Region 4 Collaborative Project Laboratory Quality Improvement (Newborn Screening by MS/MS)

Piero Rinaldo, MD PhD

T. Denny Sanford Professor of Pediatrics
Professor of Laboratory Medicine
Mayo Clinic College of Medicine, Rochester, MN

Washington, May 18th, 2007
Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

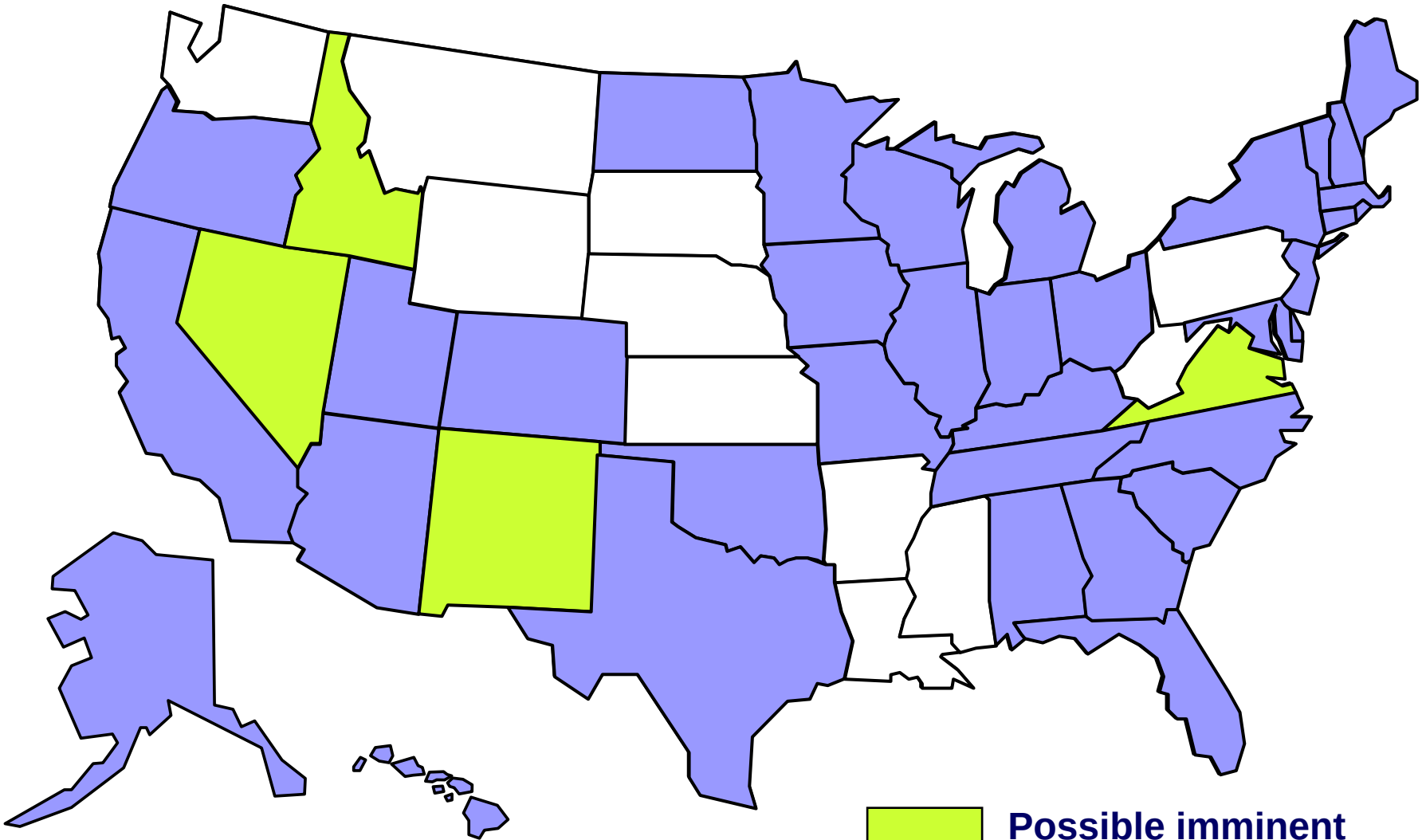
Regional 4 Collaborative Project

