

CHALLENGES FOR THE LONG-TERM SURVEILLANCE OF METABOLIC DISORDERS DETECTED BY NEWBORN SCREENING

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Expanded Newborn Screening

The advent of expanded newborn screening by tandem mass spectrometry (MS/MS) has allowed the identification and early treatment of patients with a number of metabolic disorders.



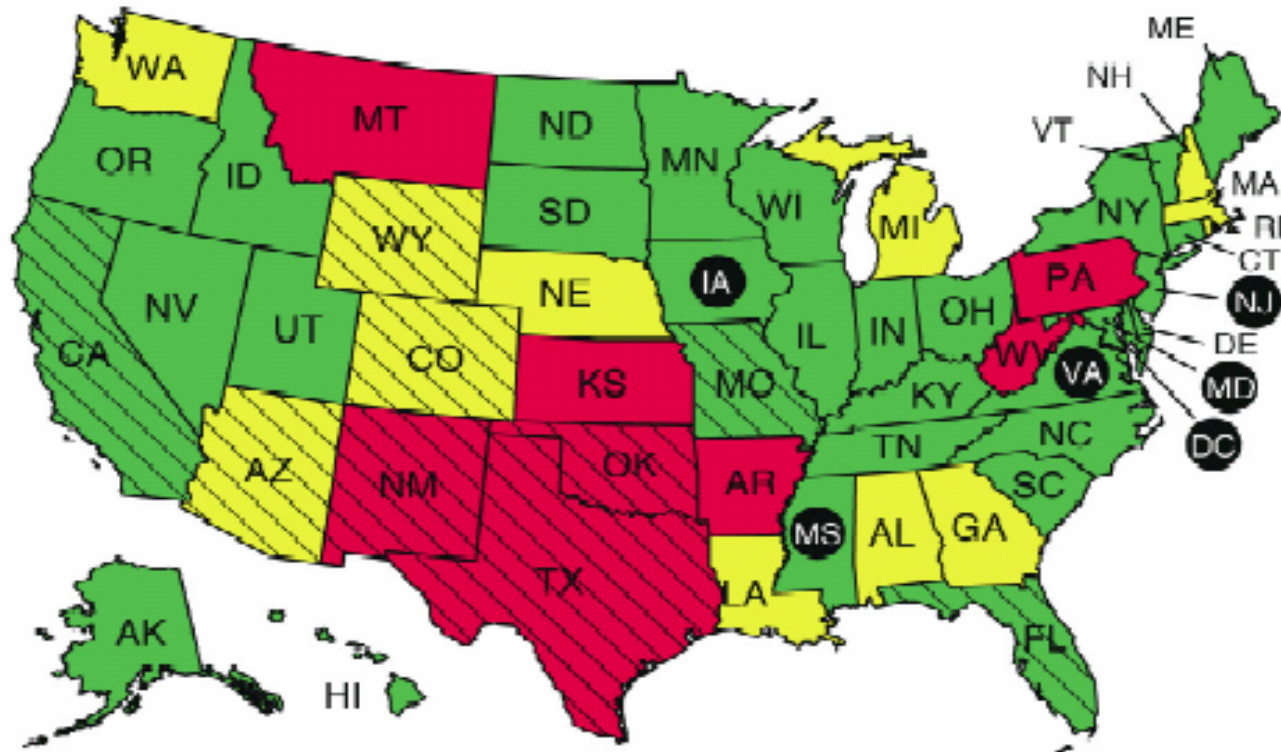
Expanded Newborn Screening

Challenges created by this new technology include the identification of patients with mild forms of classic disorders (Isovaleric acidemia, MCAD deficiency, and others) and disorders whose natural history is poorly known and for which it is unclear whether therapy is beneficial.

