

**Progress Report July 2007**

**Newborn Screening Registry and Surveillance System Planning Project:  
Mountain States Genetics Regional Collaborative Center**

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**Project Director:**

Jeffrey R. Botkin, M.D., M.P.H.  
Professor of Pediatrics and Medical Ethics, Associate Vice President for Research  
University of Utah  
Research Administration Building  
75 South 2000 East #108  
Salt Lake City, Utah 84112-8930  
Phone: 801-581-7170  
FAX: 801-585-9588

Signature \_\_\_\_\_

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**EXECUTIVE SUMMARY/ ABSTRACT**

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This project has supported the Mountain States Genetics Regional Collaborative Center (MSGRCC) to develop a plan for the design, development, and piloting of a dynamic regional registry system for children affected with conditions detectable through newborn screening programs. The project addresses a national priority to develop systems for long-term follow-up (LTFU) for these children. The accomplishment of the project's objectives to date is the result of the work of the Project Team under the direction of the Project Director, Jeffrey Botkin MD, MPH, and the project Workgroup. The project objectives were to develop broad outlines of a sustainable LTFU system, initiate planning for key components of the system, identify regional and national experts for system components, and begin the collaborative process through two meetings hosted at the University of Utah. These goals were accomplished and significant progress was made in the development of a detailed implementation plan of a LTFU system for the region.

Specific activities included the initial organization of the Project Team – the leadership group based primarily at the University of Utah. The Project Team subsequently was responsible for background literature analysis, initial system design, identification of collaborators, and planning and the conduct of the two Workgroup meetings in September and December, 2006. The Workgroup involves collaborators from the states in the Mountain States region and national experts in selected domains. Also supported was collaboration with separately funded projects by Drs Nicola Longo and Janet Thomas and with Region 4, the Heartland Region, and the Western States Region. The result of the work was the plan presented in the Priority 2 application for the MSGRCC. We propose that the development, and selective piloting of the LTFU system can be conducted through collaboration among these and other regional and national experts and stakeholders under the oversight of the Project Director with the support of the Project team with the collaborators and contributors over a 5-year period. To date, the project has secured the support of twenty individuals and their institutions. Future collaboration with the HRSA supported National Coordinating Center will be essential to the Priority 2 activities.

The proposed plan anticipates longitudinal data collection from data sources including state newborn screening programs, subspecialty clinics, the Medical Home, families, and educational records of affected children. Accordingly, the project has supported active engagement of experts in medical informatics, metabolic diseases, hemoglobinopathies, endocrinopathies, developmental pediatrics, Medical Home, psychosocial impacts of screening, family perspectives, economic impacts, quality improvement, medical and research ethics, and education research. The Priority 2 project will develop a web-based registry database, with the informed permission of the parents of enrolled children that will offer a dynamic resource of information for those involved including families, the Medical Home, and subspecialists. The proposed registry will provide an essential resource for assessing the outcomes with valid and reliable data of affected children and their families and will enable correlations between those outcomes and other key variables including treatment and prevention approaches, phenotypes, genotypes, demographic information, and measures of adherence, among others. The Priority 2 funding will build on this successful work to date. A detailed description of the Priority 2 activities is provided in the Priority 2 application.

*Goals and objectives of the original project*

It has been widely recognized that maximizing the efficacy and safety of newborn screening programs is inhibited by the lack of information on the longer-term outcomes of affected children (Association of Maternal and Child Health Program, 2007). NBS programs currently do not include data collection on long-term outcomes and the development of data collection systems for long-term follow-up (LTFU) has become a national priority. Our project undertook planning of an integrated information system for the regional assessment of NBS outcomes. *Our overall objective longer-term is to implement a system to assess performance and outcome measures of newborn screening through a regional and national data collection system.* The current project entailed the plan for the design, development and pilot implementation of such a system. (We are calling our proposed system a registry with the understanding that this term is used to describe data collection systems of variable complexity.) It included the development of a regional framework to assess the long-term impacts of newborn screening.

The following were our objectives for the funded project:

**Objective 1:** a) Develop a proposed framework for data collection to assess the long-term outcomes of affected children identified through newborn screening programs. b) Identification of regional and national collaborators and team building to assess and further develop the proposed registry system. Expertise was sought in several domains including clinical status, psychosocial functioning, economic impact, school performance, and family functioning.

**Objective 2:** Collaborate with Dr. Nicola Longo's project at the University of Utah involving pilot tests of database software tool in his metabolic clinic to identify strengths, weaknesses, and opportunities of current database tools. The initial tool under assessment was developed by Oregon Health Science University through funding by the Center for Disease Control specifically for long-term follow-up of NBS.

**Objective 3:** Collaborate with Dr. Janet Thomas's project at the University of Colorado Denver, Health Sciences Center (UCDHSC) to develop disease specific care plans with defined process and outcome measures for all metabolic disorders diagnosed by newborn screening. Process and outcome measures for metabolic conditions will be established and used to identify process and outcome measure of other NBS conditions, including endocrinopathies and hemoglobinopathies.

*Revised goals and objectives and rationale for change*

The goals and objectives of this project were accomplished as planned. There were no revisions necessary. However, significant weaknesses of the Oregon database software were identified. While Oregon's work on the development of the data elements and measures informed this project, a more robust and appropriate database platform will be need for implementation of a regional registry

*Methodology for achieving project goals and objectives***Objective 1**

Meeting this objective required local and regional agreement on a number of issues including conditions to be included, control groups, outcome measures, conceptualizing a framework for data collection, ethical issues, and the identification of key regional workgroup contributors and collaborators. This was accomplished through development of background, team identification and building, a literature review and initial concept development by the Project Team, followed by two workgroup meetings of collaborators with the Project Team. The product of this project is an implementation plan for a regional NBS Registry System for the Mountain States Region. The workgroup meetings were held in September and December 2006.

