Systematic Data Collection to Inform Policy Decisions:

Using the Laboratory Performance Database – Region 4 Stork (R4S) MS/MS Data Project to Improve Newborn Screening in Washington State

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Washington Newborn Screening

- Screening panel determined by the State BOH
- Screen for 19 conditions using MSMS
  - FAP: VLCAD, MCAD, LCHAD, TFP, and CUD
  - AAP: PKU, CIT, ASA, HCY, MSUD, and TYR-I
  - OAP: PROP, Cbl A,B, MUT, IVA, BKT, HMG, MCD, and GA-I
- Use Multiple Reaction Monitoring (MRM) for limited number of analytes to reduce incidental findings

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Informative Markers

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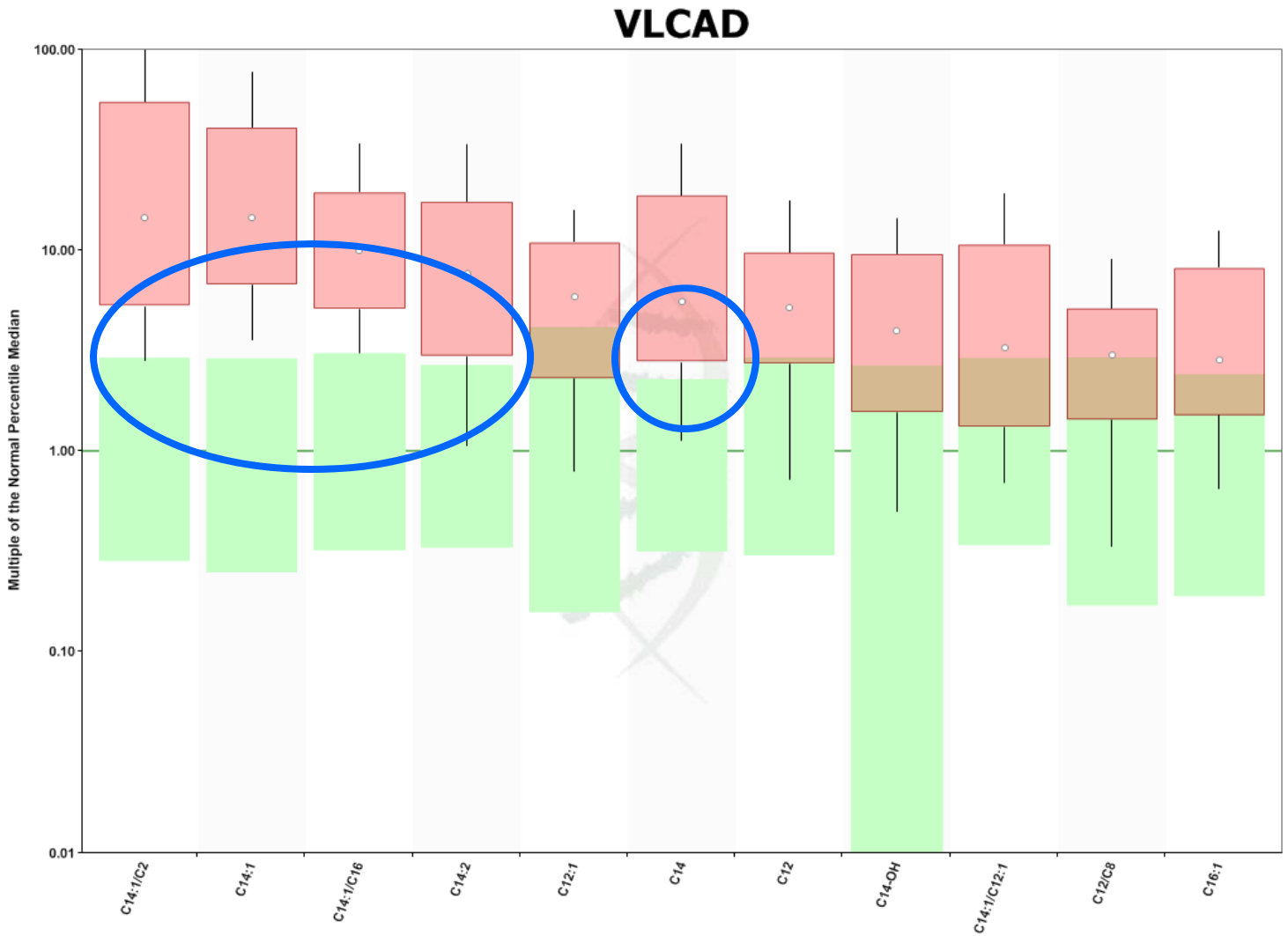
Plot by Condition