- **Project is based on active participation of NBS labs**

Active Participation

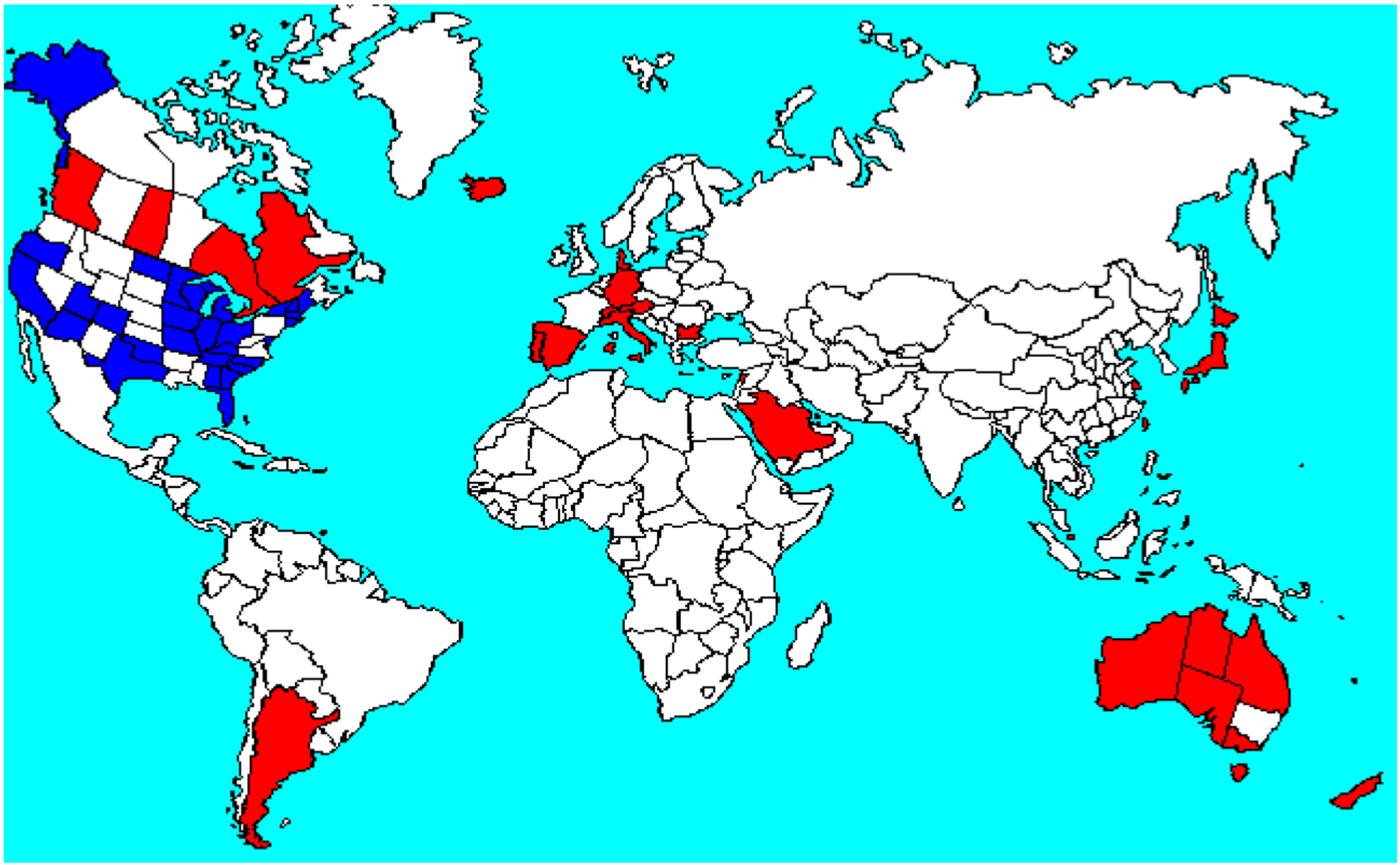
- Timely submission of data
  - %iles of normal population
  - Cutoff values
  - True positive cases
  - Performance metrics
- Involvement in other activities
  - Sample exchange
  - Conference calls
  - Training courses
  - Working group meetings

Active US Participants
(as 05/17/07)