The first Workgroup meeting of collaborators with the Project Team under the direction of the PI was held September 1, 2006 to discuss and critique the preliminary framework developed by the PI with the support of the Project team. The meeting participants included the project's Project Team, MSGRCC executive leadership, experts from the area's of bioethics, biomedical informatics, CDC Birth Defects Networks, clinical metabolics, data systems development, Family Voices, genetic counseling, HRSA Genetics Branch, NBS follow-up programs, NBS laboratory programs both public and private, nursing and public health genetics (Appendix II). The work by the PI and Project Manager on building this regional and national collaborative team was further by this meeting. (Appendix III). The product of the meeting was a conceptual framework for the registry. The PI and Project Team then translated the Framework into a draft implementation plan with consultation by regional and national experts, such as Dave Ross and Ellen Wild at the Public Health Informatics Institute. Following the first meeting additional in-kind Project Team member with bio-informatics expertise were identified, Catherine Staes MPH, PhD, RN and Reid Holbrook MD.

The second MSGRCC NBS Registry Meeting was convened December 14<sup>th</sup> 2006 for review of the draft plan to finalize the draft into MSGRCC Registry Implementation Plan that was then translated into a funding application for the MSGRCC Priority 2 activity. The contributors and collaborators included additional regional and national experts as recommended and identified by the Project Team. The evolving Collaborators and Contributors Workgroup included, in addition to the participants at the September Workgroup meeting, clinical hemoglobinopathies expertise, Logical Observation Identifiers Names and Codes (LOINC®) workgroup participant, Medical Home project expertise, National Library of Medicine Genetics Home Reference project executive leadership, National Newborn Screening and Genetic Resource Center affiliates, other regions NBS long-term follow-up project experts, psychosocial experts, Public Health Informatics Institute, school system expertise, state Children with Special Health Care executive leadership, state laboratory executive leadership, and statistics expertise (Appendix IV). This Workgroup represented experts and service providers of five states of the MSGRCC and from five Regional Collaborative Centers. The product of this was the MSGRCC Priority 2 funding application and was distributed to all meeting participants and contributors (Appendix V).

**Objective 2**

Nicola Longo is a key member of the Project Team. He has collaborated in all aspects of Objective 1's activities. For the pilot of the database tool in the metabolic clinic, a multidisciplinary team with clinical metabolic, bioethics and informatics has been meeting to develop a protocol for testing of the database and received IRB approval (Appendix V). The objectives of this subproject are to 1) assess the flow of information within Dr. Longo's metabolic clinic from an informatics perspective, 2) assess the attitudes of parents of children with metabolic conditions with respect to a registry, 3) assess the willingness of parents to consent to include their children in this pilot registry, and 4) assess the utility of the existing database in capturing relevant data from the medical records of participating children. Dr. Reid Holbrook, with the support of Dr. Catherine Staes, is performing a systematic review of registries, a system analysis and has made multiple visits to the metabolic clinic to assess the policies and procedures with respect to the acquisition, sharing, storage, and security of clinical information. This effort is essential to understanding how quality data from clinics can be captured for a registry system and for understanding information needed from non-clinic sources to manage and evaluate LTFU. A schematic diagram of the metabolic clinic information follow is one of the completed products from this objective that will inform the implementation of the MSGRCC NBS Registry (Appendix VI). Dr. Holbrook also will assess Dr. Janet Thomas' metabolic clinic for the same parameters through an on-site process. The longer-term objective of this activity is to develop methods to electronically capture relevant data from an electronic medical record for the registry without the need for a human intermediary.

A questionnaire was developed to test parental attitudes toward inclusion of their child in a long-term registry, retention of residual blood spots, and estimated need for informed consent. A parallel project is obtaining informed consent from diagnosed patients to be included in a long-term registry. Both projects were IRB approved. Recruitment of participants is underway. Following recruitment of the target number of participants, the survey's will be analyzed, interviews will be conducted, the medical records of the participants will be reviewed for data elements included on the database software instrument and data will be transferred.

### **Objective 3**

**Outcome Measures:** The Mountain States Genetics Regional Collaborative Center currently is independently supporting Dr. Janet Thomas to develop shared baseline for clinical evaluation for children with IEB. The baselines provide recommendations on physical and developmental examinations, laboratory tests, and frequencies of evaluations. Our registry project will use these baselines to establish a core dataset for the registry system. That is, if there is some consensus in the metabolic field about core data elements for each clinical visit for affected children, we can use the data elements, or a subset, as core elements for the registry. Dr. Thomas' baselines also will be used as a model for development of shared baseline for endocrine and hematology disorders through collaboration with Dr. Mary Murray at the University of Utah and Dr. Kathryn Hassell, at the UCDHSC.

Dr. Thomas is working extensively with regional and national colleagues in the development of the metabolic shared baselines. In addition, the Mountain States region is collaborating with Western States region and Region 4, both of which have pilot

projects involving the development of data elements for long-term follow-up (see below). Sharing of these baseline and consensus development will be part of the design phase of the project. Similar outcome measures appropriate for the Medical Home will be developed and instruments for developmental, psychosocial, and economic evaluations will be assessed and developed by regional and national experts in these domains.

The disease specific care plans project began in 2005 with support from the MSGRCC. A meeting was held in July, 2006 where the regional care providers met, discussed, and agreed upon the minimum guidelines as well as performance indicators and outcome measures. Seven care plans were completed. A second meeting was held in conjunction with the Registry meeting in December of 2006 and third will be held in July 2007.

Progress to date for Dr. Thomas' project:

- Completion of disease-specific shared baselines and outcome measures for all metabolic disorders detected by MS/MS. Baselines were reviewed by metabolic physicians representing AZ, CO, MT, NM, TX, UT, and WY in July 2006 and December 2006. Modifications were made following these meeting with final drafts distributed throughout the region. A workgroup is planned for July 2007 to finalize these baselines.
- Implementation of the baselines in at least five of the states (CO, MT, NM, TX, and WY) within the region and beginning of coordinated care within the region.
- Evaluation of other databases being utilized throughout the country (for example the databases from Oregon, Iowa, or Minnesota) to ensure that similar data is being collected for very broad, long-term, outcome measures. This is in collaboration with Nicola Longo.
- Continued collaboration with Region IV's MCADD long term outcome follow-up study.
- Development of parent handouts of baseline for each disorder to be reviewed by Metabolic physicians at workgroup in July 2007.
- Development of data collection tools by Informatics at University of Utah, Nicola Longo, to be reviewed by Metabolic physicians at workgroup July 2007.