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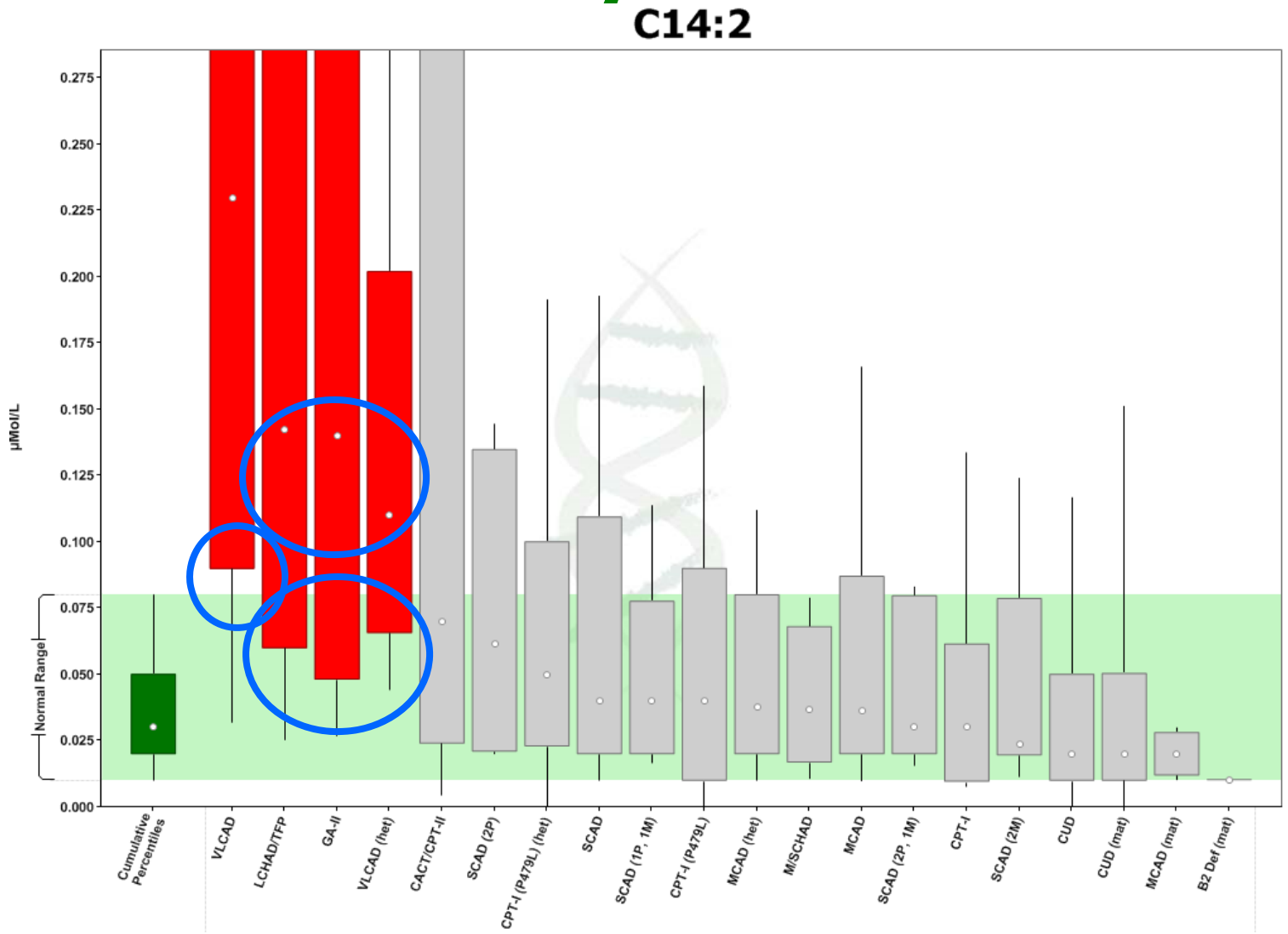
Plot by Marker



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Informative Markers

	Analyte	CUD	LCHAD /TFP	MCAD	VLCAD	CUD (mat)	MCAD (het)	MCAD (mat)	VLCAD (het)	Ga-II	CACT/ CPT-II	CPT-I	CPT-I (P479L)	M/SCHAD	RED	SCAD
H	C10:1															
H	C10															
H	**C3DC**															
H	C5DC															
H	C12:1															
H	**C12**															
H	**C14:2**															
H	C14:1															
H	C14															
H	C14-OH															
H	C16:1															
L	C16															
H	C16															
L	C18:2															
H	C18:2															
L	C18:1															
H	C18:1															
L	C18															
H	C18															