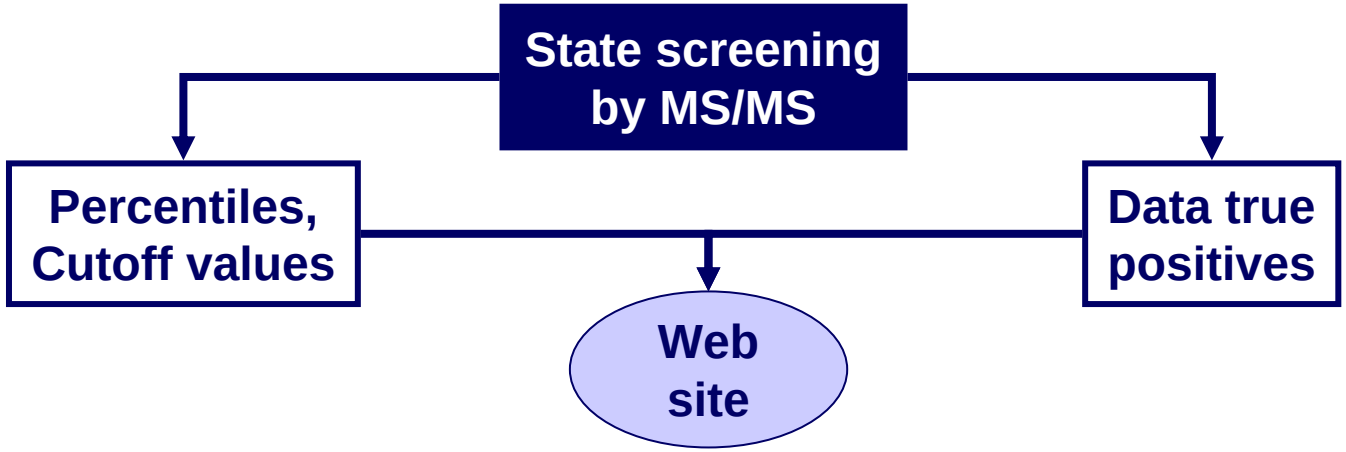
Possible imminent addition

Active International Participants
(as 05/17/07)



Regional 4 Collaborative Project

- **Project is based on active participation of NBS labs**
- **Standardized collection of NBS data (MS/MS only)**
- **<u>Data collected</u>**
  - **%iles of normal population (AA, AC, ratios)**
  - **Cutoff values (as used in local routine practice)**
  - **AA and AC values of confirmed positive cases**
  - **Performance metrics (PPV, FPR, det. rate)**



Region4
Genetics Collaborative

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- Home
- Advisory Group
- Newborn Screening by MS/MS
- Clinical Diagnosis & Management
- Access to Services for Underserved Populations
- Community Collaboration & Family Support
- Data Systems Integration
- Implementation Of Medical Homes
- Long-term Follow-up and Evaluation of Outcomes
- Public and Professional Education
- State NBS and Short-term Follow-up

Region 4 Genetics Collaborative

Improving Access to Genetic Resources on a Regional Basis

Seven states (Illinois, Indiana, Kentucky, Michigan, Minnesota, Ohio, and Wisconsin) have joined together as the Region 4 Genetics Collaborative in a project to address inequities in genetics resources across the region. The Michigan Public Health Institute Systems Reform Program is acting as the lead agency for the project, which is funded by the Federal Maternal and Child Health Bureau and the Health Resources Services Administration.

NCC Conference Call
March 15th, 2007

- Implementing Medical Homes
- On-line course: *Newborn Screening – What Caregivers Need to Know*
- New Grant Cycle

