MSGRCC Metabolic Newborn Screening Long-term Follow-up Study: The Good, the Bad, and the Ugly

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Mountain States Genetics Regional Collaborative Center

The MSGRCC

- Mountain States Genetics Regional Collaborative Center
- One of seven regional collaborative centers covering the nation
- Federally funded by the US. Department of Health and Human Services, Health Resources and Services Administration (HRSA), Genetic Services Branch

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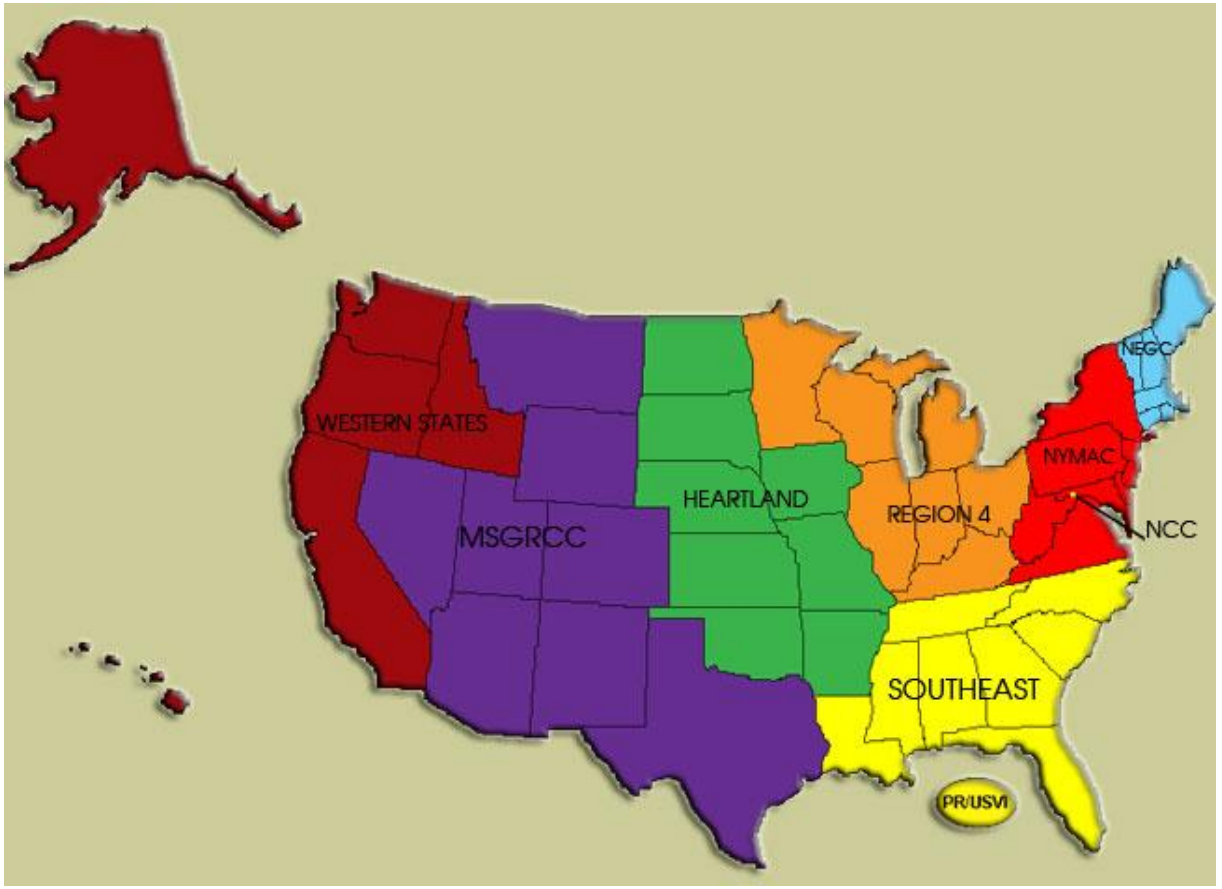
The Mountain States

- Arizona
- Colorado
- Montana
- New Mexico
- Nevada
- Texas
- Utah
- Wyoming



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MSGRCC
Metabolic Newborn Screening
Long-term Follow-up Study

- A collaborative multi-state approach to newborn screening outcome research
- Biochemical geneticists, metabolic dietitians, genetic counselors, nurses, and consumers throughout the 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