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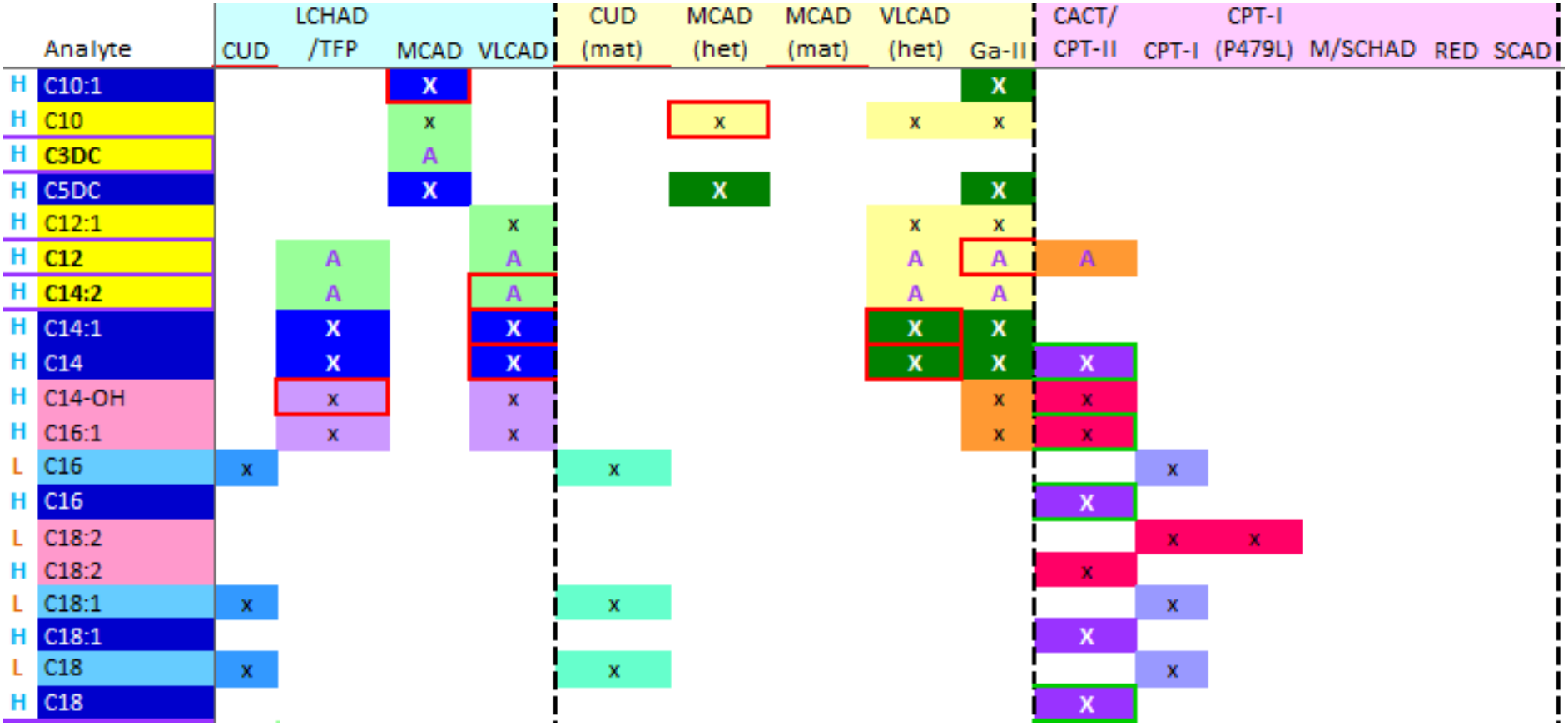
Informative Markers



	Analyte	LCHAD CUD	LCHAD /TFP	LCHAD MCAD	LCHAD VLCAD	CUD (mat)	MCAD (het)	MCAD (mat)	VLCAD (het)	VLCAD Ga-II	CACT/ CPT-II	CPT-I CPT-I	CPT-I (P479L)	CPT-I M/SCHAD	CPT-I RED	CPT-I SCAD
H	C10:1			X						X						
H	C10			x			x		x	x						
H	C3DC			A												
H	C5DC			X			X			X						
H	C12:1				x				x	x						
H	C12		A		A				A	A	A					
H	C14:2		A		A				A	A						
H	C14:1		X		X				X	X						
H	C14		X		X				X	X	X					
H	C14-OH		x		x					x	x					
H	C16:1		x		x					x	x					
L	C16	x				x						x				
H	C16										X					
L	C18:2											x	x			
H	C18:2										x					
L	C18:1	x				x						x				
H	C18:1										X					
L	C18	x				x						x				
H	C18										X					

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Informative Markers

- Added 9 new analytes
- Created 9 new ratios
- 12 of the 18 new markers are informative for a condition on our panel
- Impacted 9 conditions on our panel

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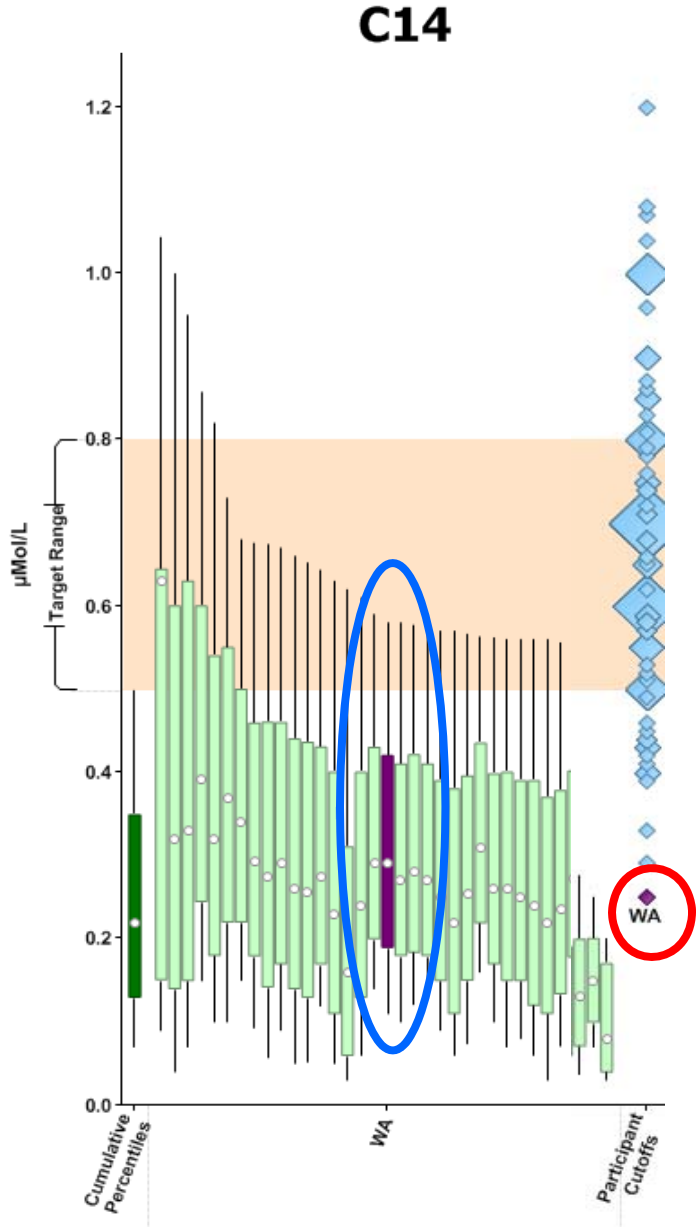
Cutoff Review