The care plans can be implemented by the regional metabolic care providers, however the key will be data collection and data entry into a user-friendly, portable, integrated database that is available to the regional clinics at a reasonable cost in terms of hardware, software, and personnel. Dr. Janet Thomas plans to continue to work closely with Drs. Nicola Longo and Jeffrey Botkin regarding database development as well as investigate options that may be available from other collaborators across the country (e.g. Oregon, Minnesota).

#### *Accomplishments*

The project achieved the objective of development of a framework and implementation plan for the regional assessment of NBS outcomes. Funding is being sought for implementation of the plan for the development of this complex system. (Funding for actual implementation will require additional funding with regional and national

collaboration in the future.) The project developed a detailed consensus based implementation plan for a regional framework to assess the long-term impacts of newborn screening and build a team of collaborator / contributors from the region and nationally. The work of the PI and Project Team brought these individuals together and build the foundation for two successful workgroup meetings.

#### Objective 1:

This objective was accomplished through detailed planning by the Project Team and with two large workgroup meetings of regional and national collaborators in 2006. Work products to date consist of a set of initial conclusions and plans for the design and implementation of a registry system.

#### Specific Aims of a Registry developed by Project Director and Project Team consensus of the Collaborators Workgroups:

- Collaborate with existing public health programs and projects supported through the MSGRCC and other collaborating regions to design and develop a registry system for tracking information gathered during LTFU.
- Provide a resource for the Medical Home, subspecialty care providers, and family members to obtain current, accurate information about the management of children with a particular heritable disorder.
- Provide information about specific patients to care providers, after access and permission issues have been resolved.
- Provide information about populations of patients included in the registry that will support quality improvement and research projects relevant to children identifiable through newborn screening.

#### Components of the proposed system:

- All specific conditions will need to be defined, outcome measures identified, and data collection procedures outlined.
- Data will be obtained from children and families with informed permission of the parents. Informed consent process and content will be developed.
- The target geographic location is the Mountain States region (AZ, CO, MT, NM, NV, TX, UT, & WY).
- Children and their families will be followed and assessed through a variety of outcome measures using a dynamic, interactive web-based system.
- The objectives of this registry system will be to provide data on the natural history of rare conditions, identify variations in treatments utilized, examine factors that influence and predict outcomes, assess costs associated with care, and provide a mechanism to provide feedback to primary stakeholders including families, the Medical Home, and subspecialty care providers.
- The design, development, and selective piloting of the system will be conducted through collaboration among regional and national experts and stakeholders over a 5-year period.
- Year 1 will consist of activities within the Mountain States region to define the critical components of the system, the resources required to implement a system, and to determine the scope of the activities needed during years 2-5.
- During year 1, we will build on current regional efforts to further define protocols for long-term follow up (LTFU), and define the data elements to be collected, data sources, database specifications, patient and provider recruitment,

ethical and legal requirements, quality assurance, and data access, analysis, and reporting requirements.

- During Year 2, the system design will be refined through small pilot studies within the Mountain States region and through consultation with experts and stakeholders at the national level.
- During Year 3, the system will be pilot tested within selected subspecialty clinics and participating Medical Homes in the Mountain States Region.
- Year 4 will involve a formal design of the pilot implementation region-wide of the complete system and pursuit of additional external funding for implementation of the system.
- Year 5 activities will include modifications of the system based on evaluations and pilot projects to conduct data analysis and implementation if additional resources are obtained.
- We anticipate that our regional efforts will provide a model for a national system including metabolic clinic, informatics, economic evaluation, medical home, health department, ELSI, and school-based assessments.

#### Objective 2:

Collaboration with Dr. Longo and a protocol for testing of database has been implemented. Ongoing collaboration with Nicola Longo and a research team is underway for separately funded activities. Following is the protocol that has IRB approval and is recruiting participants. Currently 15 participants have been recruited. Completion of Dr. Longo's project will provide valuable information on the attitudes of parents regarding a registry, parental willingness to enroll in a pilot registry. Further, a systems analysis of data acquisition, sharing, storage and security in 2 metabolic clinics will provide essential information on how to efficiently capture accurate data from this source.

#### Objective 3:

The regional collaborative disease specific care plans for all ACMG recommended disorders are complete. Dr. Thomas intends to implement these guidelines in a trial basis within the region. This pilot will provide essential information on their utility. Dr. Thomas' pilot project and the Susan Berry's pilot project in Region 4 are not directly supported by our proposed Priority 2 activity but we are in active communication and collaboration to support their activities while learning from their experience.

#### *Evaluation of project*

Continuous evaluation of the timeline and activities of the project have been the responsibility of the PI and Project Team. This has been accomplished through regular face-to-face meetings of the PI and Project Team and with electronic communication. Formal evaluation of the presentation of the project at the MSGRCC NBS Mid Year meeting was conducted (N=21). The significant majority answered that the NBS

Surveillance System, as presented by the Jeffrey Botkin MD, was “Extremely Important” or “Important” (72.2%)

The application for the Priority 2 activity, the major product of this project, was evaluated for completeness and feasibility by the collaborators and contributors as recommended by the grant reviews of this application. Recommended revisions and additions were included in the final product, then disseminated to the collaborators and contributors.

#### *Lessons learned*

Priority 2 activities will be enhanced by more aggressively promoting collaboration with all states in the Mountain States region. While our initial pilot activities will focus primarily on Utah and Colorado, given the level of interest and expertise in these states, we will need to extend our project to include active collaboration with all states in the region. In addition, we will more aggressively pursue collaboration and consultation with national experts, other regional collaboratives, and federal agencies interested in promoting LTFU systems. We hope that the NCC will provide support and leadership for this national dialogue and collaboration.

We have found that inadequate communication is the most frequent cause of problems/issues. The need for ongoing bidirectional communication under cooperative agreements is key to achieving the goals of the funding agency and objectives of projects. Future undertakings will establish a plan for frequent communication and reporting as agreed on by the funders and investigative team with communication to all individuals who have a stake in the project. Confirmation of receipt of materials and electronic reporting will be done by the Project Director.

#### *Summary of disposition of equipment*

There was no equipment purchased.

#### *Future plans/Next steps*

The Priority 2 proposal represents the future plans/next steps.

#### *Activities to be continued*

The Priority 2 proposal represents our activities to be continued.

#### *Designee to oversee continued activities*

Jeffrey R. Botkin, MD, MPH will have primary responsibility for continued activities for Priority 2.

