California Tandem MS Research Project

Final Results

Jan, 2002-July, 2003

2004 Newborn Screening and Genetic Testing Symposium,
Atlanta, GA, May 3-6, 2004

Original Legislative Mandate

- AB 2427 (Kuehl) – state will implement a pilot project for ms/ms testing
- The pilot will determine how best to implement ms/ms to mandatory program through a development and evaluation effort
- $3.9 million appropriated for pilot

Model for the ms/ms research project

- To be conducted as research project with state IRB review process and informed consent
- Optional to parent
- No additional charge to parent
- Follow-up provided including diagnostic work-up
- Mandatory NBS specimen used
- Specimens sent to GDL after mandatory testing
- No negative reports sent during pilot

Model for ms/ms research project – follow-up and evaluation

- All positive flags reviewed by clinical chemist
- All referred cases directed to metabolic specialists
- Follow-up from central GDB site until case is resolved with a diagnosis or as normal
- Periodic meetings with metabolic specialists for input
- Evaluation team

HRSA funded grant for evaluation

- 3 years for evaluation of ms/ms implementation and development of recommendations for other states
- California and Hawaii (via Oregon)
- Diagnostic data, lab data, throughput, parent focus groups, cost studies

Challenges – IRB issues

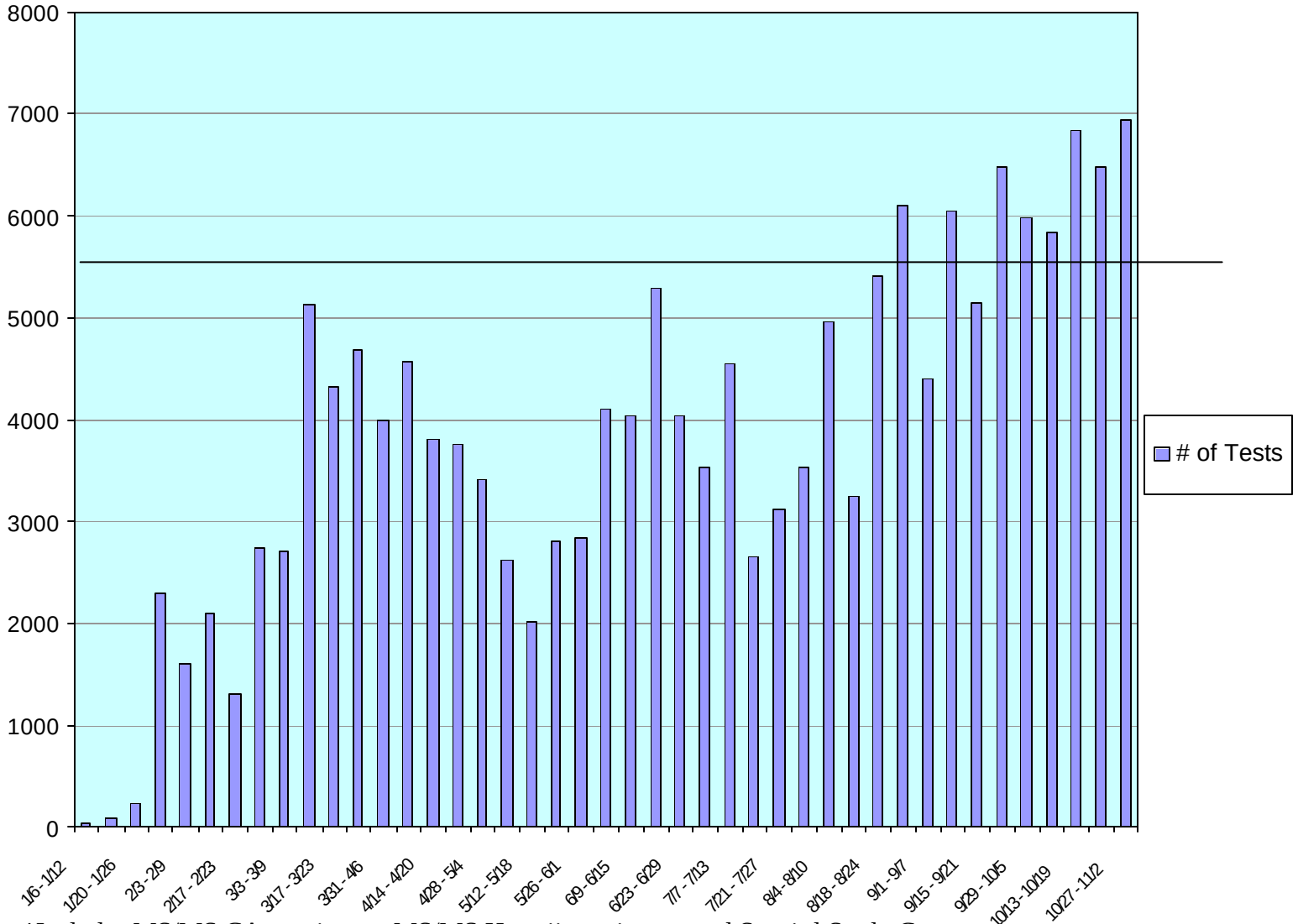
- Informed consent (research) vs. dissent in mandatory program
- State IRB was problematic and time-consuming
- Despite approval, many hospitals would not use state-approved IRB despite HRSA support
- Time delays, bureaucracy, and lack of participation resulting from individual hospital IRBs
- Decreased participation as a result