Analyte Comparison



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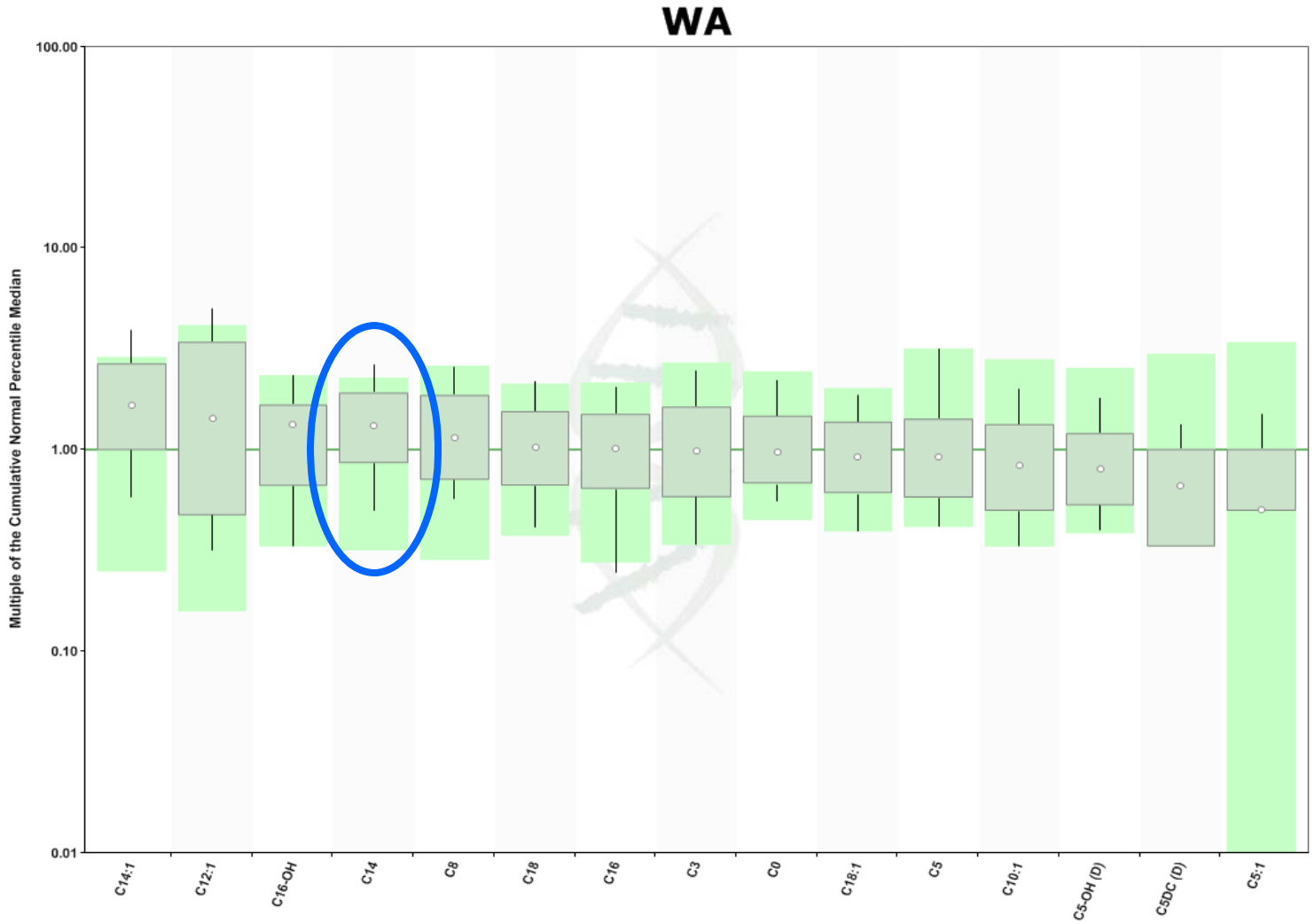
Normal Percentile Comparison