Andresen BS, Dobrowolski SF, O'Reilly L, Muenzer J, McCandless SE, Frazier DM, Udvari S, Bross P, Knudsen I, Banas R, Chace DH, Engel P, Naylor EW, Gregersen N (2001) Medium-chain acyl-CoA dehydrogenase (MCAD) mutations identified by MS/MS-based prospective screening of newborns differ from those observed in patients with clinical symptoms: identification and characterization of a new, prevalent mutation that results in mild MCAD deficiency. Am J Hum Genet 68(6): 1408-1418

Ensenauer R, Vockley J, Willard JM, Huey JC, Sass JO, Edland SD, Burton BK, Berry SA, Santer R, Grunert S, Koch HG, Marquardt I, Rinaldo P, Hahn S, Matern D (2004) A common mutation is associated with a mild, potentially asymptomatic phenotype in patients with isovaleric acidemia diagnosed by newborn screening. Am J Hum Genet 75(6): 1136-1142

Newborn Screening Tests by U.S. States, 2006



- More than 20 core conditions (31)
- 10–20 core conditions (12)
- Fewer than 10 core conditions (8)
- Hatch marks indicate testing for some conditions required but not yet implemented.

Screening 29 Core Conditions
District of Columbia
Iowa
Maryland
Mississippi
New Jersey
Virginia

Source: March of Dimes. Data reported from NNSGFIC as of June 1, 2006.
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Expanded Newborn Screening

Most of the knowledge about these rare metabolic disorders derives from the study of a limited number of symptomatic individuals in selected centers

For some disorders, there are major gaps in our understanding of long-term outcomes

Controversies with Expanded Newborn Screening

For disorders such as short-chain acyl-coenzyme A dehydrogenase (SCAD) or 3-Methyl Crotonyl CoA carboxylase (3-MCC) deficiency some studies advocate discontinuation of their inclusion in screening programs

Stadler SC, Polanetz R, Maier EM, Heidenreich SC, Niederer B, Mayerhofer PU, Lagler F, Koch HG, Santer R, Fletcher JM, Ranieri E, Das AM, Spiekertkotter U, Schwab KO, Potzsch S, Marquardt I, Hennermann JB, Knerr I, Mercimek-Mahmutoglu S, Kohlschmidt N, Liebl B, Fingerhut R, Olgemoller B, Muntau AC, Roscher AA, Roschinger W (2006) Newborn screening for 3-methylcrotonyl-CoA carboxylase deficiency: population heterogeneity of MCCA and MCCB mutations and impact on risk assessment. *Hum Mutat* 27(8): 748-759.

van Maldegem BT, Duran M, Wanders RJ, Niezen-Koning KE, Hogeveen M, Ijlst L, Waterham HR, Wijburg FA (2006) Clinical, biochemical, and genetic heterogeneity in short-chain acyl-coenzyme A dehydrogenase deficiency. *JAMA* 296(8): 943-952.

Newborn screening surveillance program

An ongoing program that follows over time each newborn identified by a newborn screening program

A well-constructed surveillance program can help define the natural and modified history of metabolic disorders and evaluate whether or not screening is beneficial

Newborn screening surveillance program

Key elements of a suitable surveillance program include:

- **unbiased enrollment (all positive cases)**
- **longitudinal component (to assess long-term outcomes)**
- **common core data elements and data sharing agreements (to allow data sharing necessary for evaluating rare conditions)**

Newborn screening surveillance program

Aims of the first phase included:

- **developing goals and objectives of surveillance**
- **identifying key legal, social, ethical, and technical issues**
- **defining parameters to evaluate morbidity and mortality, risks, benefits, and costs associated with the programs and care of affected children**
- **identifying suitable data sources**
- **developing efficient abstracting procedures.**

Registries and Surveillance Systems

There are many registries of genetic disorders, including neurofibromatosis, lysosomal storage disorders, and cystic fibrosis

Some important goals of these registries include characterizing key clinical issues such as:

- natural history of disease (and complications)**
- effect of interventions**
- genotype-phenotype correlations**

Registries and Surveillance Programs

Surveillance programs emphasize

- systematic, timely, ongoing data collection, analysis, and sharing the data with those who need to know
- generating information for action
- not only on clinical but also on public health issues

Models with decades of experience include birth defect surveillance programs, with population-based, active ascertainment, and follow-up

Newborn screening surveillance program

Newborn screening surveillance can answer additional questions:

- **Is newborn screening beneficial?**
- **Is it cost-effective?**

Newborn screening surveillance program

Ethical issues: Informed Consent

While several states mandate the collection of a minimal set of data, a useful core set might include additional parameters