Challenges – Selection of analytes

- Lack of interpretive software - clinical chemist
- Decided on reporting full spectrum:
- ✓ - easier to collect data and delete later
- ✓ - what to do if only selected disorders reported but see other elevations – research model collecting all data possible
- ✓ - no cutoffs for a few analytes until more known
- ✓ - metabolic specialists' request

Weekly Count of MS/MS Specimens Transmitted*

January 7 – November 2, 2002



*Includes MS/MS CA specimens, MS/MS Hawaii specimens, and Special Study Cases

Challenges – Establishment of Cutoffs

- 10,000 anonymous specimens before startup
- Statistical analyses with emphasis on tails and percentiles
- Projected positive rates and workload
- Other states' experiences and cutoffs – limited
- Analyte by analyte adjustments – e.g. tyrosine
- Primary vs. secondary marker etc.
- Disorder considerations may affect cutoff

Challenges – Establishment of Cutoffs II

- Meeting with metabolic specialists after two months
- Elimination of valine, glutamate, and aspartate cutoffs – lack of disorder relevance and/or false positive issues

Challenges – Cutoffs III – 40,000 Specimens

- After five months, additional cutoff changes were proposed to metabolic specialists and instituted

- Cutoffs raised due to positive rate and more data (e.g. C2, C3, C5, C5OH)

- Cutoffs lowered due to more data and acceptable positive rate (C14, C16OH, C18OH)

- Cutoffs implemented where none previously (C3DC, C12, C14OH)

Effect of Cutoff Changes and Review on initial positive and referral rates

- Prior to cutoff changes after 40,000 specimens – Initial positive rate = 0.7%
- After cutoff changes – Initial positive rate =0.14%
- Referral rate after clinical review:
  - 0.49% before changes
  - 0.08% after changes

-California does not repeat positive specimens on initial or recall specimens – what do other states do?

Evaluation of Cutoffs – Diagnosed Cases Registry

- Registry of all flagged and confirmed cases
- Registry of pre-ms/ms confirmed cases pulled from frozen storage and tested
- Registry of cases reported after ms/ms testing began but not offered screening – tested with consent
- Registry of cases missed by ms/ms screening
- Gradual implementation on more ratios - input

Example –MSUD Screening

- Five (5) known cases: frozen (2), not screened (2), missed (1)
- By leu/ile cutoff (350) - 3 detected, 2 not detected
- By initial valine cutoff (dropped) – 5 detected
- New cutoff for MSUD being implemented – leu > 300 AND leu/ala > 1.75 – 5 detected

California Department of Health Services, Genetic Disease Branch

Tandem Mass Spectrometry

Supplemental Newborn Screening Research Results

*** ACTION REQUIRED ***

Date: 10/11/2002

Patient:

Lastname	First name	Aka:
TEST	BABYFIRS	TESTAKA

Physician:

Lastname	First name
RHIM	JEAN

1150 VETERANS BLVD.

REDWOO CITY | CA | 94063

Hospital Name: SAN LUIS OBISPO CO HEALTH DEPT

Medical Record #: 10925198

Date of Birth: 9/20/2002 2:25:00 AM **Gender:** M **I Number:** 17169749825

Blood Collection Date: 9/21/2002 5:50:00 AM **Birth Weight:** 2975 **Accession Number:** 77777777777777

Hours at Collection: 27 **Transfusion Flag:** N

During this research project, the following unusual patient results were obtained:

Amino Acids:	Value	Flag	Range
Glycine	382		0 - 1500
Alanine	211		0 - 1200
Valine	139		NC
Leucine/Isoleucine	131		0 - 350
Phenylalanine	46.9		0 - 210
Tyrosine	55		0 - 800
Methionine	18.2		0 - 100