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Score Card

C14

Normal Population (NP)							Target Range	
Percentiles (µM) (Median of *N* lab %ile values)							NP 99%ile	DR 5%ile
Analyte	*N*	1%	10%	50%	90%	99%	Not %ile Based	
C14	*110*	0.070	0.13	0.22	0.35	0.50	*0.50* -	*0.80*

Disease Range of True Positives (DR)									
Percentiles (µM) (Based on *N* values per analyte in reported cases)									
N	1%	5%	10%	25%	50%	75%	90%	99%	Condition
125	0.13	0.27	0.37	0.74	1.44	2.36	3.85	7.39	GA-II
70	0.24	0.40	0.48	0.73	1.24	1.67	2.92	4.81	CACT/CPT-II
588	0.25	0.49	0.62	0.79	1.22	2.39	4.10	7.43	VLCAD
175	0.31	0.46	0.50	0.61	0.71	0.84	1.00	1.46	VLCAD (het)
212	0.15	0.22	0.27	0.41	0.63	1.03	1.45	2.67	LCHAD/TFP

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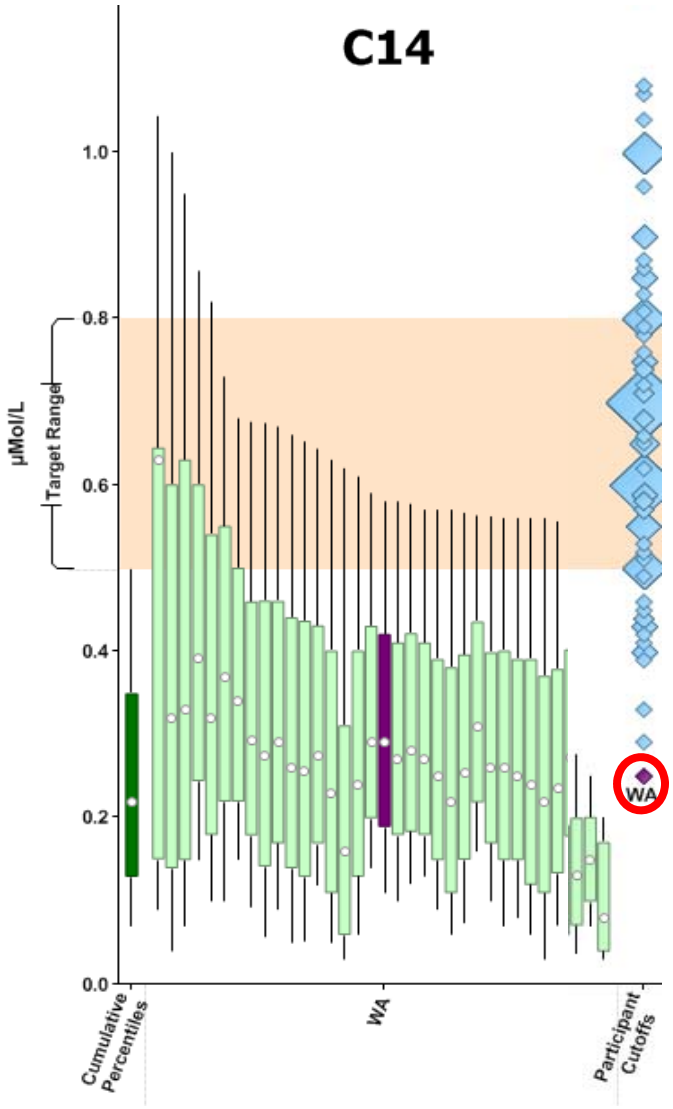
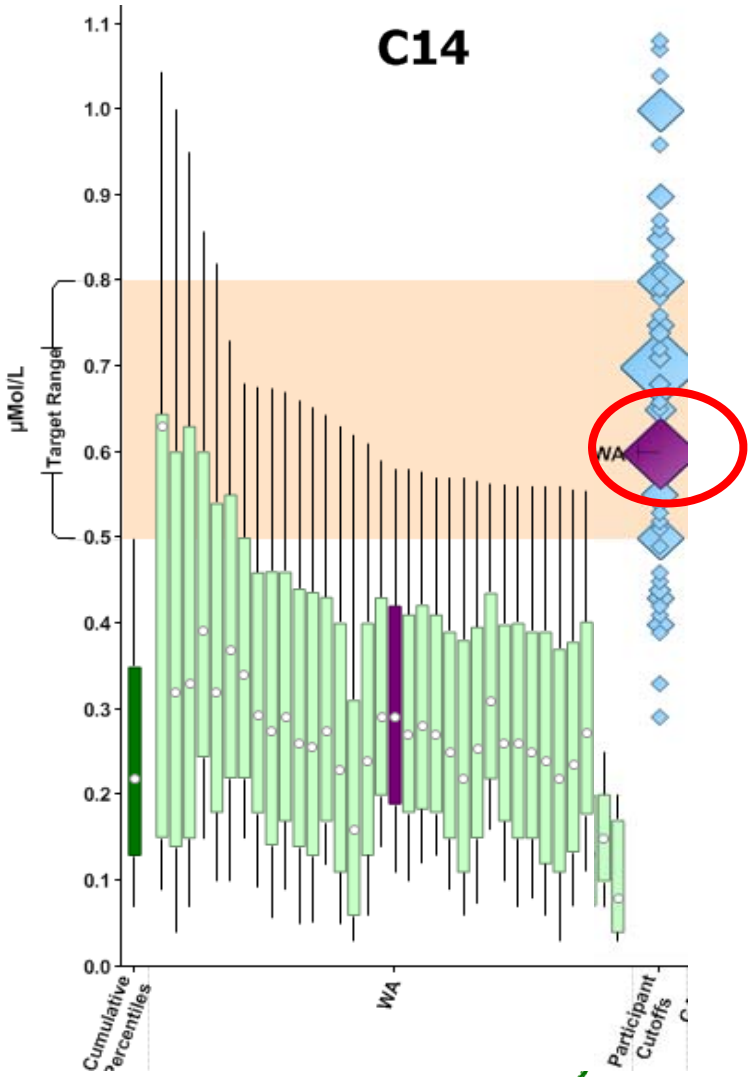
Analyte Comparison