In addition, the program should be set up to allow sharing of data across State boundaries, to collect sufficient numbers of cases of rare conditions

Patients with a confirmed diagnosis are relatively few compared to people screened. Obtaining informed consent for registry participation is feasible and advised

Newborn screening surveillance program

**IRB application was submitted to the
University of Utah**

**A questionnaire was designed
(mostly by Dr. Jeff Botkin and
Rebecca Anderson) to investigate
the attitude of parents toward a
registry for metabolic disorders
and toward the need for informed
consent.**

ELEMENTS IN SURVEILLANCE PROGRAM

- List of patients enrolled
- For each patient, summary of completed items
- Items

Demographics – Unique identifier

Diagnosis (with enzyme/transporter assay and DNA studies if feasible)

Status at Enrollment

Follow-ups

Quality of life (family/patient)

Development

Transfers/Discontinuation/Death

Comments

ELEMENTS IN SURVEILLANCE PROGRAM

While the type of data is similar for all diseases, the specific data collected will be different in different diseases.

There are disparities in how patients with metabolic disorders are diagnosed and followed in different States.

There needs to be a minimum set of parameters that should be collected and entered into the database.

ELEMENTS IN SURVEILLANCE PROGRAM

Dr. Janet Thomas (University of Colorado) chaired a group of metabolic specialists, genetic counselors, and nutritionists to define minimum care standards for different disorders.

The panel met twice and discussed the most common disorders identifiable by newborn screening reaching a consensus on forms of the disease, diagnostic standards, minimal frequency of monitoring visits, laboratory testing, performance indicators, and outcome measures.

ELEMENTS IN SURVEILLANCE PROGRAM

The conditions analyzed were:

CUD	CACT	CPT-1	CPT-2
SCAD	MCAD	VLCAD	LCHAD/TFP
PKU	ARG	CIT	ASAL
MSUD	TYR-1	TYR-2/3	HCY
MET	GA-1	GA-2	PPA
MMA	IVA	3MCC	BIOT
GAL			

ELEMENTS IN SURVEILLANCE PROGRAM

**We are in the process of developing
disorder-specific measures of
compliance and outcome**

**These measures need to be selective and
specific for each disorder**

**They should be followed over time for a
true surveillance program.**

HOW TO COLLECT DATA SYSTEMATICALLY

One appealing possibility from bio-informatic standpoint is the automatic transfer from the electronic medical record into a database

		Amino Acids, Plasma Quant. Show more...				
		Last Ref. Range	Units	03/16/07 12:15	10/30/06 11:35	06/26/06 12:50
Test Status				Final	Final	Final
Amino Acid Interp., Ur				* SEE NOTE	Normal	Normal
Alanine	240-600	umol/L		530	316	395
Arginine	40-160	umol/L		114	71	51
Aspartic Acid	0-20	umol/L		9	4	8
Citrulline	10-60	umol/L		23	31	22
Cystine	7-70	umol/L		27	32	16
Glutamate	10-120	umol/L		49	27	47
Glutamine	410-700	umol/L		582	515	413
Glycine	140-490	umol/L		323	251	218
Histidine	50-130	umol/L		104	84	117
Homocystine	NDT	umol/L		* NOT DET	* NOT DET	* NOT DET
Hydroxyproline	6-50	umol/L		26	10	0 L
Isoleucine	30-130	umol/L		144 H	63	62
Allo-Isoleucine	NDT	umol/L		* NOT DET	* NOT DET	* NOT DET
Leucine	60-230	umol/L		247 H	110	106
Lysine	80-250	umol/L		85	84	92
Methionine	17-53	umol/L		33	17	20
Ornithine	20-135	umol/L		93	80	113
Phenylalanine	30-80	umol/L		82 H	55	57
Proline	110-500	umol/L		368	189	232
Serine	60-200	umol/L		170	130	113
Taurine	25-80	umol/L		103 H	68	96 H
Threonine	60-220	umol/L		158	107	94
Tyrosine	30-120	umol/L		111	71	76
Valine	140-350	umol/L		* 401 H	* 237	238

HOW TO COLLECT DATA SYSTEMATICALLY

Not all data in the electronic medical record will be relevant and can create problems in term of size