*Future funding sources*

We are seeking funding for our Priority 2 activities to continue the work described.

*Plans for sustainability after GSB funding( if applicable)*

LTFU of children and families identified through newborn screening is a national priority. Additional funding for implementation will be sought as our Priority 2 project evolves.

*Status of peer reviewed publication/ presentations*

- Completed
  - Botkin JR, Anderson RA, Staes C. American Public Health Laboratories 2007 Newborn Screening meeting, Round Table Presentation May 2007
  - MSGRCC NBS Mid Year meeting, invited Podium presentation- Salt Lake City, April 2007
  - Anderson RA. Regional Collaborative National Coordinating Center Principal Investigator meeting, Invited Presentation- Falls Church VA October 2006
  - Holbrook RA, Staes C, Mitchell J, Anderson R, Botkin J. Region-Wide Collaboration on Newborn Screening Outcomes Surveillance. 2007 Utah Health Services Research Conference. Salt Lake City, UT; 2007
  - Holbrook RA, Staes C, Mitchell J, Anderson R, Botkin J. Region-Wide Collaboration on Newborn Screening Outcomes Surveillance. 2007 AMIA Spring Congress. Orlando, FL; 2007.
  - Botkin JR. MSGRCC NBS Registry. Mountain States Genetics Annual Meeting- July 2007
- Upcoming
  - Botkin JR, Longo N, University of Utah's, Pediatric Department Biological Basis Conference –September 2007
  - Holbrook RA, Staes C, Longo N, Botkin J, Anderson R, Mitchell J. Development of Requirements and a Pilot Registry for Long-Term Follow-Up of Children with Heritable Conditions. 2007 AMIA Fall Congress. Chicago, IL; 2007. (accepted).
- In draft
  - Botkin JR, Anderson RA, Longo N, Staes C, Holbrook RA. Manuscript: “Developing a National Registry for Conditions Identifiable through Newborn Screening”

*Products*

- Completed
  - Botkin JR, MSGRCC NBS Registry Project Team, MSGRCC NBS Registry Workgroup MSSGRCC Priority 2 application
  - Holbrook, RA. July 2007 Metabolic Clinic Information Follow Models

*References*

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- Botkin, J. R. (2005). Research for Newborn Screening: Developing a National Framework. *Pediatrics*, 116(4), 862-871.
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Appendix I

MSGRCC NBS Registry Collaborators and Contributors

**Mountain States Genetics Regional Collaborative Center  
Newborn Screening Registry Inaugural Workgroup Meeting  
September 1<sup>st</sup>, 2007**

**Rebecca Anderson, BS, MSc, RN**  
**Project Manager**  
University of Utah GeneSIS  
Center  
Assistant Director  
75 South 2000 East # 008  
Salt Lake City, UT 84112  
(801) 587-2884  
rebecca.anderson@hsc.utah.edu

**Jeffrey Botkin, M.D., M.P.H.**  
Principal Investigator  
University of Utah  
Professor, Pediatrics &  
Medical Genetics  
Associate Vice President for  
Research  
75 South 2000 East #108  
Salt Lake City, UT 84112  
(801) 581-7170  
jeffrey.botkin@hsc.utah.edu

**Lorenzo Botto, M.D.**  
University of Utah  
Assistant Professor, Medical  
Genetics  
50 North Medical Drive  
Salt Lake City, UT 84132  
(801) 257-0566  
lorenzo.botto@hsc.utah.edu

**Linda Carr-Lee**  
**Project Team Research Assistant**  
University of Utah Division of  
Medical Ethics  
325 8<sup>th</sup> Avenue  
Salt Lake City, Utah  
(801) 408-1701  
Linda.Carr-  
Lee@intermountainmail.org

**William Dudley, Ph.D.**  
University of Utah  
College of Nursing  
10 South 2000 East  
Salt Lake City, UT 84112-5880  
(801) 587-7866  
william.dudley@nurs.utah.edu

**Joyce Hooker**  
Mountain States Regional  
Collaborative Center  
Executive Director  
8129 W. Fremont Avenue  
Littleton, CO 80128  
(303) 978-0125  
mostgenes@msn.com

**John Johnson, M.D.**  
Shodair Hospital  
Director, Medical Genetics  
PO Box 5539  
Helena, MT 59604-5539  
(406)-444-7586  
JJohnson@shodair.org  
**Nicola Longo, M.D., Ph.D.**  
University of Utah  
Professor, Pediatric Medical  
Genetics  
50 North Medical Drive  
#2C412  
Salt Lake City, UT 84132  
(801) 587-9071  
nicola.longo@hsc.utah.edu

**Marie Mann, M.D., M.P.H.**  
Deputy Chief  
Genetic Services Branch  
DSCSHN/MCHB/HRSA/H  
HS  
5600 Fishers Lane, 18A-19  
Rockville, MD 20857  
301-443-1080 (phone)  
mmann@hrsa.gov

**Lynn Martinez**  
Utah State Health  
Department  
MSGRCC Board Member  
44 North Medical Drive  
(801) 538-9308  
lynnmartinez@utah.gov

**Joyce Mitchell, Ph.D.**  
**Project Team**  
University of Utah  
Department Chair,  
Biomedical Informatics  
26 South 2000 East # 5750E  
Salt Lake City, UT 84112  
(801)581-4080  
joyce.mitchell@hsc.utah.edu

**Chuck Norlin, M.D.**  
**Project Team**  
University of Utah  
Division Chief, General  
Pediatrics  
Director Utah Medical Home  
Project  
50 North Medical Drive  
#2A152  
Salt Lake City, UT 84132  
(801) 587-9978  
chuck.norlin@hsc.utah.edu

**Marzia Pasquali, Ph.D.**  
**Project Team**  
University of Utah  
Assistant Professor,  
Pathology  
500 Chipeta Way  
Salt Lake City, UT 84108  
(801) 583-2787 ext. 2853  
PASQUAM@aruplab.com

**Gina Pola-Money**  
Utah Sate Health Department  
Director, Family Voices of  
Utah Center  
44 N. Medical Drive  
Salt Lake City, UT 84114  
(801) 584-8236  
utahfamilyvoices@juno.com

