program as well. We now have clearly defined state statutes, inclusive of everyday program operations, to guide the Program. The Program continues to function thereby fulfilling the MDH’s mission to “protect, maintain and improve the health of all Minnesotans.”

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Summary

The Minnesota Department of Health (MDH) Newborn Screening Program was greatly impacted by the Minnesota Genetic Privacy Act (GPA) (Minnesota Statutes, section 13.386) passed in 2006. The GPA restricts the collection, storage, use, and dissemination of genetic information without informed consent. After an unsuccessful attempt to resolve the potential conflict between the GPA and the newborn screening mandate, a lawsuit (Bearder v State of Minnesota) was filed against the Program in Proceedings of the 2014 APHL Newborn Screening and Genetic Testing Symposium, Anaheim, CA, October 27-30, 2014
2009. The lawsuit alleged that MDH was in violation of the GPA by storing dried blood spots and using them for purposes other than newborn screening. MDH moved to dismiss the lawsuit which was granted by both the District Court and the Court of Appeals.

However, the lawsuit was eventually brought to the Minnesota Supreme Court and on November 16, 2011, it ruled that the Newborn Screening Program did not have express authority to store or use samples beyond testing. The Court ruled that both blood samples and newborn screening tests are genetic information. The Minnesota Supreme Court remanded the case back to the District Court to determine whether any of the plaintiffs were entitled to remedies for violation of the GPA.

In response to the 2011 Minnesota Supreme Court ruling, the 2012 Minnesota Legislature changed the newborn screening statutes to specifically authorize storage and use of blood spots and test results for program operations. Program operations are quality assurance and quality control activities that were suspended after the November 16, 2011 ruling. Under the 2012 legislative changes, unless a parent or guardian provided written informed consent for extended storage and use of blood samples and test results, the MDH Newborn Screening Program would automatically destroy newborn screening test results and leftover blood spots according to the following timelines:

- Blood spots with negative test results at 71 days
- Blood spots with positive test results at 24 months
- All test results 24 months after they are reported

The revised legislation allowed the Minnesota Newborn Screening Program to resume program operations including:

- All laboratory quality control and quality assurance activities
- Calibration and testing of equipment
- Evaluating and improving the accuracy of newborn screening tests for conditions approved for screening by the MDH
- Validation of equipment and screening methods
- Continuity of operation drills to ensure testing can continue as required by Minnesota law in the event of an emergency

The lawsuit was settled on December 30, 2013. As a result, the District Court order to preserve the blood spots and test results was lifted and in accordance with Minnesota Statutes and the 2011 Minnesota Supreme Court ruling, the Department destroyed approximately 1.1 million archived blood spots and over 9 million test results.

This massive destruction created challenges such as:

- Monitoring false positives and negatives for rare disorders with only 2 years of data
- Generating long term trend data for disorders on the panel with a limited data set
- Refining cut-off values
- Fulfilling parental requests to retrieve specimens for extended storage and use before the 71 day destruction
- Redacting validation and verification data
- Providing financing and staff time to carry out destruction and consent processes
During the 2014 legislative session, the Minnesota Legislature with the advocacy of the Minnesota American Academy of Pediatrics (MNAAP) again made changes to Minnesota’s newborn screening statute. As a result, retention practices regarding blood spots and test results have changed. As of August 1, 2014, all dried blood spots and test results are now automatically retained indefinitely by the Program, unless a parent or guardian directs MDH to destroy them.

With written informed consent, the dried blood spots and test results can be used for public health studies or research not related to newborn screening. Access to blood spots or test results will be granted only to researchers whose public health studies are approved by the MDH Institutional Review Board (IRB). IRBs assure the protection of all individuals participating in research studies.

The impact of all these changes affects not only the Newborn Screening Program, but public health in general. Other programs within the MDH Public Health Laboratory have had to update statute language to prevent unintended consequences of the GPA.

Not all of these changes have been negative. Some have provided benefit to the Newborn Screening Program such as:

- Improved education for the community and primary care providers; and prenatal education for parents about newborn screening
- Clearly defined state statutes with explicit language for program operations and research studies
- Enhanced data practices and records retention schedules

The Program continues to find ways to improve and fulfill MDH’s mission to “Protect, maintain and improve the health of all Minnesotans.”