

Newborn Screening for Infants With Suspected Very Long-Chain Acyl-CoA Dehydrogenase Deficiency in the Western United States.

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Western States Genetic Services Collaborative

- The Western States Genetic Services Collaborative is a federally funded multi-state project that seeks to coordinate and increase access to genetic services among the participating states and territory including:
 - Alaska, California, Guam, Hawai`i, Idaho, Oregon, and Washington
- www.westernstatesgenetics.org
- Goal of improving the health of children with disorders detected by NBS or with birth defects and other genetic disorders.

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VLCADD

(Very Long-Chain Acyl-CoA Dehydrogenase Deficiency)

- Disorder of fatty acid beta-oxidation
 - Can't generate ketones, lack of energy production
- Present with a highly variable phenotype
 - Neonatal dilated cardiomyopathy
 - Childhood hypoketotic hypoglycemia with liver dysfunction and fatty liver infiltration
 - Adolescent or adulthood presentations of myopathy and rhabdomyolysis
- Diagnosis
 - Elevations of C14, C14:1- acylcarnitines
 - Confirmed by enzyme assay (skin biopsy, WBC) or DNA sequencing
- Current therapy
 - Avoidance of fasting
 - Diet low in long-chain fatty acids, MCT-supplemented
 - L-carnitine

Consequences of VLCADD on NBS

- Benefits

TP

- Early treatment of VLCAD – clear response to treatment
- Now infants may remain asymptomatic
- Is this from a “lack of symptoms” and effective treatment?
- Is this from an “asymptomatic form” of VLCAD ?

