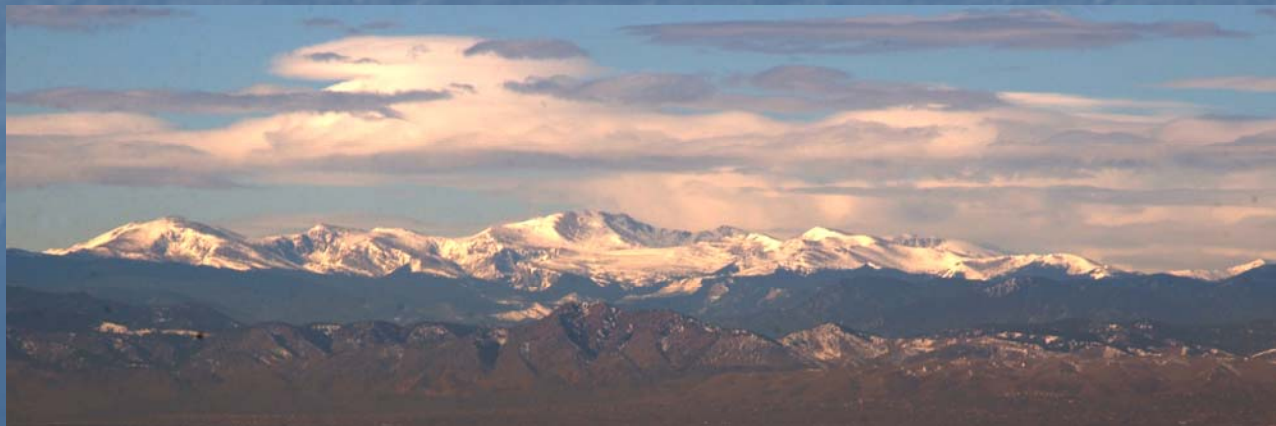


MSGRCC Metabolic Newborn Screening Long-term Follow-up Study: A Collaborative Multi-state Approach to Newborn Screening Outcome Research

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Overview

- Long-term follow-up studies for newborn screening
 - Limited published studies
 - Who is conducting LTFU
 - What challenges exist
- Mountain States Genetics Regional Collaborative Center
- MSGRCC Metabolic Newborn Screening Long-term Follow-up Study
 - Components of study
 - Factors to investigate

Questionable benefits

- Is the outcome of children with IEM disorders identified through NBS better in both overall health and development when compared to those children diagnosed clinically?
- Limited long-term follow-up studies

Schulze et. al. 2003

- Study tracked 106 newborns confirmed to have metabolic disorders by MS/MS in Germany
- 70 of those required treatment
- 6 developed symptoms despite treatment
 - 3 of those died
- 61 were asymptomatic with normal psychomotor development, no major disabilities, and no metabolic crises
- First published study of LTFU of MS/MS
- Only followed children for 42 months
- No objective measurement of development

Waisbren et. al. 2003

- Study tracked 50 confirmed to have metabolic disorders by MS/MS in M.A., M.E., and P.A.
- Relied on quantitative measurements of development and intelligence
- Tracked quantifiable outcome measures such as hospitalizations and utilization of services

Who is conducting LTFU?

- Study in 2006 found only half of the state NBS programs in U.S. conducted LTFU (AMCHP's Newborn Screening and Genetics Advisory Group 2007)
- Of those, only about half have standard protocols in place
- Great variation in how LTFU is defined, staffed, and conducted
- Study highlighted that there was no framework for LTFU

Challenges to LTFU for Metabolic Disorders

- Rare disorders
- Natural history not well understood
- Milder, possibly benign variants of disorders detected
- Controversy of inclusions of certain disorders on NBS panels

Rare disorders

- Prevalence
 - MCAD deficiency- 1 in 10,000-15,000
 - Glutaric Acidemia, type I- 1 in 40,000
 - Maple syrup urine disease-1 in 185,000
- For most disorders, it would take a single state or metabolic center many years to collect enough cases of a specific disorder to have statistical significance in outcome studies
- Great need for collaboration

...Rare disorders

- Limited literature available for many of the disorders
- Treatment can vary from clinic to clinic
- Metabolic providers rely on previous experience or even anecdotal evidence to treat
- Rely on list-serves or informal discussions with colleagues

Natural History?

- With NBS, patients identified pre-symptomatically
- Thus, early treatment prevents death and serious medical complications
- If patients live longer, are there other complications that might arise?
- When galactosemia added to NBS panels, patients began surviving the neonatal period but later developed speech dyspraxia and ovarian failure
- Maternal PKU became an issue in the late 70's when healthy girls with PKU reached reproductive age.