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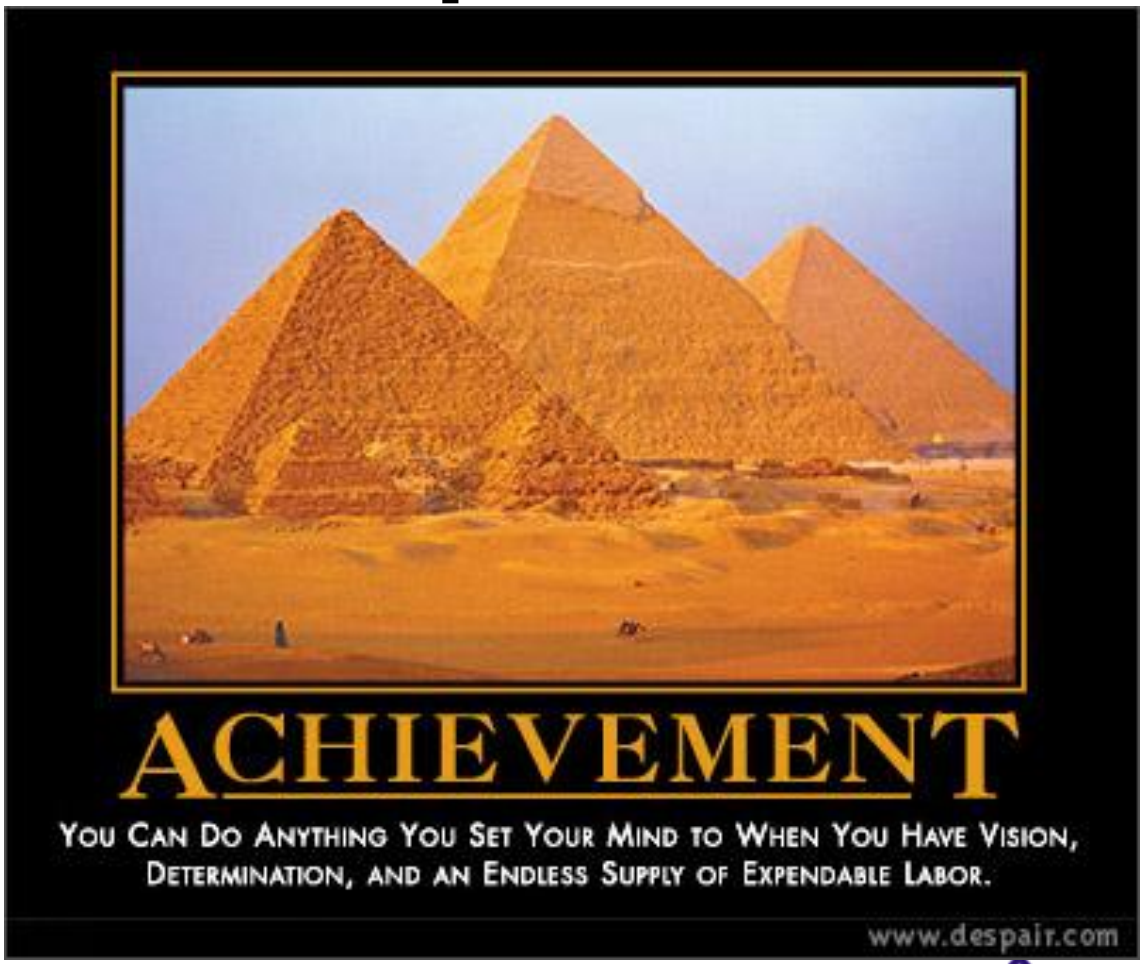
“The Good” Accomplishments



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"The Good" Accomplishments

- Establishment of multi-state Metabolic consortium
  - Biochemical geneticists, registered dietitians, genetic counselors, nurses, and consumers
  - 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
  - Pooling and sharing of resources
    - Emergency letters, parent resources

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MSGRCC Biochemical Geneticists	Regional Participants
Kirk Aleck, MD (AZ)	Hans Andersson, MD (SERC)
Debra Freedenberg, MD, PhD (TX)	Susan Berry, MD (Region IV)
Renata Gallagher, MD, PhD (CO/WY)	Stephen Cederbaum, MD (Western States)
James Gibson, MD (TX)	Sara Copeland, MD (Heartland)
Randy Heidenreich, MD (AZ/NM)	Stephen Kahler, MD (Heartland)
Celia Kaye, MD (CO)	Rani Singh, PhD, RD (SERC)
Claire Leonard, MD (NM)	Wendy Smith, MD (NEGC)
Nicola Longo, MD, PhD (UT/NV)	Judith Tuerck, RN, MS (Western States)
Marzia Pasquali, PhD (UT)	Michael Watson, PhD (NCC)
Susan Root, MD (NM)	**Neuropsychologists**
Janet Thomas, MD (CO/WY/MT)	Richard Boada, PhD (CO)
Johan VanHove, MD, PhD (CO/WY)	Jennifer Janusz, PhD (CO)
Samuel Yang, MD (MT)	Greta Wilkening, PhD (CO)
MSGRCC Genetic Counselor/Nurses	**Database Development**
Rebecca Anderson, RN, PhD (UT)	Catherine Staes, PhD (UT)
Sarah Cox, MS, CGC (AZ)	Reid Holbrook, MD (UT)
Cynthia Freehauf, RN, MS, CGC (CO)	Bruce Straw (CO)
Rena Vanzo, MS, LGC (UT)	Paul Turtle (CO)
Erica Wright, MS, CGC (CO)	Chris Wells (CO)
MSGRCC Registered Dietitians	**Consumer Representatives**
Laurie Bernstein, MS, RD, FADA (CO)	Lori Wise (CO)
Sharon Ernst, MPH, RD, CD (UT)	Joe Martinez (CO)