ATP

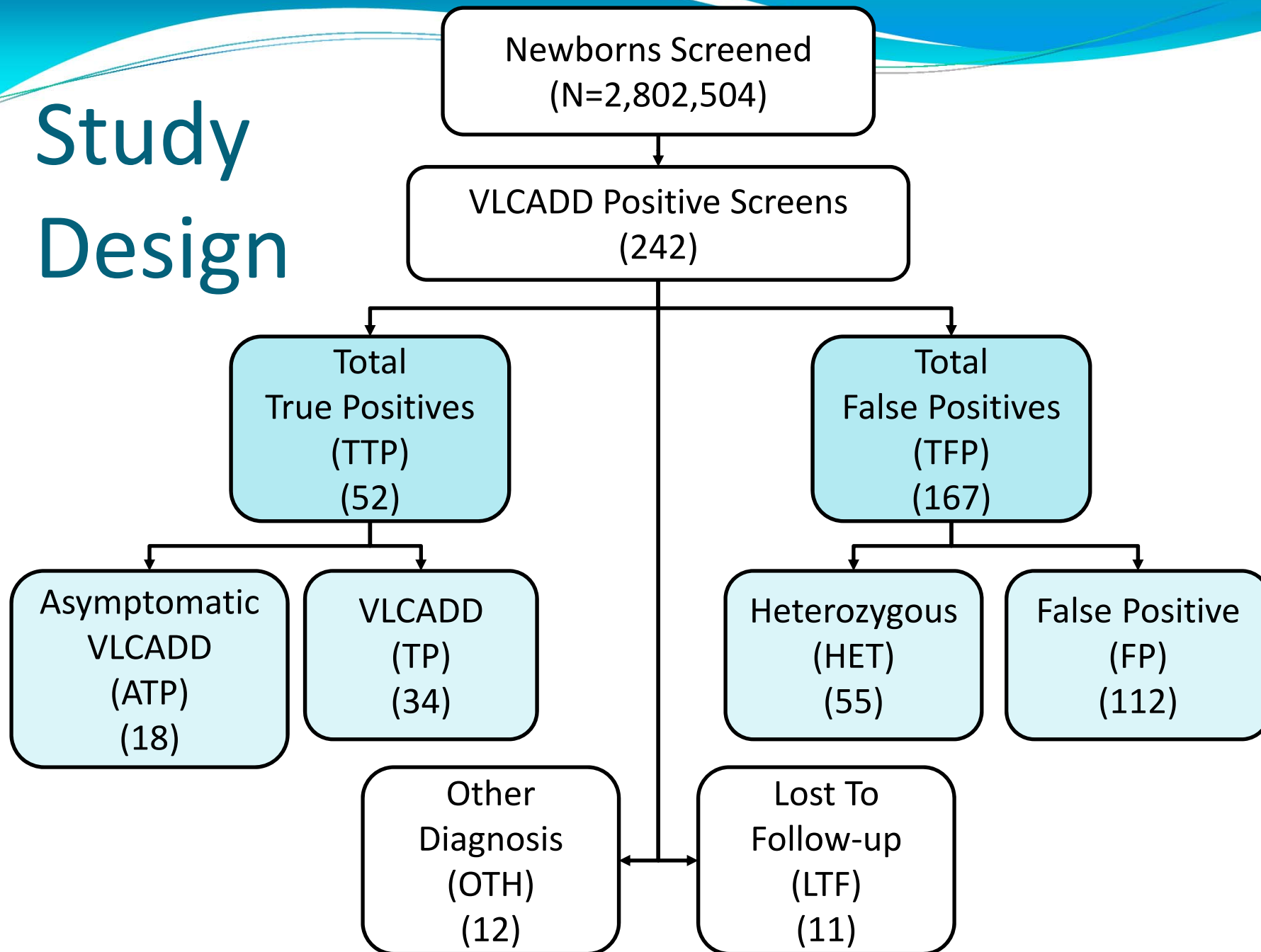
- Risks

- Higher number of false positives (family stress, “medicalization”)
- Difficulties with confirming diagnosis
- Need for, or level of, therapy required for “asymptomatic”

FP

HET

Study Design



Study Groups

	Population	Abnormal NBS	NBS+ Incidence
ALL	2,802,504	242	1 in 11,581
2005	276,422	14	1 in 19,744
2006	560,914	29	1 in 19,342
2007	633,481	60	1 in 10,558
2008	657,982	71	1 in 9,267
2009	673,705	68	1 in 9,907

Overall disease incidence:

All VLCADD – 1 in 53,894 (1.86 per 100,000)

Symptomatic VLCADD – 1 in 82,427 births

Group	Group Incidence
TTP	1 in 4.65
TP	1 in 7.12
ATP	1 in 13.4
TFP	1 in 1.45
HET	1 in 4.4
FP	1 in 2.16

Other Diagnoses Found

- CPT-2 deficiency x2
- Other FAO x4
- LCHAD deficiency x4
- SCAD deficiency
- Unknown

Demographics

	ALL	TP	TPA	HET	FP	OTHER	LOST
Male	157	20	9	38	78	7	5
Female	85	14	9	17	34	5	6
Twin	15	0	2	4	8	0	1