**Alfred Romeo, R.N., Ph.D.**  
Care Coordinator Specialist  
and MedHome Portal  
Manager  
Utah Integrated Services  
Project  
Utah Department of Health  
BCSHCN  
44 Medical Drive  
Salt Lake City, UT 84114-4610  
(801) 584-8535 (or 585-5902)  
alromeo@utah.gov

**Erica Savino, MS, CGC**  
The Children's Hospital  
Certified Genetics Counselor  
1056 E. 19<sup>th</sup> Ave. B153  
Denver, CO 80218  
(303) 861-6974  
savino.eric@tchden.org

**Heather Sudbury**  
University of Utah GeneSIS  
Center  
Executive Assistant  
75 South 2000 East #108  
Salt Lake City, UT 84112  
(801) 581-7170  
heather.sudbury@hsc.utah.edu

**Janet Thomas, M.D.**  
**Project Team**  
The Children's Hospital IMD  
Clinic  
Assistant Professor, Pediatrics  
1056 E. 19<sup>th</sup> Ave, Box B-153  
Denver, CO 80218  
(303) 861-8647  
thomas.janet@tchden.org

**Judi Tuerck, R.N, MS**  
Oregon Health & Science  
University  
Assistant Professor, Child  
Dev & Rehab Center  
707 SW Gaines RD  
Portland OR 97239  
(503) 494-2776  
tuerckj@ohsu.edu

**Christiane Winter**  
Oregon Health & Science  
University  
Data Systems Analyst  
Office of Program Evaluation  
& Research  
(503) 494-0461  
winterch@ohsu.edu

Appendix II

MSGRCC NBS Inaugural Registry Workgroup Meeting

September 1, 2006

# Agenda

## NBS Surveillance Planning Project

September 1, 2006

8:30 to 5:00 PM

University of Utah

Research Administration Building

Room 117

Salt Lake City

### Invitees:

Rebecca Anderson (UT), Jeffrey Botkin (UT), Lorenzo Botto (UT), Linda Carr-Lee (UT), William Dudley (UT), Joyce Hooker (CO), John Johnson (MT), Nicola Longo (UT), Maria Mann (DC), Lynn Martinez (UT), Joyce Mitchell (UT), Chuck Norlin (UT), Marzia Pasquali (UT), Gina Pola-Money (UT), Erica Savino (CO), Heather Sudbury (UT), Janet Thomas (CO), Judi Tuerck (OR), Christiane Winter (OR),

## Agenda topics

8:00	Continental breakfast	
8:30	Introduction	Jeff
8:40	HRSA	
8:50	MSGRCC	John and Joyce H
9:00	GeneSIS	Jeff
9:10	Project review	
	• Planning grant	Jeff
	• Metabolic protocol	Janet
	• Data base pilot	Nicola
	• Discussion	
10:30	Break	
10:45	Collaborators	
	• Birth Defects Network	Lorenzo
	• Oregon database	Judi
	• Medical Home	Gina
	• Informatics	Jeff
	• Discussion	
12:00	Lunch provided	
12:30 PM	Focus issues	
	• Conditions to be included	Jeff / Group

3:00	<ul style="list-style-type: none"><li>• Data base development</li><li>• Control groups</li><li>• Outcome/performance measures</li><li>• Consent and IRB</li><li>• Tissue Banking/Cell lines</li><li>• Data acquisition protocols-control, kids not seen in sub-specialty clinics</li></ul>	
3:15	Break	
4:00	Planning <ul style="list-style-type: none"><li>• Medical Home collaboration</li><li>• Family collaboration</li><li>• Other Key Issue</li><li>• Identification of collaborators</li><li>• Meetings</li><li>• Teleconferences</li><li>• Funding opportunities</li><li>• Timeline</li></ul>	Jeff/Group

Appendix III

December 2006 MSGRCC NBS Workgroup Meeting

Regional and National Participants and Contributors

**Nicola Longo, M.D., Ph.D.**  
**Project Team Member**  
Professor, Pediatric  
Medical Genetics  
University of Utah  
(Metabolic Geneticist)

**Joyce Mitchell, Ph.D.**  
**Project Team Member**  
Department Chair,  
Biomedical Informatics  
University of Utah  
(Geneticist, Informatics)

**Chuck Norlin, M.D.**  
**Project Team Member**  
Division Chief, General  
Pediatrics  
Director Utah Medical  
Home Project  
University of Utah  
(Medical Home)

**William Dudley, Ph.D.**  
College of Nursing  
University of Utah  
(Statistics)

**Catherine Staes, B.S.N., M.P. H., Ph.D.**  
**Project Team Member**  
Assistant Professor  
Department of  
Biomedical  
Informatics  
University of Utah  
(Informatics)

**Marc Williams, MD**  
Director, Clinical  
Genetics  
Institute, Intermountain  
Health  
(Quality Management,  
Genetics)

**Mary Murray, MD**  
Associate Professor of  
Pediatrics  
Division of  
Endocrinology  
University of Utah

**Susan Berry, M.D.**  
Professor Pediatrics &  
Genetics  
University of Minnesota  
(Region 4 RCC)

**Joyce Hooker**  
Mountain States  
Regional  
Collaborative Center  
Project Manager

**Julio Facello, PhD**  
Center for high  
performance computing  
University of Utah  
(Informatics)

**John Johnson, M.D.**  
Shodair Hospital  
Director, Medical  
Genetics  
(Co-PI, MSGRCC)  
HRSA-07-016  
13

**Margaret Lubke, Ph.D.**  
Professor of Education  
Utah State University  
(School-based Data)

**Gina Pola-Money**  
Utah State Health  
Department  
Director, Family Voices  
of  
Utah Center  
(Family Advocacy)

**Harper Randall, M.D.**  
Utah Department of  
Health  
Bureau Director,  
Children  
with Special Health  
Care  
Needs

**Patrick Luedtke, MD, MPH**  
Utah Department of  
Health  
State Laboratory  
Director

**Reid Holbrook, M.D., M.P.H.**  
**Project Team Member**  
University of Utah  
Department of  
Bioinformatics  
(Business Analyst)

**Joanna Fanos, Ph.D.**  
Dartmouth University  
Assistant Professor  
Dartmouth Medical  
School  
(Psychosocial  
Outcomes)

**Susan Waisbren, Ph. D.**  
Senior Psychologist  
Metabolic Program  
Children's Hospital of  
Boston  
(Developmental  
Outcomes)