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…Accomplishments

- Development of disease-specific care plans for majority of metabolic diseases detected by newborn screening
  - Traditional and MS/MS panel
  - 34 in all
    - Includes maternal disorders DX by NBS
  - 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

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…Accomplishments

- Development of outcome measures for each disorder
  - "shared datasets"
  - Allows for systematic collection of data
  - Performance Indicators
    - Benchmark 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.

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MSUD dataset

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

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…MSUD dataset

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 µmol/L), Isoleucine (>100µmol/L), valine (>100µmol/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 •Neuropysch @ 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

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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 (<500µmol/L)
4. Therapy during initial care
    1. Enteral MSD formula vs. dialysis
    2. Track edema, Leu level (>600 µmol/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 µmol/L), Isoleucine (>100µmol/L), valine (>100µmol/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

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…Accomplishments

- Database development
  - Web-based application designed and maintained by Colorado Department of Public Health and Environment (CDPHE)
    - Initially, CDPHE IT staff designed LTFU database for free. Progress was slow.
    - In November 2009, CDPHE in conjunction with our metabolic clinic at Children's Hospital Colorado received "Effective Follow-up in Newborn Screening" grant funded by HRSA
    - Allowed for a complete overhaul of the existing database.

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…Accomplishments

- Database known as “Integrated Data System (IDS)”
  - Contains data fields for all LTFU performance indicators and outcome measures
  - Links to electronic birth certificates
  - Also tracks STFU and hearing screening
- Since web-based, IDS can be used by other metabolic clinics for LTFU

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…Accomplishments

- Thus far, LTFU for 72 patients has been entered in IDS
  - 65 NBS patients
  - 7 clinically diagnosed patients
  - Followed by the metabolic clinic at Children's Hospital Colorado
  - All patients are consented prior to data entry via our IRB protocol for LTFU

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“The Bad” Barriers

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Barriers

- Data collection and data entry
  - Large number of data points
    - Overzealous with performance indicators and outcome measures
  - Can be disruptive to clinic flow and efficiency
  - Data points extracted from medical charts retrospectively
    - Requires skilled individual with solid understanding of metabolic diseases
    - Labor-intensive + time consuming = $$$
      - Especially clinically diagnosed patients

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…Barriers

- Collection of developmental data
  - Questionnaires
    - Time-consuming
    - Disrupt clinic flow
    - Families often take questionnaires home but rarely send them back
  - Assessments
    - Time-consuming
    - If child appears to be developmentally appropriate, family often not interested in assessment
    - Not always covered by insurance

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“The Ugly”

- Institutional review boards
  - Colorado has an IRB approved protocol and consent for LTFU data entry into IDS.
    - Includes the use of aggregate data for research purposes
    - Recently updated to include clinically diagnosed patients.
  - However, each clinic will need to adapt this protocol in order to get it cleared through their IRBs prior to data entry.

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…"The Ugly"

- Obtaining data from other states /clinics
  - Direct entry into IDS
    - Need to train individuals at each center
  - Entry into Excel spreadsheet
  - Send trained personnel to other states/clinics to extract data from medical records
- Integration with other databases
  - Collaboration with Region IV and NBSTRN

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Clint Eastwood's favorite Clint Eastwood movies

- Bird ***
- Letters From Iwo Jima ***
- Million Dollar Baby
- Mystic River ***
- The Outlaw Josey Wales
- Unforgiven

***directed by Mr. Eastwood

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Resources

- *MSGRCC Metabolic Newborn Screening Long-Term Follow-up Study: A collaborative multi-site approach to newborn screening outcome research.* E. Wright, J. Van Hove, J. Thomas. Genetics in Medicine. 2010 Dec;12(12 Suppl):S228-41.
- www.MountainStatesGenetics.org

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Thank you!

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  - Chris Wells

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Thank You!

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