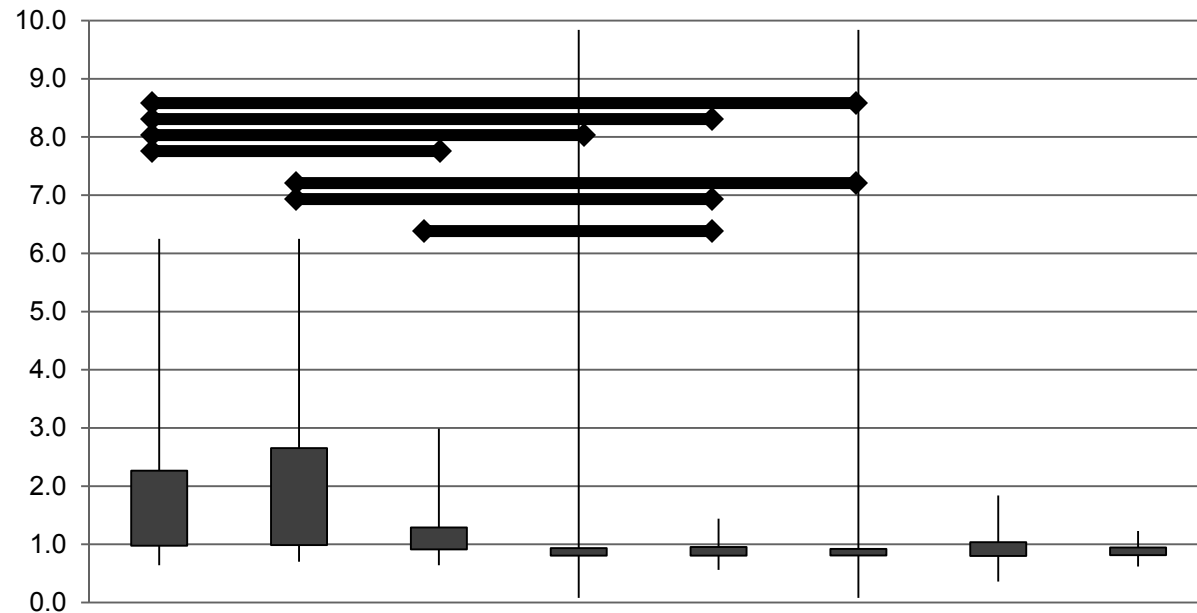
- No differences in other areas
 - Age of collection, birth weight, twins, in NICU, or receiving TPN, steroids, antibiotics, transfusions
- Male/Female comparison
 - ALL 157 vs. 85 p-value<0.0001
 - HET male vs. female p-value=0.0046
 - FP male vs. female p-value=0.0001



Clinical Info Obtained

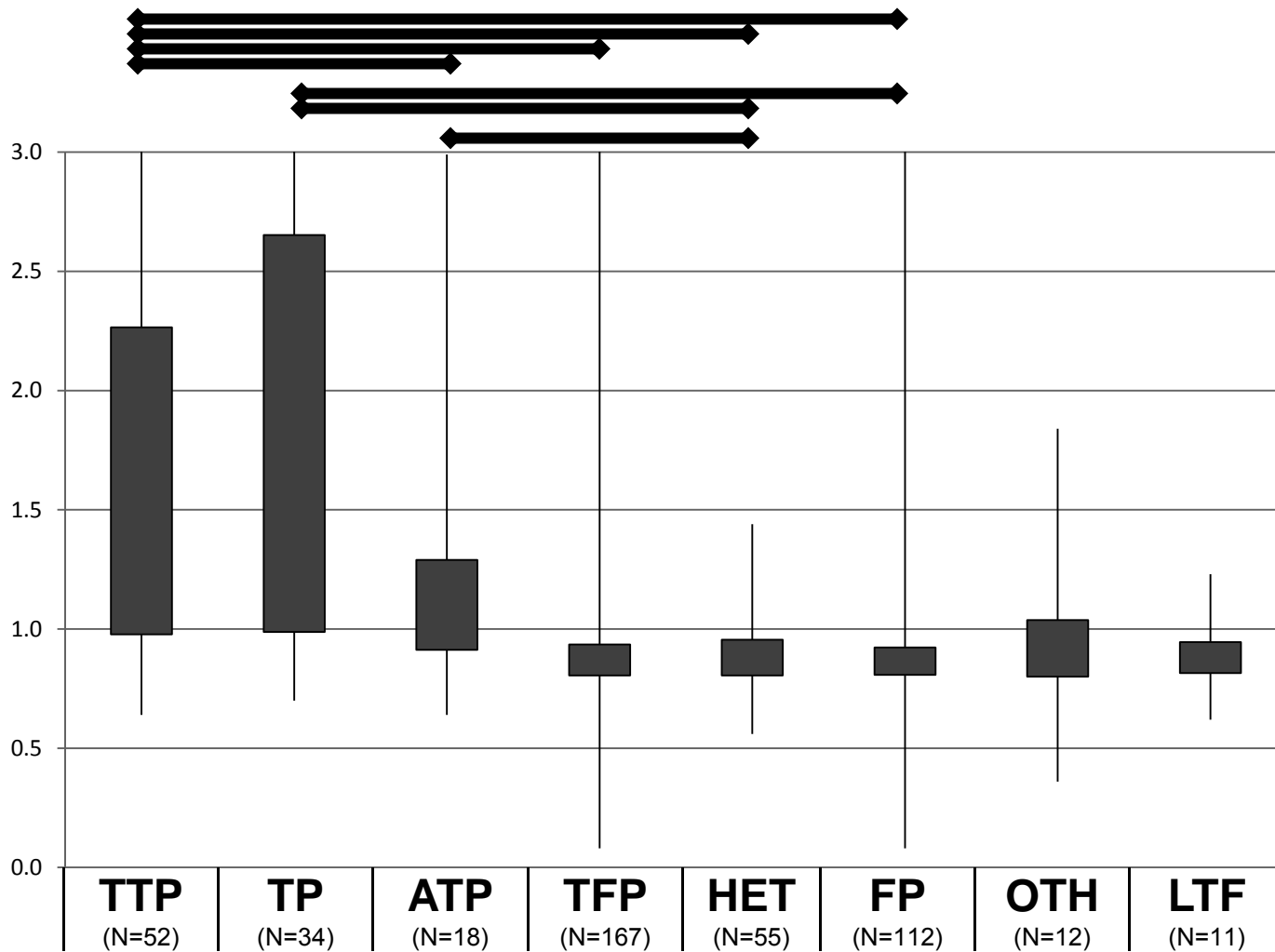
- TP symptoms – 15 children w/ info provided
 - Deceased – 3 (dehydration/lethargy/poor feeding; renal disease/respiratory disease; sudden cardiac dysrhythmia)
 - Cardiomyopathy x4, Dehydration x7, Lethargy x5, Vomiting x9, Poor Feeding x8, Diarrhea x5, Enteral Feeding/G-tube, Poor Muscle Tone/Hypotonic x2, Poor weight gain x4, Respiratory disorders x2, Irritability x3, Renal disease, low glucose x2.
- ATP Symptoms – no symptoms on follow-up at 1 year
 - Hawaii homozygous p.T40M variants – 6 children
 - 2 with normal FAO probe assays, none with symptoms
- HET, OTH, LOST – no symptoms reported
- FP – 3 with maternal B12 deficiency, trisomy 21, in NICU (poor feeding)
- DNA testing in only 10 TP, 10 ATP, 38 HET, 22 FP