Milder or benign forms of some disorders

- Identification by NBS of milder or benign affected individuals
- Previously, those children would have never have been diagnosed as their disease did not inflict harm or was not serious enough to warrant specialty evaluation
- Greater number of patients identified that previously would have thought
- Isovaleric Acidemia, VLCADD, MCADD, SCADD, and 3-MCC deficiency
- Need for Genotype / Phenotype correlation

Controversy

- What disorders belong on the panel?
 - SCAD deficiency
 - 3-MCC deficiency
- Are these diseases?
- Do they cause harm?
- Do they need treatment?
- Parental anxiety, “vulnerable child syndrome”

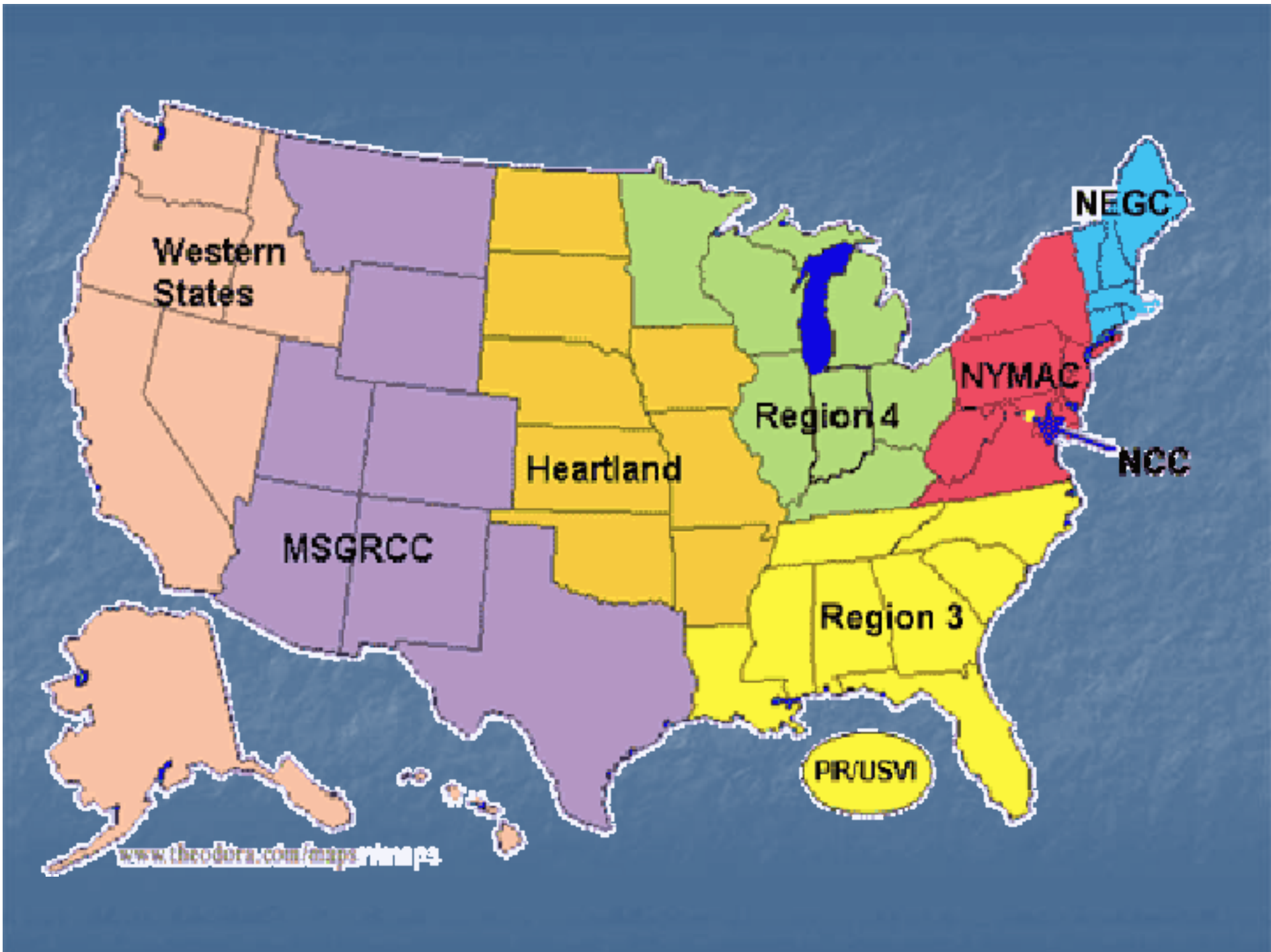
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Metabolic Newborn Screening Long-term Follow-up Study

- A collaborative multi-state approach to newborn screening outcome research
- Biochemical geneticists, dietitians, genetic counselors and nurses throughout Mountain States region set out to develop a framework for LTFU of newborn screening
- Goal:
 - Develop LTFU program over a large population in a systematic manner to study the factors that affect outcome of all metabolic disorders detected by NBS