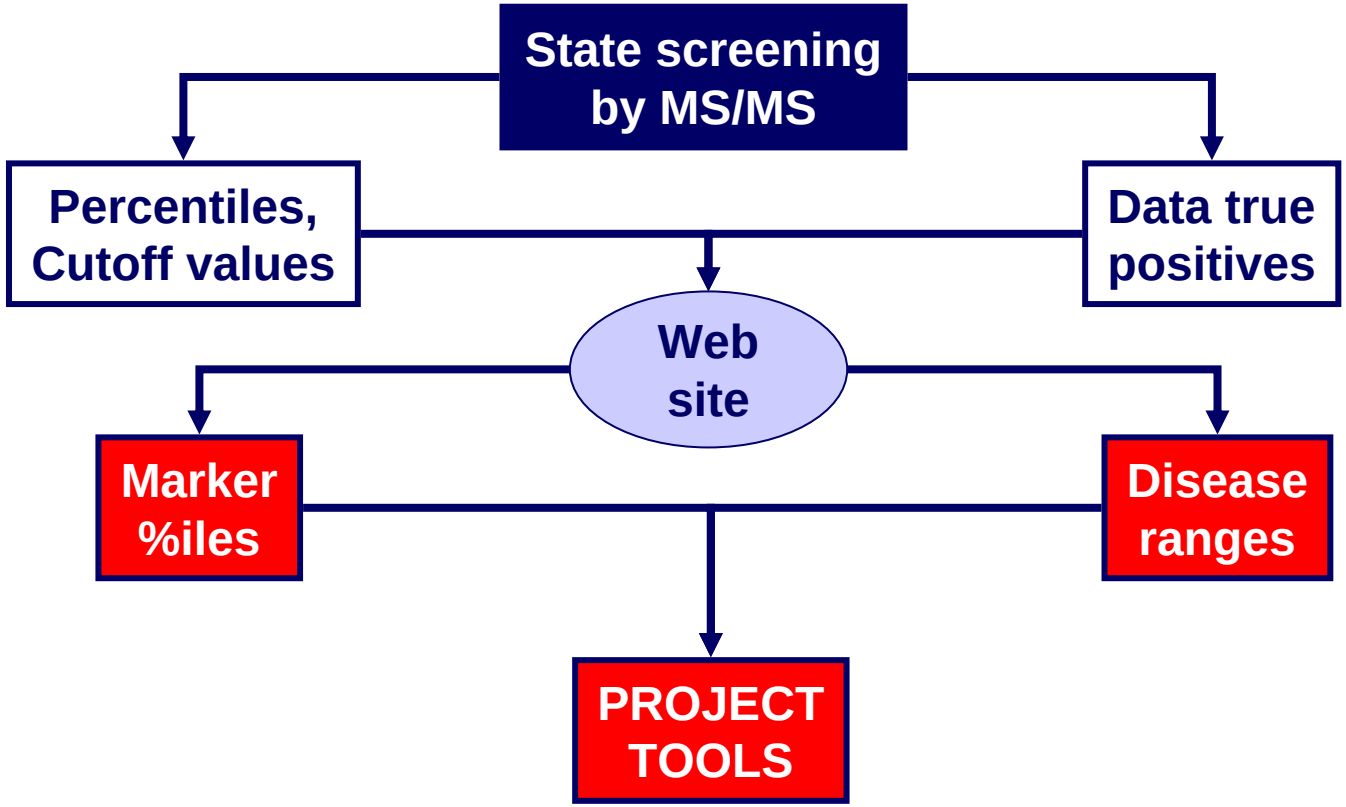
Region 4

MCHB

Website hotlinks and referrals to other websites, publications, or information resources do not constitute the endorsement of those websites or resources by the Region 4 Genetics Collaborative, its agents or its representatives. This site is for informational purposes only and does not provide medical advice.