C14:1-Acylcarnitine Values on 1st NBS

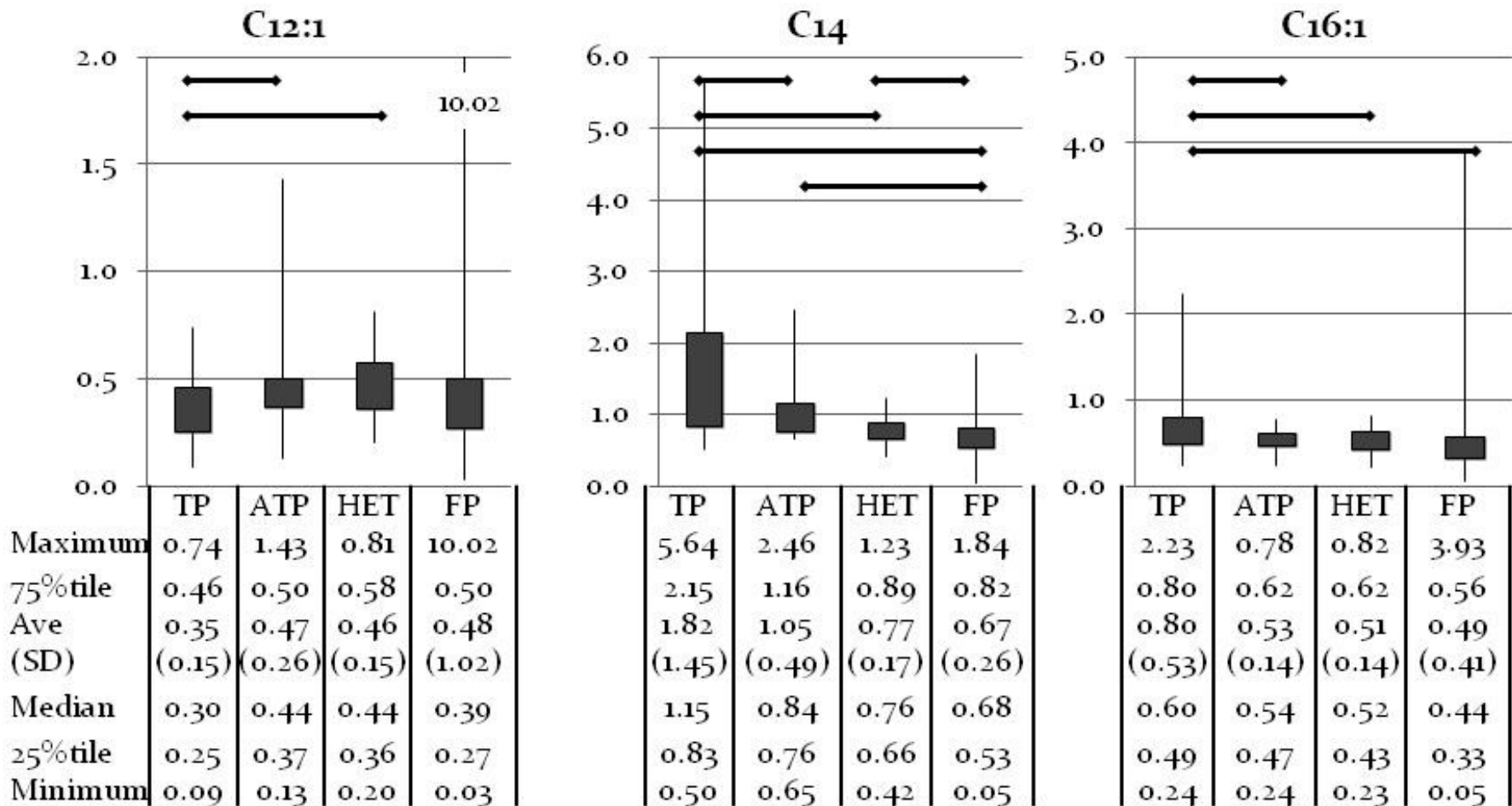


	TTP (N=52)	TP (N=34)	ATP (N=18)	TFP (N=167)	HET (N=55)	FP (N=112)	OTH (N=12)	LTF (N=11)
Maximum	6.25	6.25	5.33	9.84	1.44	9.84	1.84	1.23
75%tile	2.27	2.45	1.54	0.94	0.96	0.92	1.04	0.95
Average (SD)	1.77 (1.26)	1.90 (1.34)	1.55 (1.13)	0.93 (0.72)	0.89 (0.16)	0.95 (0.87)	0.97 (0.37)	0.91 (0.17)
Median	1.25	1.34	1.13	0.84	0.89	0.83	0.86	0.87
25%tile	0.98	0.98	0.94	0.81	0.81	0.81	0.80	0.82
Minimum	0.64	0.70	0.64	0.08	0.56	0.08	0.36	0.62