Mountain States Genetics Regional Collaborative Center

- 1 of 7 regional collaborative centers
- Arizona, Colorado, Montana, New Mexico, Nevada, Texas, Utah, and Wyoming
- Funded by US Dept of Health and Human Services, Health Resources, and Service Administration (HRSA) Genetic Services Branch
- Provide infrastructure to support regional genetics and NBS activities



...MSGRCC

- Vast geographical area
 - 1,081,813 square miles
- 38 million people with 600,000 births annually
- Much of the region is rural
 - 37 people per square mile, about half the national population density
- 1 in 4,000 babies have metabolic disorder detected by NBS
 - =150 babies born yearly that require specialty care by metabolic clinic

Components of the Study

- Establishment of multi-state Metabolic consortium
 - Biochemical geneticists, registered dietitians, genetic counselors, and nurses
 - Representation from all states in region and from other regions
 - Roundtable discussions
 - Immediate benefit for all involved
 - Continued collaboration
 - Plan to continue to meet yearly
 - Polling and sharing of resources
 - Emergency letters, parent resources

...components

- Development of disease-specific care plans for majority of metabolic diseases detected by newborn screen
 - Traditional and MS/MS panel
 - 28 in all
 - Define minimum treatment criteria
 - Special considerations for disorder
 - Diet/treatment considerations
 - Frequency of clinic visits
 - Other necessary evaluations
 - Labs
 - Initial and diagnostic
 - Monitoring
 - Yearly labs
 - Emergency management
 - Developmental assessments
 - LTFU, not to be confused with ACT sheets

...components

- Use of neuropsychological testing tools for long-term developmental outcome measures
- Protocol outlined by team of neuropsychologists from the Children's Hospital in Denver
- Yearly developmental questionnaires to be completed by parents in clinic
 - Alpern Boll Developmental profile
 - Child Behavioral Checklist (available in Spanish)
- Developmental evals at age 3 and 6 years
- Neuropsychological evals at age 9 years
- Additional monitoring if disease-specific concerns exists
 - Speech eval for galactomsema
 - Psychiatric screening for MSUD

...components

- Development of outcome measures for each disorder
 - “shared datasets”
 - Allows for systematic collection of data
 - Performance Indicators
 - Bench mark data to measure, track, and compare
 - Age of diet initiation, freq. of clinic visits, growth parameters, ER visits, diet stats, developmental services, etc.
 - Outcome Indicators
 - End result of the intervention
 - Mortality, IQ, cardiomyopathy, neurological symptoms, bone findings, final adult growth, etc.

MSUD Care Plan

Clinical Considerations

- Stabilizing neonate (essential AA versus hemodialysis)
- Pancreatitis
- Chronic demyelination from long-term elevated Leu
- Type- intermittent, intermediate, classic

Initial labs (diagnostic & baseline)

- SAA +/- UOA
- Basic metabolic panel
- If symptomatic, osmolarity studies
- BCKAD enzyme assay or molecular confirmation

Diet considerations/ treatment

- Leu, Iso, Val restricted diet
- BCAA-free formula
- Avoid fasting
- Supplementation
 - Thiamine trial
- Consider valine/isovaline supplementation
- Iron supplementation if low

Monitoring

- Quant serum branched chain AA
- Targeted treatment range
 - Leu <500µmol/L
 - Isoleucine >100µmol/L
 - Valine >100µmol/L
- 0-6 months Every week
- 6-12 months Every 2 weeks
- 1-3 years Monthly
- >3 years Every 3 months

Frequency of visits

- 0-6 months Every 2 months⁶
- 24 months Every 3 months
- >2 yrs Every 6 months

Clinic visit labs

- See above

...MSUD Care Plan

Emergency management

- Immediate 10% dextrose with salts plus lipids
- Cerebral edema risk-may need hemodialysis
- Consider CT scan if edema present.
- Track edema, Leu level ($>600 \mu\text{mol/L}$), Isoleucine ($>100 \mu\text{mol/L}$), valine ($>100 \mu\text{mol/L}$), use of dialysis, +/-mannitol, coma score, and osmolarity

Labs to obtain during illness

- Quant plasma amino acids
- Basic metabolic panel
- Osmolarity
- Amylase and lipase

Other evaluations

- Brain MRI @ 1, 3, 6, & 9 yrs
- Bone health
 - DEXA-spine @ 9 & 18 y
- Yearly developmental questionnaires (to be completed by parents)
- Developmental eval @ 3 & 6 yrs
- Neuropsych @ 9 & 18 yrs
- Psychiatric screening @ 18y

- Consider referring to Liver for transplant

Yearly labs

- Basic metabolic panel
- Prealbumin
- Plasma ferritin or transferrin
- Amylase and Lipase
- Consider essential fatty acid panel