**Lynn Martinez**  
Utah State Health  
Department  
MSGRCC Board  
Member

**Alfred Romeo, R.N., Ph.D.**  
Care Coordinator  
Specialist & MedHome  
Portal Manager  
Utah Integrated Services  
Project Utah  
Department  
of Health BCSHCN

**Linda Carr-Lee**  
**Project Team Member**  
Research Assistant  
University of Utah  
Division of Medical  
Ethics

**Sara Copeland, M.D.**  
Assistant Professor  
Medical Genetics  
University of Iowa  
(Heartlands RCC)

**James Gibson, M.D.**  
Genetics & Metabolic  
Disorders  
Goldsbury Center for  
Children & Families

**Kathryn Hassell, M.D.**  
Colorado Sickle Cell  
Treatment and Research  
Center  
(Hemoglobinopathies)

**Celia Kaye, M.D.**  
University of Colorado  
Health Sciences Center  
Professor & Senior  
Associate Dean for  
Education, Office of  
Educational  
Development  
and Research

**Marzia Pasquali, Ph.D.**  
**Project Team Member**  
Assistant Professor,  
Pathology  
University of Utah  
(ARUP Laboratories)

**Erica Savino, MS, CGC**  
Genetics Counselor  
Metabolic Clinic  
Denver Children's  
Hospital

**Ann Comeau**  
Deputy Director  
New England Newborn  
Screening Program  
(NERGG)

**John Moeschler, MD**  
Medical Genetics  
Dartmouth Hitchcock  
Medical Center  
(NERGG)

**David Ross, ScD**  
Public Health  
Informatics  
Institute

**Ellen Wild, MPH**  
Public Health  
Informatics  
Institute

**Kerry Silvey, MA, GCG**  
Public Health Genetics  
Specialist  
Oregon Health &  
Services  
University  
(Western States RCC)

**Janet Thomas, M.D.**  
**Project Team Member**  
Assistant Professor,  
Pediatrics, Univ of  
Colorado  
The Children's Hospital  
IMI Clinic  
HRSA-07-016  
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**Judi Tuerck, R.N, MS**  
Assistant Professor,  
Child Dev & Rehab  
Center  
Oregon Health &  
Science University  
(Western States RCC)

**Christiane Winter**  
Oregon Health &  
Science University  
Data Systems Analyst  
Office of Program  
Evaluation

Appendix IV

MSGRCC NBS Registry Workgroup Meeting

December 14, 2006

GeneSIS Center, University of Utah  
December 14<sup>th</sup>, 2006

Agenda

- **Welcome** (8AM – 8:15AM) Jeffrey Botkin
  - Introductions
  - Meeting Overview and Logistics
  
- **NBS Registry Overview** (8:15AM – 9:00AM)
  - Goals & Objectives Jeff
  - 5 Year Timeline Jeff
  - Target Conditions/Control Groups Jeff
  - Dynamic Registry System 2020 Joyce Mitchell
  
- **MSGRCC Priority 2 Application** (9:00 AM – 10:00AM)
  - Overview Rebecca Anderson
  - Administration Joyce Hooker
  - Texas Health Institute (THI) Camille Miller
    - Priority 2 application Liza Creel

**BREAK**

- **Proposal Overview** (10:15AM – 12:00PM)
  - Working Groups Jeff
    - Core Work Group
    - Domain Leaders
    - Participating Members
    - National Advisory Group
  - Work Plan/ Business Plan Catherine Staes
  - Budget Rebecca
  - Letters of Support Liza

**LUNCH** (12:00PM – 12:30PM)

- **Domain Discussions** (12:30PM – 3:30PM)
  - Western States Region Collaboration Kerry  
Silvey
  - Heartlands Region Collaboration Sara Copeland
  - NERG Collaboration Susan  
Waisbren
  - Clinical Outcomes Nicola Longo

- Metabolic I Janet Thomas
- Metabolic II Susan Berry
- Endocrine Jeff
- Hematologic Kathryn Hassell
- Medical Home Al Romeo
- Informatics Reid Holbrook
- Family Collaboration Gina
- Pola-Money
- Developmental Outcomes Susan Waisbren
- Family Psychosocial Outcomes Joanna Fanos
- Quality Management
- Quality Management Marc Williams
- School System Collaboration Margaret Lubke
- Public Health Patrick Luedtke
- Statistical Support and Planning William Dudley
- ELSI Jeff
- Economic Analysis Jeff

**BREAK**

- **Open Discussion (3:45PM – 4:30PM)**

Next Steps

- 
- **Summary of Tasks/ Assignments (4:30PM – 5PM)**
    - Letters of support

For more information contact:  
 Rebecca Anderson RN,  
 Assistant Director, GeneSIS Center,  
[Rebecca.anderson@hsc.utah.edu](mailto:Rebecca.anderson@hsc.utah.edu),  
 801/587-5884

Appendix V

PROTOCOL SUMMARY

PILOT PROGRAM – REGISTRY METABOLIC DISORDERS DATABASE

# **PROTOCOL SUMMARY**

## **PILOT PROGRAM – METABOLIC DISORDERS SURVEILLANCE PROGRAM**

### **Principal Investigator**

**Nicola Longo MD PhD  
2C412 SOM  
801-587-9071**

### **Co-Investigator(s)**

**Jeffrey Botkin MD MPH  
Joyce Mitchell PhD FACMI FACMG  
Catherine Staes BSN MPH PhD  
Reid Holbrook MD MPH**

**Rebecca Anderson/Linda Carr-Lee – Study Coordinators  
75 South 2000 East  
587 5884**

**Protocol Title: Pilot Program – Metabolic disorders surveillance program**  
(IRB # 21107)

*PI Nicola Longo MD PhD, Medical Genetics/Pediatrics, University of Utah, 2C412 SOM, 50 N Medical Dr, Salt Lake City UT 84132, 801 585 2457, Nicola.Longo@hsc.utah.edu*

## **1. Background and Introduction:**

Each baby born in Utah is screened for a number of genetic conditions through mandated newborn screening. These disorders include galactosemia, biotinidase deficiency, hemoglobinopathies, congenital hypothyroidism, congenital adrenal hyperplasia, many inborn errors of amino acid metabolism (including phenylketonuria), disorders of fatty acid oxidation (including MCAD deficiency), and organic acidemias. 2-3 babies every thousand will have a metabolic disorder. Several of these disorders are extremely rare and little is known about the natural history of the disease and whether early identification by newborn screening is beneficial. The goal of this project is to define appropriate parameters for a registry/surveillance program to follow the long-term outcome of patients with metabolic disorders. This registry will help in defining the natural history of rare disorders identifiable by newborn screening and determine whether early diagnosis and treatment are beneficial.