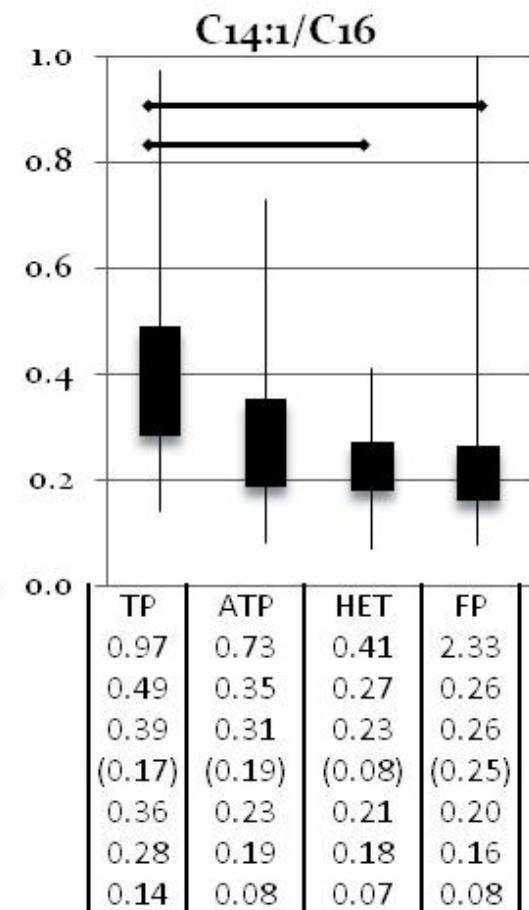
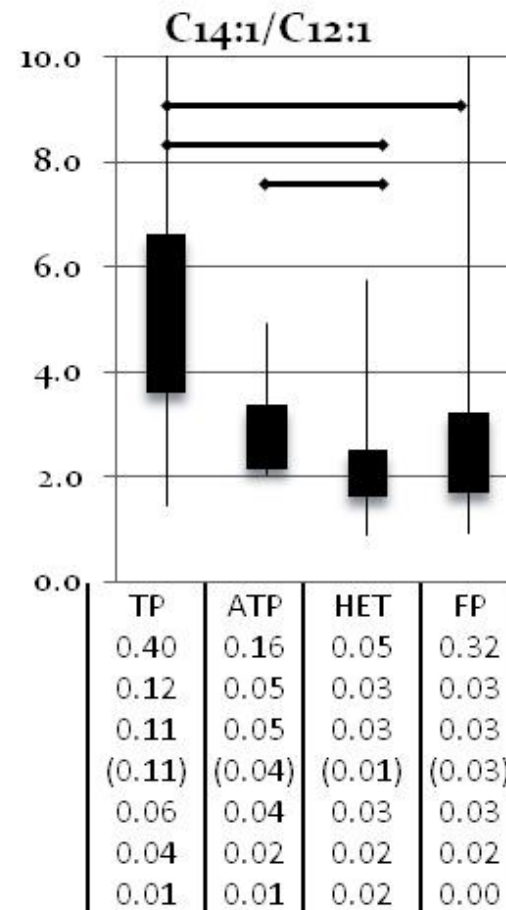
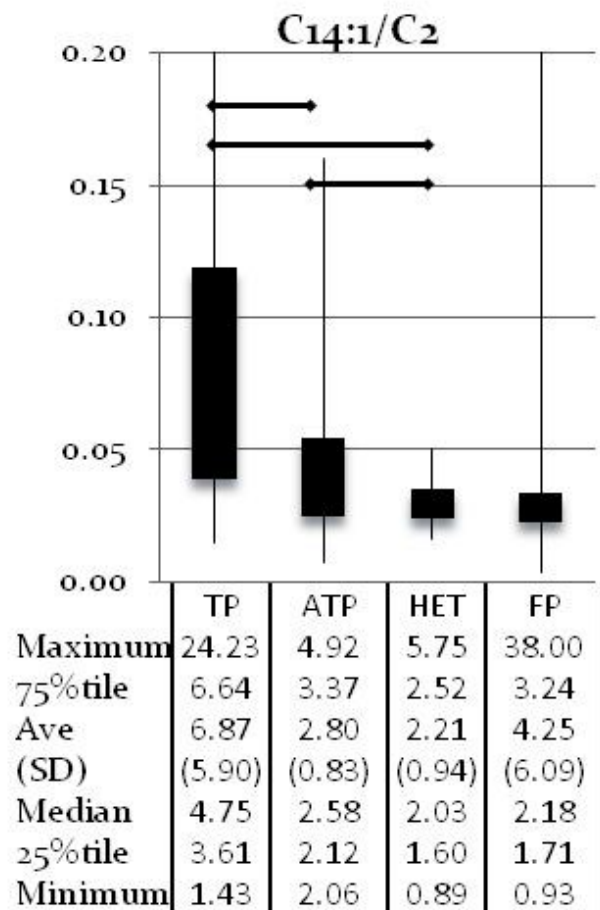
C14:1 (expanded view)