Performance Measures

1. Age of diagnosis (both positive NBS and confirmatory SAA)
2. Presence of illness at time of diagnosis.
3. Days until Leucine is within treatment range ($<500\mu\text{mol/L}$)
4. Therapy during initial care
 1. Enteral MSD formula vs. dialysis
 2. Track edema, Leu level ($>600\mu\text{mol/L}$), use of dialysis, +/- mannitol, coma score, and osmolarity
5. Frequency of clinic visits and compliance with visits
6. Biochemical control
 1. Quantitative plasma amino acids
7. Laboratory studies
 1. Metabolic panel, prealbumin, ferritin or transferritin, amylase & lipase, fatty acid panel
8. Total decompensations and hospitalizations.
 1. Track edema, Leu level ($>600\mu\text{mol/L}$), Isoleucine ($>100\mu\text{mol/L}$), valine ($>100\mu\text{mol/L}$), use of dialysis, +/- mannitol, coma score, and osmolarity
9. DEXA results and number of fractures
10. Neuropsychology evaluation results
11. Growth parameters
 1. Ht, wt, OFC, BMI
12. Type of MSUD
 1. Classic
 2. Intermediate
 3. Intermittent
 4. Thiamine responsive
 5. Lipoamide dehydrogenase (E3) deficiency
13. Diet
 1. Frequency of Dietician visits
 2. Frequency of dietary analysis (3 day diet records)
 3. Natural protein intake (tolerance)
 4. Formula (Y/N)
 5. Medical foods (Y/N)
 6. Mode
14. Transplant (Y or N)
15. Developmental services (PT, OT, speech, & IEP)

Outcome measures

1. Mortality
2. Development
 1. IQ
 2. Level of functioning
 3. Decline in IQ or level of function
3. History and/or presence of ADHD and use of medication
4. History and/or presence of psychiatric issues (generalized anxiety, panic, and/or depression)
5. History and/or presence of osteopenia
6. History and/or presence of abnormal MRI findings
7. Outcome of liver transplantation
8. Growth
 1. Final adult parameters

...components

- Utilization of a database to track measurable outcomes
 - Data collection must be easily integrated into clinical care
 - Not everyone has access to computers in clinic
 - Multiple Electronic medical records in multiple clinics
 - Web-based databases \$\$\$
 - Clinics have minimal resources for data entry
 - Data must be accurate
- Dr. Nicola Longo (UT) and team of health informatics specialists developing data collection tools
- In Colorado, revamping existing database of CHIRP for use in LTFU

Factors to investigate

- Disease-specific information
 - Natural History
 - Heterogeneity – disease spectrum
 - Genotype / Phenotype correlation
- Treatment
 - Established minimal treatment criteria through care plans
 - Capture clinic to clinic variation
 - Examples
 - Compare # of clinic visits with compliance
 - Carnitine dosage with overall health
 - Percentage of MCT oil with overall health

...Factors to investigate

- Socio-economical variables
 - Achievable through diverse population
 - Examples
 - Urban versus rural
 - Formula /medical food coverage
- Organizational variables
 - Multiple components to NBS
 - Timing of results and follow-up treatment
 - Centralized approach to care

MSGRCC Metabolic Consortium

■ Biochemical Geneticists

- Kirk Aleck, MD (AZ)
- Renata Gallagher, MD, PhD (CO/WY)
- James Gibson, MD (TX)
- Celia Kaye, MD (CO)
- Claire Leonard, MD (NM)
- Nicola Longo, MD (UT/NV)
- Susan Root, MD (NM)
- Janet Thomas, MD (CO/WY/MT)
- Johan VanHove, MD, PhD (CO/WY)

■ Health Informatics

- Reid Holbrook, MD (UT)
- Catherine Staes, PhD (UT)
- Bruce Straw (CO)
- Paul Turtle (CO)

■ Genetic Counselors/Nurses

- Rebecca Anderson, RN, MPH (UT)
- Sarah Cox, MS, CGC (AZ)
- Cindy Freehauf, RN, CGC (CO)
- Erica Wright, MS, CGC (CO)

■ Registered Dietitians

- Laurie Bernstein, RD (CO)
- Sharon Ernst, MPH, RD, CD (UT)

■ Neuropsychologists

- Richard Boada, MD (CO)
- Greta Wilkening, MD (CO)

■ Other regional participants

- Sue Berry, MD (Region IV)
- Judith Tuerck, RN, MS (Region VII)

Conclusions

- Advent of tandem mass spectrometry changed newborn screening
- Great need for LTFU in newborn screening
- MSGRCC Metabolic Newborn Screening LTFU Study paving the way

Thank you!

- MSGRCC and Joyce Hooker
- Janet Thomas, MD
- Johan Van Hove, MD, PhD
- Nicola Longo, MD, PhD
- All members of the Consortium
- All of our families



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