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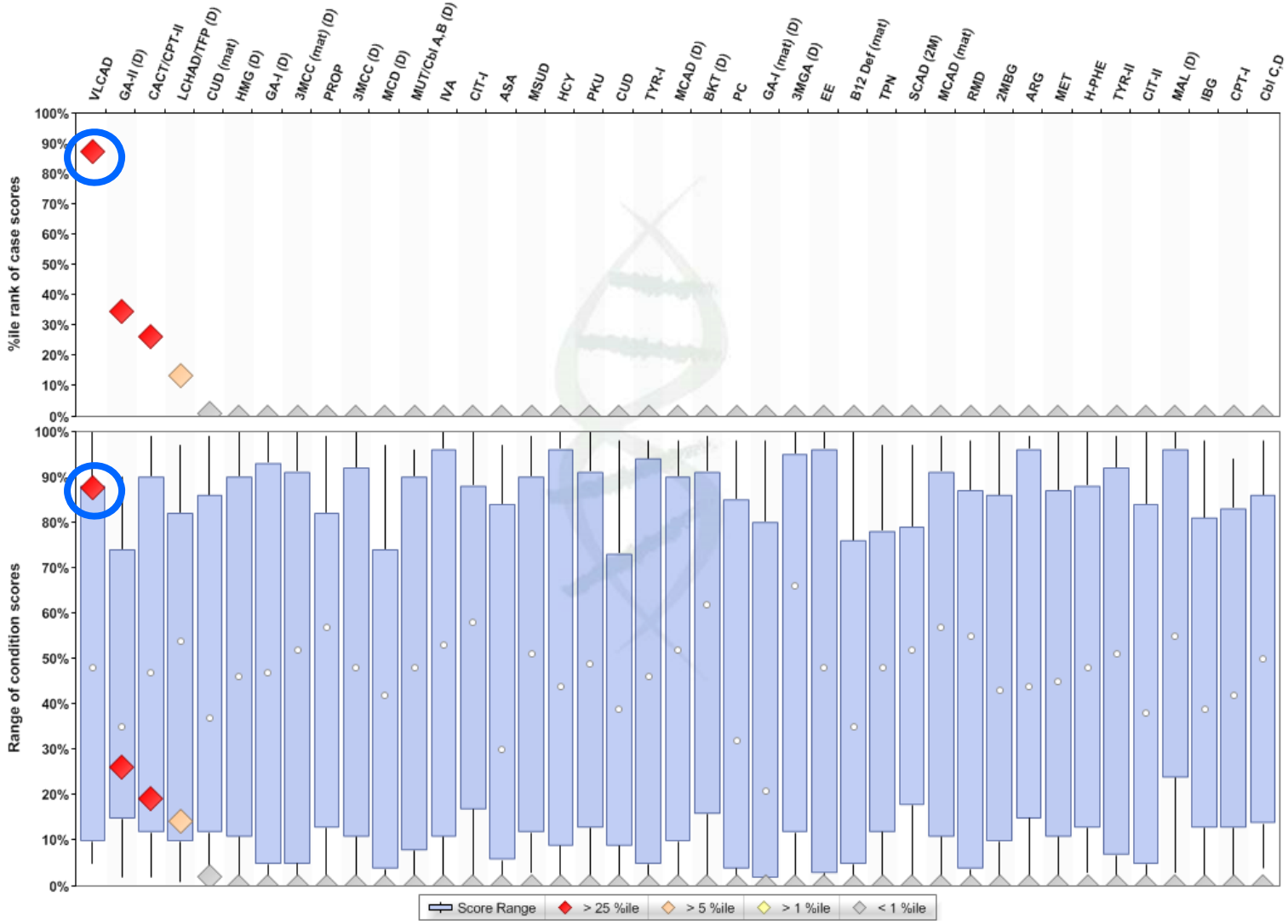
Post-Analytical Tools