Other Acylcarnitines



Acylcarnitine Ratios



Region 4 VLCAD Tools

		Total Cases	Not Run	Total Run	% Run	Very Likely	Likely	Possibly	NI	% Informative
VLCADD General Tool	ALL	242	145	97	40.1%	16	23	22	36	
	TTP	52	37	15	28.8%	7	5	3	0	
	TFP	167	100	67	40.1%	4	14	18	36	
VLCADD Tool #1	ALL	242	0	242	100.0%	48	92	79	23	90.5%
	TTP	52	0	52	100.0%	30	14	8	0	100.0%
	TFP	167	0	167	100.0%	14	67	63	23	86.2%
VLCADD Tool #2	ALL	242	29	213	88.0%	47	69	42	55	74.2%
	TTP	52	2	50	96.2%	28	15	4	3	94.0%
	TFP	167	27	140	83.8%	13	48	33	46	67.1%

NI=score not informative

Region 4 VLCAD Dual Scatter Tool

	Total Cases	Not Run	Total Run	% Run	Likely HET	NI	Likely VLCADD	% Predicted HET	% Predicted VLCADD
ALL	242	145	97	40.1%	62	13	22	63.9%	22.7%
TTP	52	37	15	28.8%	6	1	8	40.0%	53.3%
TFP	167	100	67	40.1%	46	12	9	68.7%	13.4%
TP only	34	21	13	38.2%	5	1	7	38.5%	53.8%
ATP only	18	16	2	11.1%	1	0	1	50.0%	50.0%
HET only	55	28	27	49.1%	23	4	0	0.0%	0.0%
FP only	112	72	40	35.7%	23	8	9	57.5%	22.5%

NI=score not informative

VLCAD (het) vs VLCAD 013 2011-06-21 [Dual]



Future Directions/Conclusions

- There appear to be differences between:
 - True positives with symptoms and without symptomatic
 - Between true positives and false positives using ratios
- Limited by “beneficence” of clinicians
 - Need for complete data
- Expansion of study
 - Obtaining detailed clinical information in all groups
 - Overlap between heterozygotes and asymptomatic TP
- Analysis of post-analytical tools
 - Good sensitivity, need to work on specificity
 - Has a tangible benefit in reducing some false positives now



Thank You

- Questions?

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Abstract (as submitted)

The Western States Regional Genetics Services Collaborative is a federally funded multi-state project that seeks to coordinate and increase access to genetic services. A workgroup was created to study the outcomes of infants with a positive newborn screening (NBS) result for very long-chain acyl-CoA dehydrogenase deficiency (VLCADD) using a retrospective evaluation of newborns born between July 2005 and December 2009 in California, Hawaii, Oregon, and Washington. VLCADD is a fatty acid oxidation disorder classically presenting with cardiomyopathy, hypoketotic hypoglycemia, or rhabdomyolysis with elevations of C14:1, C14, C16 acylcarnitines on NBS. Expanded NBS has led to the finding of VLCADD in a growing number of asymptomatic children, making NBS interpretation difficult. This study explored the relationship between NBS values, available diagnostic testing results, and clinical outcomes. Cases were classified as true positive (TP), asymptomatic-true positive (ATP), heterozygote (HET), false positive (FP), other diagnosis (OTH), or lost to follow-up (LOST).