Project in Numbers

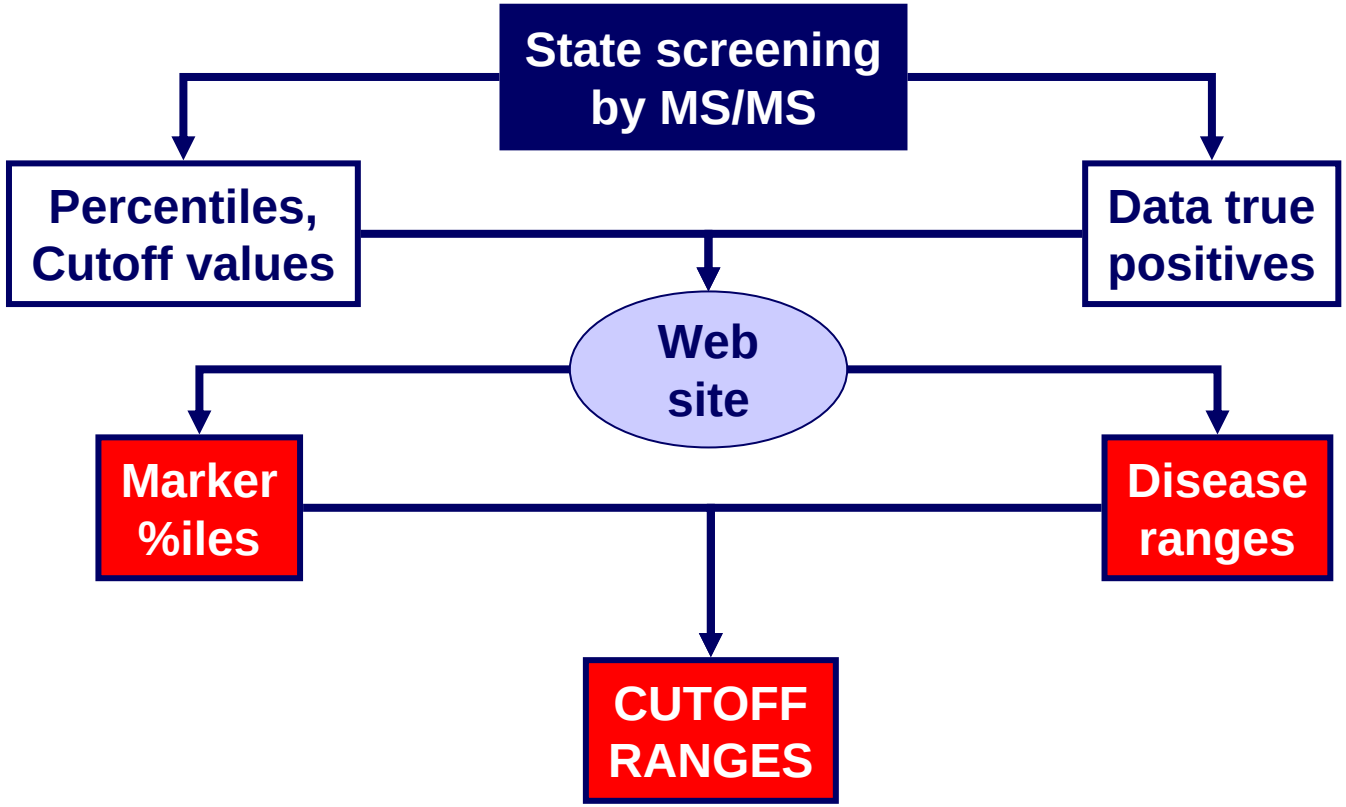
	Dec-06	May-07	Delta
US participants	30	38	27%
International participants (countries)	28 (16)	33 (20)	18% (25%)
True positive cases	2,950	3,865	31%
Collected data points			
True positive analytes & ratios	149,948	168,086	12%
Informative markers	8,676	11,497	36%
Percentiles (contributors)	3,756 (19)	7,822 (37)	108% (95%)
Cutoff values (contributors)	1,493 (35)	2,345 (57)	57% (63%)
Conditions with >50 cases			
Uniform panel	14/20	14/20	0% (2>40)
Secondary targets	3/22	3/22	0% (2>40)