All Condition tool



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One Condition Tool

Cumulative Normal Percentile & VLCAD Disease Range Overlap Values

Analyte	Normal	Overlap	Disease Range				Case
	99%ile	%ile	1%ile	5%ile	10%ile	50%ile	Values
C16	5.98	73.5 %	0.92	2.13	2.55	4.41	5.74
C2	51.39	97.9 %	7.18	10.31	12.40	21.69	7.13
	99%ile	%ile	1%ile	5%ile	10%ile	50%ile	Values
C14:1	0.35	0.0 %	0.57	0.71	0.85	1.74	3.31
C14:1/C16	0.12	0.0 %	0.14	0.18	0.21	0.40	0.58
C14:1/C2	0.02	0.2 %	0.02	0.03	0.03	0.08	0.46
C14	0.50	4.1 %	0.34	0.53	0.64	1.22	2.99
C14:2	0.08	5.9 %	0.05	0.07	0.10	0.23	0.34
C12:1	0.26	30.8 %	0.05	0.10	0.15	0.37	0.38
C14:1/C12:1	4.53	43.0 %	1.33	1.71	2.13	5.10	8.81

NP - DR Overlap

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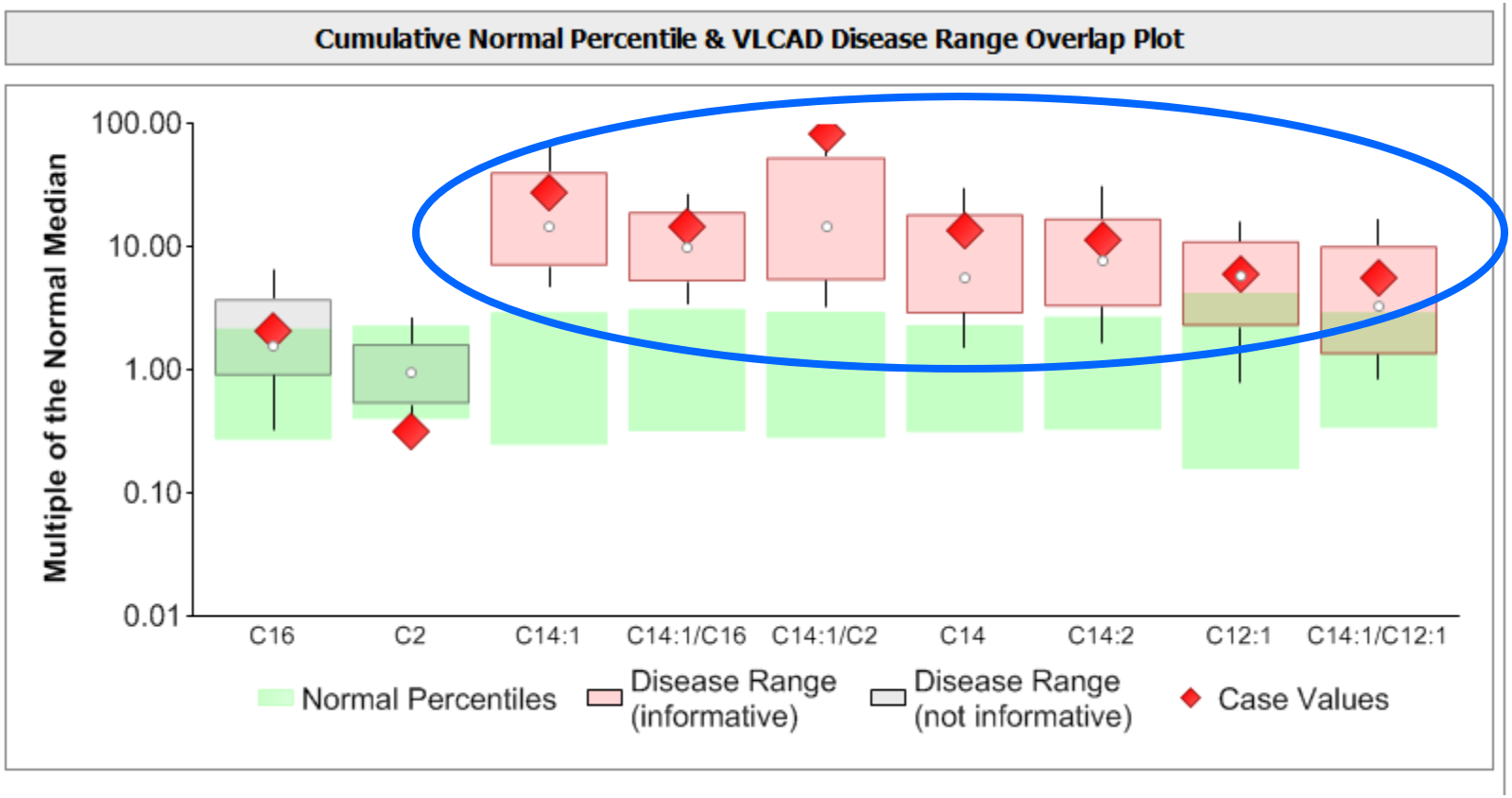
One Condition Tool



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One Condition Tool

Case Score

384	387	N/A
All	United States	Washington

View Calculations

%ile Rank of all VLCAD Scores:

87 %	86 %	N/A
All	United States	Washington

Count of VLCAD Scores

261	145	1
All	United States	Washington

Score Interpretation Guidelines

This tool has been validated only for neonatal (<10 days) blood spots. Use of this tool is not advised to calculate scores for older patients.