Among 2.8 million children screened there were 242 screen positive cases for VLCADD. There were 52 TP cases of which 20 were ATP, 55 HET, 112 FP, 11 LOST, and 12 OTH. No differences in age at collection and birth weight were seen. Male infants were more common in the FP or HET groups ($p < 0.05$). Statistically significant differences were seen between TP or ATP cases and FP or HET ($p < 0.0001$). The positive predictive value for VLCADD with a NBS C14:1 value of $\geq 2.0 \mu\text{M}$ was 94.4 %, 54% at $\geq 1.0 \mu\text{M}$, and 23% at $\geq 0.7 \mu\text{M}$. Post-analytical tools also predicted 100% of all TP cases and 54% all FP cases.

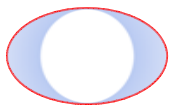
This study is the largest currently reported follow-up of infants with NBS positive for suspected VLCADD reported to date providing a foundation for further analysis and for long-term clinical follow-up studies being developed.



Extra slides for reference/questions

Demographics

	ALL	TP	ATP	HET	FP	OTHER	LTF
1st NBS	242	34	18	55	112	12	11
2nd NBS	66	4	6	24	29	3	0
3rd NBS	7	0	0	1	6	0	0
Information obtained from NBS Card							
Male	157	20	9	38	78	7	5
Female	85	14	9	17	34	5	6
Twin	15	0	2	4	8	0	1
NICU	18	2	0	2	10	4	0
TPN	6	0	0	0	4	2	0
Steroids	0	0	0	0	0	0	0
Antibiotics	0	0	0	0	0	0	0
Transfused	5	0	0	0	4	1	0
1st NBS AAC hours (SD)	34.3 (16)	36.4 (24)	33.7 (13)	33.6 (10)	32.8 (15)	42.5 (27)	38.5 (12)
1st NBS BW grams (SD)	3174 (523)	3237 (546)	3247 (389)	3132 (412)	3181 (540)	2935 (932)	3250 (377)
Clinical testing reported by provider							
Plasma AC	39	13	7	11	3	5	0
Organic acids	17	5	1	0	8	3	0
FAO probe	10	1	2	4	3	0	0
DNA testing	84	10	10	38	22	3	1
Liver testing	17	4	0	3	6	4	0
Cardiac testing	13	13	0	0	0	0	0
Clinical treatment reported by provider							
Carnitine	16	11	2	1	2	0	0
Fasting	18	5	8	3	1	0	1
MCT	33	16	5	6	3	3	0





Short-term Clinical Observations

- Symptoms vs. C14:1 Values
- C14:1 >5.0 uM 3 cases
 - Dehydration, Diarrhea, Irritability, Lethargy, Poor Feeding, Vomiting
 - Deceased - Renal disease, Respiratory disease
 - Encephalopathic and appeared septic, Hypoglycemia, Poor Feeding, Vomiting; Hypoglycemia, Poor Feeding, Vomiting, Hypertrophic cardiomyopathy (all in year one) with continuation of some symptoms through age 3
- C14:1 3-5 uM 2 cases
 - Cardiomyopathy, Dehydration, Lethargy, Vomiting
 - Deceased - baby seemed to be doing fine and died quite suddenly at 2 days of life. “PROBABLE CARDIAC DYSRHYTHMIA”

Clinical Observations (2)

- C14:1 2.0-3.0 uM 9 cases
 - low glucose upon clinical eval
 - Cardiomyopathy, Dehydration, Diarrhea, Enteral Feeding/G-tube, Poor Feeding, Poor Muscle Tone/Hypotonic, Poor weight gain, Respiratory disorders, Vomiting
 - Deceased - Dehydration, Lethargy, Poor Feeding
 - Poor Feeding, Poor Muscle Tone, Poor Weight Gain, Vomiting
 - 5 cases – no info
- C14:1 1.0-2.0 uM 11 cases
 - Poor weight gain, Vomiting
 - Dehydration, Poor feeding, Poor weight gain
 - Diarrhea, Irritability, Poor feeding
 - Irritability, Vomiting
 - Dehydration, Diarrhea, Lethargy, Poor feeding, Vomiting
 - 6 cases – no info
- C14:1 0.7-1.0 uM 9 cases
 - 1 cases – dehydration, diarrhea, vomiting
 - 8 cases – no info