A more immediate alternative would be to collect data during metabolic visits. These data would be entered in a clinic form and reviewed by a clinician before entry into the database

HOW TO COLLECT DATA SYSTEMATICALLY

RE:
DOV:

Nervous, Vision, Hearing: Normal
Respiratory: Normal
Cardiac: Normal
G-I: Normal
G-U: Normal
Skin: Normal
Endocrine: Normal
Hematologic: Normal
Allergies: Normal

PHYSICAL EXAMINATION:

General:
Head: Normal
Hair: Normal
Ears: Normal
Eyes: Normal
Nose: Normal
Pharynx: Normal
Teeth: Normal
Neck: Normal
Facial Features: Normal
Nails: Normal
Chest: Normal
Lungs: Normal
Cardiovascular: Normal
Abdomen: Normal
Genitalia: Normal
Skin: Normal
Musculo/Skeletal: Normal
Extremities: Normal
Neurological: Normal

NUTRITION:

Books/Lists/References:
Favorite Foods:
Dislikes:
Food/Income Assistance Programs:

Medical Food/Prescription:

Current Prescription Intake:	mg phe;	g protein;	kcal
Current Dietary Intake/Day:	mg phe;	g protein;	kcal
Per kg:	mg phe;	g protein;	kcal

Diet Records Analyzed:

GENETIC COUNSELING:

CURRENT MEDICAL PROBLEMS

PHYSICAL EXAM

ECONOMIC FACTORS

DIETARY TOLERANCE

DIETARY COMPLIANCE

HOW TO COLLECT DATA SYSTEMATICALLY

RE:
DOV:

ASSESSMENT:

- 1)
- 2)
- 3)

PLAN:

- 1)
- 2) Labs: Plasma amino acids
- 3) Diet Prescription:
- 4) Prescription given: ? cans of ? and ? cans of ? for ? months, filled at ? Pharmacy.

TEACHING PHYSICIAN ATTESTATION:

The patient was seen personally by me and the information from the resident was reviewed and discussed. The following pertinent conclusions were reached:

- 1)
- 2)

RETURN TO CLINIC:

This service required ___ minutes more than 50% of the time was devoted to nutritional analysis and counseling of _____.

Examined By: _____, MD Resident Also Seen By:

Attending:

cc: Parents, _____, MD

Addendum:

Labs drawn on _____
Phenylalanine: ___ umol/L (normal range 30-80 umol/L) or ___ mg/dL (treatment range 1-6 mg/dL)
Tyrosine: ___ umol/L (normal range 30-120 umol/L)
Interpretation: PKU in excellent/ good/ moderate/ less than optimal dietary control.

**LABS/METABOLIC CONTROL
AT TIME OF THE VISIT**

DATA COLLECTION

To facilitate data sharing and assessment, we are working with other metabolic clinics in our region to define set of common data and procedures, including specific parameters and summary forms

Data are then transferred into databases, developed from commercial products or free sources

To facilitate regional and national data sharing, databases need to speak the same language

DATA COLLECTION

We had observers coming to clinic to identify how the process can be improved:

Several data are entered more than once

There is not yet a mechanism for the systematic collection of all data

DATA ANALYSIS

We have designed a small database to contain identifiers of our patients with PKU and relevant laboratory data (phenylalanine levels at different ages) and results of age-appropriate developmental tests.

We are requesting a waiver of consent for this project to see how multiple data on a relatively frequent metabolic disorder can be analyzed locally.

Newborn screening surveillance program

Surveillance programs require an active search for patients that might be missed by newborn screening programs or metabolic clinics

Examination of medical records/death certificates of patients with ICD-9 codes possibly associated with metabolic disorders can help identify and assess cases missed by newborn screening

Newborn screening surveillance program

There is the need for a national data collection system into which to enter data collected locally.

The local and national system need to speak the same language.

SUMMARY

The expansion of newborn screening programs provides the opportunity to assess the long-term outcome of affected patients

We are working at the regional levels to define appropriate parameters to evaluate therapy and outcomes

Patients and their families will play an important part in data collection and in providing consent for inclusion in these studies

There is the need for defining, collecting, and sharing homogenous sets of data, so that the experience from different metabolic clinics in the nation can provide useful information for patients with rare conditions.

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