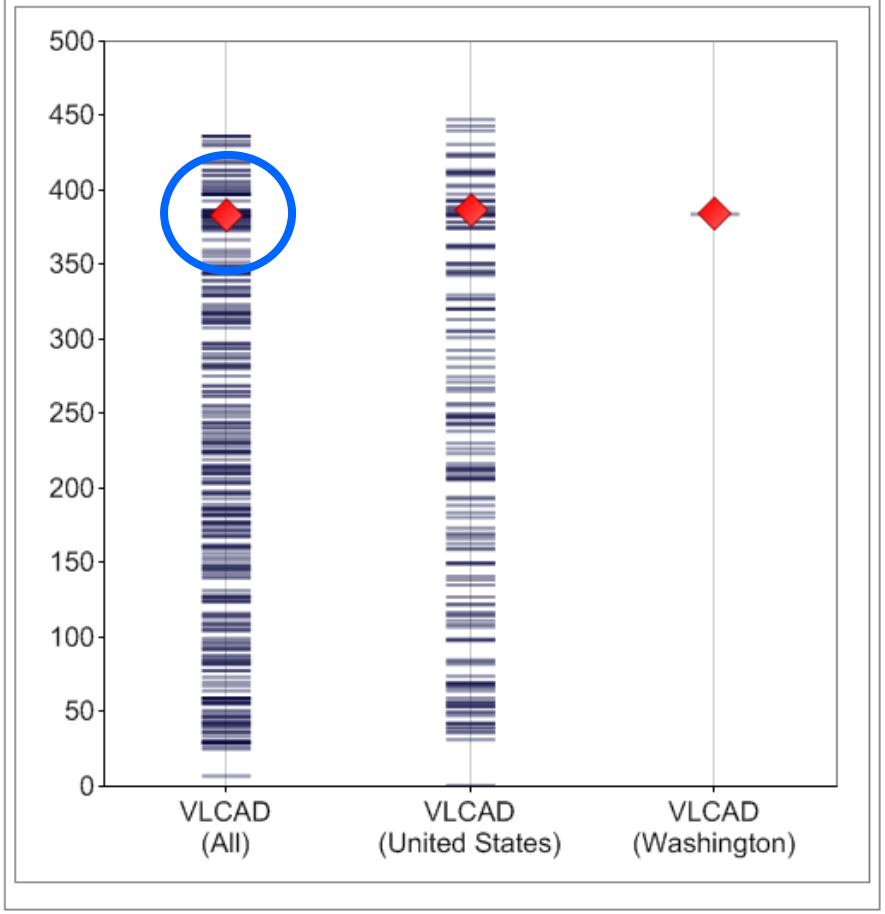
Score is >= 110
Condition is very likely VLCAD.

Score is >= 50 and < 110
Condition is likely VLCAD.

Score is >= 30 and < 50
Condition is possibly VLCAD.

Score is < 30
Profile is not informative for VLCAD.

Score Comparison Plot



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C3 R4S Tools			
Interpretation	**Outcome (n)**		**PPV (%)**
PROP Tool	**PROP**	**NORM**	
Very Likely	2	0	100
Possibly	0	4	
Not Informative	1	12	
Mut/Cbl A, B Tool	**Mut/Cbl A, B**	**NORM**	
Very Likely	5	8	39
Likely	0	7	
Possibly	0	1	
Cbl C, D Tool	**Cbl C, D**	**NORM**	
Very Likely	3	5	38
Likely	0	5	
Possibly	0	1	
Not Informative	0	2	
B12Def (mat) Tool	**B12Def(mat)**	**NORM**	
Very Likely	5	13	28
Likely	0	2	
Possibly	1	1	

C3 R4S Tools			
Interpretation	**Outcome (n)**		**PPV (%)**
PROP Tool	**PROP**	**NORM**	**All Scores= 33**
Very Likely	2	0	100
Possibly	0	4	
Not Informative	1	12	
Mut/Cbl A, B Tool	**Mut/Cbl A, B**	**NORM**	**All Scores=24**
Very Likely	5	8	39
Likely	0	7	
Possibly	0	1	
Cbl C, D Tool	**Cbl C**	**NORM**	**All Scores=21**
Very Likely	3	5	38
Likely	0	5	
Possibly	0	1	
Not Informative	0	2	
B12Def (mat) Tool	**B12Def**	**NORM**	**All Scores=27**
Very Likely	5	13	28
Likely	0	2	
Possibly	1	1	

C3 R4S Tools		
Interpretation	**Outcome (n)**	
All C3 Tools	**True Positive**	**NORM**
Very Likely	15	26
Possibly	0	14
Likely	1	7
Not Informative	1	14
PPV= 25%	**Sensitivity = 94%**	

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Dual Scatterplots			
Interpretation	**Outcome (n)**		
VLCAD vs VLCAD (het) Tool	**VLCAD**	**VLCAD(het)**	**NORM**
VLCAD	1	0	0
VLCAD(het)	0	3	5
VLCAD or VLCAD (het)	1	10	1
None	0	0	2
MCAD vs MCAD(het)	**MCAD**	**MCAD(het)**	**NORM**
MCAD	3	0	0
MCAD(het)	0	0	1
PKU vs H-Phe	**PKU**	**H-Phe**	**NORM**
PKU	1	0	0
PKU or H-Phe	3	4	0

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Thank You!!!

Washington NBS Program

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- Tim Davis, BS
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Come visit our lab!