Amino Acids:	Value	Flag	Range
Citrulline	17.4		0 - 100
Ornithine	60.2		0 - 400
Arginine	6.58		0 - 140
Proline	59.2		0 - 500
5-Oxoproline	21.8		0 - 250
Glutamate	340		NC
Aspartate	69.4		NC

Acylcarnitines:	Value	Flag	Range
FC	27.7		10.0- 170
C-2	16.6		4.0- 70.0
C-3	1.33		0 - 14.00
C-3DC	0.127		0- 2.00
C-4	0.254		0 - 2.50
C-4DC	0.38		0 - 4.50
C-5	8.45	H	0 - 2.30
C-5:1	0.0845		0 - 0.70
C-5OH	0.211		0 - 2.30
C-5DC	0.0423		0 - 0.75
C-6	0.0605		0 - 2.00
C-8	0.254		0 - 1.50
C-8:1	0.0845		0 - 1.50
C-10	0.133		0 - 1.50

Acylcarnitines:	Value	Flag	Range
C-10:1	0.133		0 - 1.30
C-12	0.211		0- 2.50
C-12:1	0.317		NC
C-14	0.385		0 - 2.00
C-14:1	0.165		0 - 1.50
C-14OH	0.11		0- 1.20
C-16	2.08		0 - 13.00
C-16:1	0.169		0- 2.25
C-16OH	0.113		0 - 1.85
C-18	0.415		0 - 4.50
C-18:1	0.831		0 - 4.50
C-18:2	0.125		NC
C-18OH	0.0416		0 - 0.80
C-18:1OH	0.0416		0 - 0.85

H= High; L=Low; Values and ranges are in micromol/L *NC=No cut-offs established at this time*

Summary: **Amino Acid Profile:**

Acylcarnitine Profile: **Positive Screen: Follow-Up Required**

Recommendation: Immediate referral to a CCS-Approved Metabolic Center to rule out the possibility of an amnio acid, fatty acid or organic acid disorder is required.

Call 866-954-BABY or (866-954-2229) if you have any questions or e-mail us at msms@dhs.ca.gov.

John Sherwin, Ph.D., Chief
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Results as of June 30, 2003:N = 354,074

Disorder	Detected (ms/ms)	Missed (ms/ms)	Prevalence
MCADD	13		1/27,000
SCADD	18		1/20,000
MMA/PA	11		1/32,000
LCHADD		1	1/354,000
GA-1	1		1/354,000
GA-II	2		1/177,000
3-MCC	2		1/177,000
Argininemia	1		1/354,000
VLCADD	1	1prenat-dx/tx	1/354,000
MSUD	1	1	1/354,000
Total	50	3	1/6680 (no PKU)

Non-screened cases reported to Genetic Disease Branch January 2002-June 30, 2003

Disorder	Total	Screened (previous slide)
MCADD	**1**	13
SCAD/EMA	**0**	18
MMA/PA	**2**	11
LCHADD	**1**	1
GA-1	**1**	1
GA-II	**0**	2
3-MCC	**0**	2
Argininemia	**0**	1
VLCADD	**0**	2
MSUD	**3**	2
IVA	**1**	0
Total	**9**	53

Additional Cases

(incompletely defined or benign)

- Biotin Metabolic Defect **C5OH = 4.28**
- Probable Mitochondrial Energy metabolism Deficiency **Gly = 1260**
- Methionine adenosine transferase deficiency (MAT) (no further tx) **Meth = 113**
- Hypermethioninemia (typically benign) **Meth = 137**

Testing of Stored Frozen Blood Spots

- 45 cases of metabolic disorders with known diagnoses retrieved from frozen storage (-20 C)
- From birth years 1983-2002 (excluding those screened during ms/ms pilot)
- 23 positive by ms/ms after storage, 20 had no elevations, 4 had unknown or nonspecific dx, 2 had dx of “mild MMA” , 2 were OTC (not detectable by ms/ms)

Frozen Specimens Cont'd

Disorder	Reported Dx	MS/MS Result confirmed
MCADD	9	8*
MSUD	2	1**
PA	6	5
MMA	4 (2 "mild")	0
LCHADD	3	2
VLCADD	3	2

*C8 = 1.49 (cutoff 1.5); C8/C10 high

**Pos by old valine cutoff (280)

Summary/Conclusions

- Will likely continue with full-testing spectrum in mandatory program
- PKU testing analyzed independently (see poster presentation)
- Derivatized vs. Non-derivatized (see presentation)
- Lab configuration will change (1 vs. multiple)

Looking Towards the Future?

SB 142 (Alpert) This bill would mandate addition of all disorders detected by tandem mass spectrometry, as well as CAH. (exact language not finalized as of 4/22/2004)

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