A questionnaire collected as part of this study will also examine the thoughts, opinions, and concerns of parents of children with diseases detectable by newborn screening.

## **2. Objectives:**

The purpose of this project is to define the requirements for a surveillance system to track children identified with heritable disorders during newborn screening, including the parent-perceived risk, benefits, and ethical implications. This will be accomplished through the design of a **pilot registry** program in which children with metabolic disorders will be enrolled and a **parental survey** (questionnaire).

To accomplish these objectives, the following aims will be accomplished:

### **Pilot Registry**

1. Define data elements required to create a registry for long-term follow-up of children with heritable conditions.
2. Evaluate the source, availability, and structure of data to be acquired for the registry.
3. Define the requirements for coding, storage, and acquisition of data (electronic and paper forms).
4. Define the analyses and outputs required to make a registry useful for long-term follow-up and research of heritable conditions.
5. Define the structure of the data to allow continual analysis, interpretation, and growth of the registry.
6. Develop a pilot registry using retrospectively-collected data.

### **Parental Survey**

1. Describe parental opinions and concerns regarding the development of a disease registry for children with metabolic and other heritable diseases identified by newborn screening.

### **3. Participant Selection Criteria:**

Children with a confirmed diagnosis for one of the genetic disorders identifiable by newborn screening followed at the University of Utah Metabolic Clinic. We plan to enroll 40 children, including patients diagnosed with Phenylketonuria, Medium Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency, Galactosemia, and other metabolic conditions.

**Exclusion criteria:** Patients without a confirmed diagnosis. Specifically carriers for these disorders will be excluded.

The **parental survey** (questionnaire) will be offered to all parents of children with a confirmed diagnosis for one of the genetic disorders identifiable by newborn screening followed at the University of Utah Metabolic Clinic. Up to 50 families will be offered the questionnaire.

### **4. Design:**

**Pilot Registry:** Patients with metabolic disorders will be recruited in the metabolic clinic by the PI or associate. Once patients are identified, a member of the research team will administer informed consent. Once this is signed, information about this patient will be obtained from the newborn screening program, the medical record, and other records available. The patient will be provided with a unique identifier whose code will be kept in locked electronic and paper storage systems. The unique identifier is designed to prevent double entries. Data will be subsequently entered in an anonymous database.

Involvement of human subjects is limited to provision of consent for the collection of existing data. No intervention is contemplated in the proposed research.

**Parental Survey** (questionnaire): The parental survey is a descriptive study of parent's attitudes about the development of a newborn screening registry, the need for informed consent, and retention of newborn screening blood spots for research studies. Parents while waiting for their child's visit will be provided with the questionnaire cover letter, the questionnaire itself, and a self-addressed stamped envelope to return the questionnaire. If willing to take the survey, they will complete the anonymous survey, place in an envelope, seal it, and either deposit it in a closed box when complete or mail it back. Parents will be queried about the perceived need for informed consent to include their children in a surveillance program, about their willingness to allow data to be collected on their child for inclusion in a disease registry and whether they perceive as useful the retention of newborn screening blood spots (currently discarded after a certain time) for research purposes.

### **6. Study procedures:**

**Pilot Registry:** Recruitment: Patients and their parents will be informed during routine visits of the availability of the pilot project for a surveillance system and asked whether they would be interested in participating in the study. If they are, the informed consent is administered by a member of the research team. Families will be given a signed and dated copy of the consent and HIPAA Authorization form. Patients will be assigned a unique code designed to prevent double entries. Once consent is signed, information about patients will be obtained from all records available in the metabolic clinic, including the newborn screening program, the medical record, and other records

available. Data from each patient are then entered into a secure database with only the alphanumeric identifier by members of the research team or by the physicians caring for the patients and verified by a physician familiar with the specific disease. Data (de-identified) are subsequently analyzed for each disease to determine whether existing fields are adequate to collect number and type of medical complications, therapy, overall outcome, and cost of medical care. Finally, the feasibility of data analysis using standard statistical software will be evaluated. This is a pilot project and will test the system only. No definitive results will be obtained from this limited study.

**Parental Survey** (questionnaire): Parents while waiting for their child's visit will be provided with the questionnaire cover letter, the questionnaire itself, and a self-addressed stamped envelope to return the questionnaire. If willing to take the survey, they will complete the anonymous survey, place in an envelope, seal it, and either deposit it in a closed box when complete or mail it back.

**Risks:** There are no medical risks related to the registry pilot study or the parental survey. Confidentiality is theoretically an issue. The use of unique identifiers once the data have been captured and the use of aggregate measurements should prevent patient identification except to the treating physician and the research team.

## **7. Statistical methods, data analysis and interpretation:**

The database will collect a number of parameters (abnormality identified by newborn screening, results of confirmatory testing, genetic (DNA) mutation(s) causing the disease, results of ongoing metabolic testing to assess compliance with treatment, outcome data (motor and intellectual development), number of hospitalizations and complications, number of procedures performed) that will be compared between patients with the same disease identified clinically or by newborn screening (presymptomatically) using different statistical methods depending on the parameters to be compared. We will assess whether the database is adequate to collect all the parameters described above and to evaluate long-term follow-up. In the pilot project, we will only test the adequacy of the database to collect data.

Outcome analysis will use descriptive variables defining the percentage of patients having specific signs and symptoms and the average age of their appearance. For intellectual or motor outcome, scales appropriate for the patient's age are routinely used and data will be compared after normalization.

For the parental survey we will determine whether the surveillance system is overall perceived as a useful instrument by the parents/patients and their perception about the need to obtain informed consent.

## **8. Administrative responsibilities:**

**Study Resources:** This study will be conducted with the support of the GeneSIS Center at the University of Utah. This Center includes experts on the different domains of newborn long-term surveillance, including experts in medical ethics (Dr. Jeff Botkin) who will supervise the appropriateness of the parameters to be collected from an ethical standpoint, bioinformatics (Dr. Joyce Mitchell) who will help in developing the database in which to enter data and how to analyze them, expert in metabolic disorders (Dr. Nicola Longo), who will assist in the design of appropriate parameters to follow in

identified patients and the interpretation of statistical analysis, study coordinators and administrative personnel to administer informed consent and collect data. The facilities involved include the offices of the Metabolic Clinic (2C412 SOM), the Research Administration Building, and Primary Children's Medical Center. Identifiers will be kept in the secure University database and in a locked cabinet in the Metabolic Clinic. Only the Investigators of the grant will have access to the identifiers.

**Recruitment:** Subjects will be identified during their regular contacts with the health care system. Every child with a confirmed diagnosis of a metabolic disorder will be eligible to enter this long-term follow-up study during regular office visits with their specialist. If interested, the research study personnel will explain the study and administer the informed consent (all recruiting offices are on the University of Utah campus or Primary Children's Medical Center).

The parental survey will be offered to parents of all patients attending the metabolic clinic.

**Communication Plans for Multi-Center Studies (i.e. multiple sites around the nation):** The data collected in this study will be entered in a database at the University of Utah. Only de-identified data will be entered in the system. The data of the database will not be shared with other Institutions.

**Participating Sites outside the University of Utah (i.e. multiple sites around the city or state):** None.

9. *References and Appendices:*

Feuchtbaum L, Faulkner L, Verghese S. (2006) Tandem mass spectrometry program implementation challenges for state newborn screening programs: national survey of barriers and issues. *Pediatrics* 117(5 Pt 2):S253-60

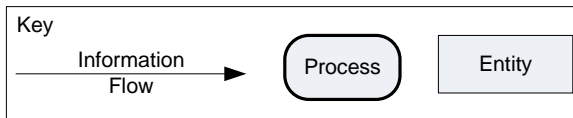
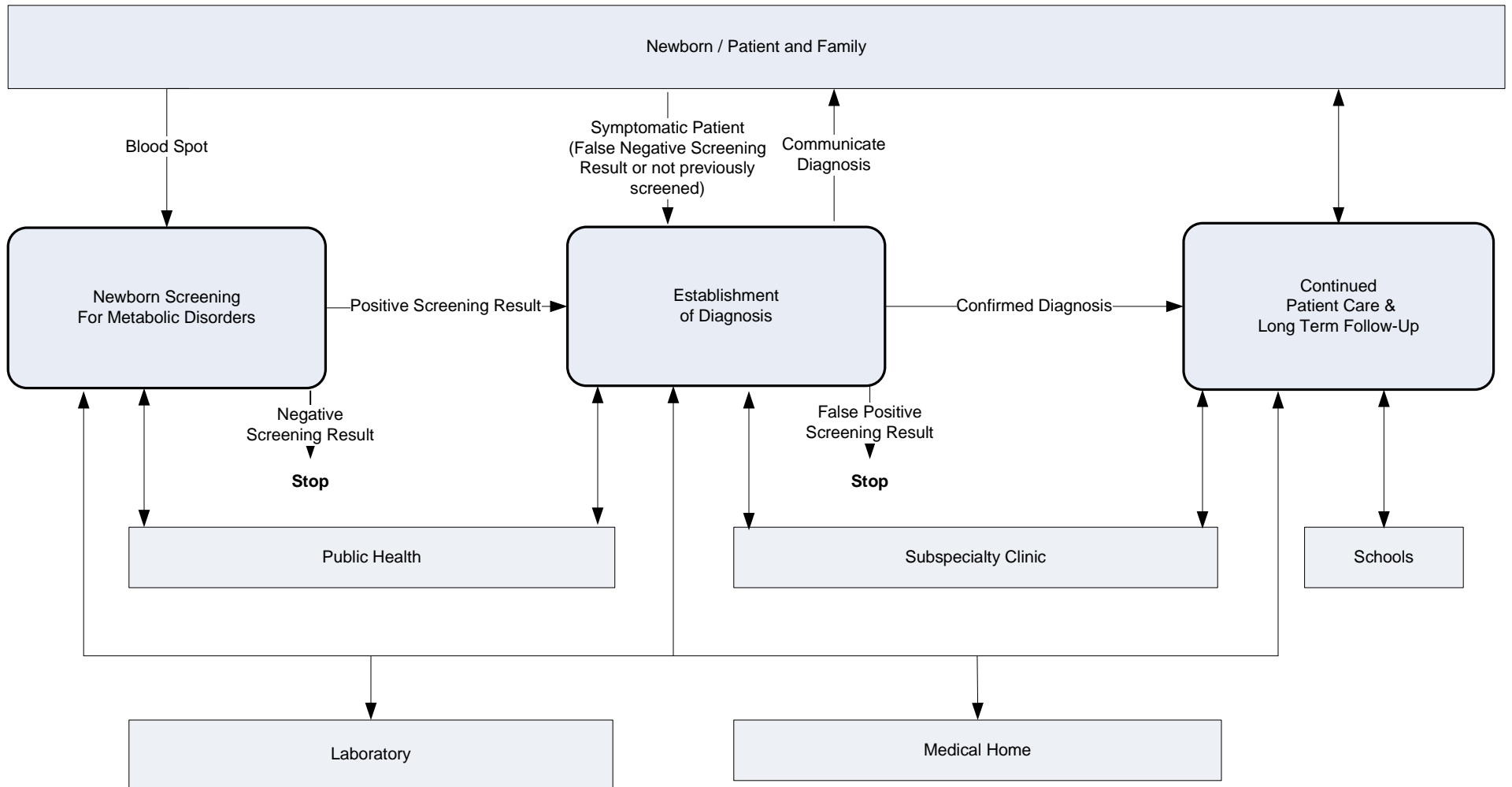
Hoff T, Hoyt A, Therrell B, Ayoob M. (2006) Exploring barriers to long-term follow-up in newborn screening programs. *Genet Med* 8(9):563-70.

## Appendix VI

### Overview of Metabolic Newborn Screening Process

#### An Information Follow Diagram

# Overview of processes associated with identifying & managing persons with metabolic conditions included in the newborn screening panel in Utah



July 06, 2007  
 Reid Holbrook, MD MPH  
 PhD Student  
 Department of Biomedical Informatics  
 University of Utah