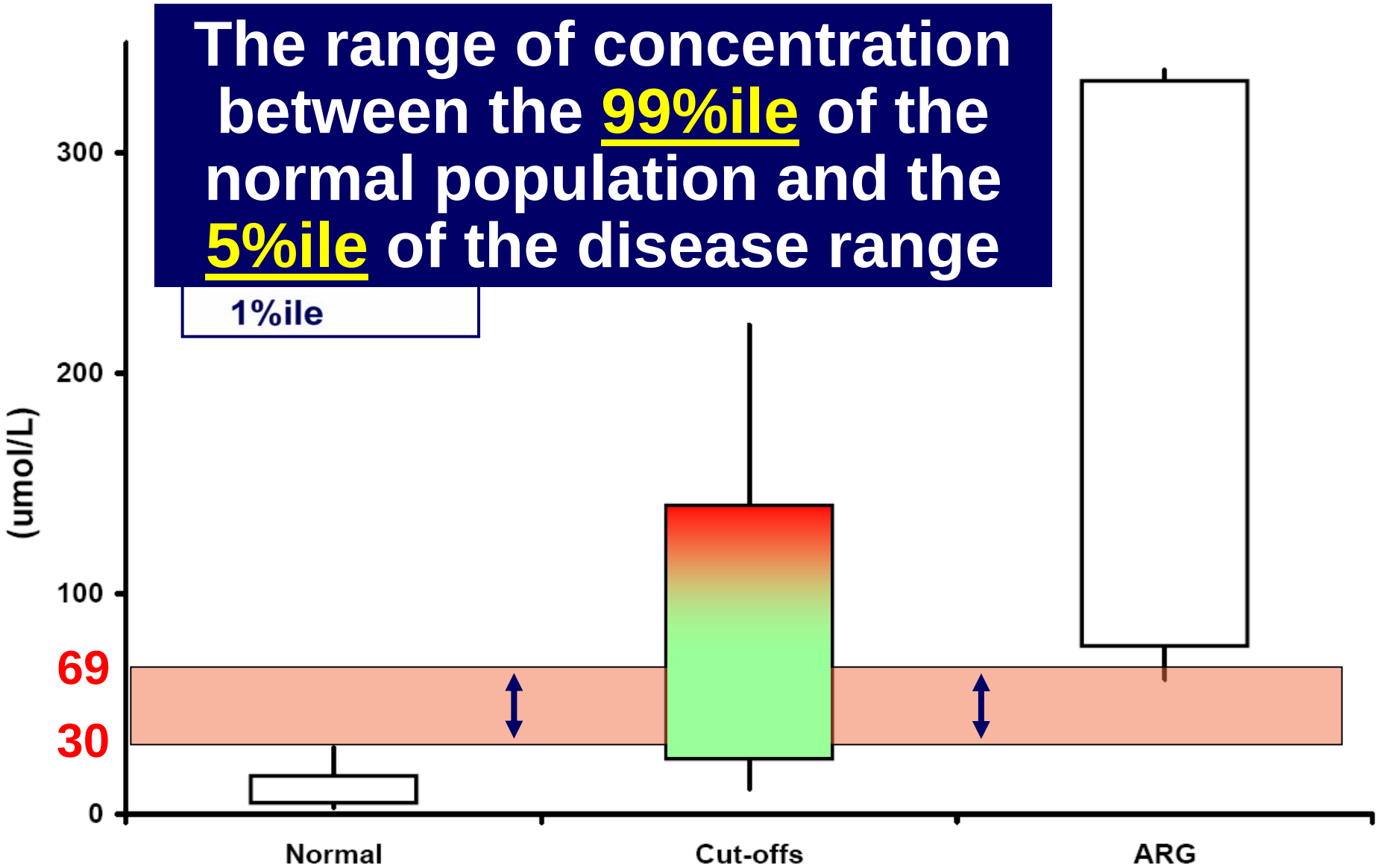
- **Monthly updates**
- **Posted on website**

Region4 Genetics Collaborative

www.region4genetics.org


State screening by MS/MS
Percentiles, Cutoff values
Data true positives
Web site
Marker %iles
Disease ranges
CUTOFF RANGES

The Cutoff Target Range (ARG)



The Score Card (AA)

Region 4 - Laboratory Quality Improvement Collaborative Project (NBS by MS/MS)

State/Lab	Enter Name and 2-4 letter code	
	Minnesota	MN

AMINO ACIDS

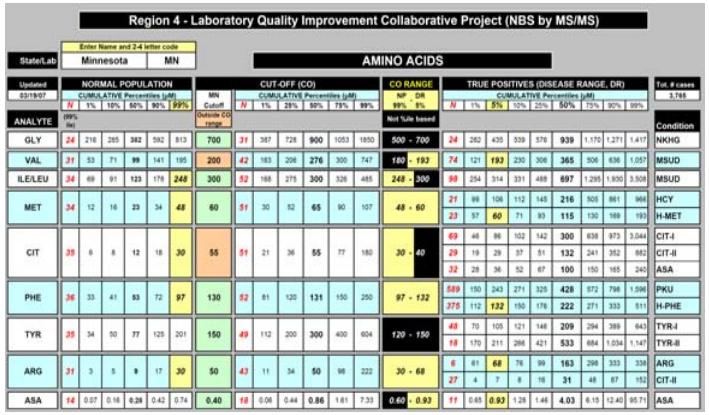
Updated	NORMAL POPULATION						CUT-OFF (CO)						CO RANGE	TRUE POSITIVES (DISEASE RANGE, DR)									Tot. # cases
05/07/07	CUMULATIVE Percentiles (µM)						MN	CUMULATIVE Percentiles (µM)					NP - DR	CUMULATIVE Percentiles (µM)									3,856
ANALYTE	N (99% ile)	1%	10%	50%	90%	99%	Cutoff Outside CO range	N	1%	25%	50%	75%	99%	99% - 5% Not %ile based	N	1%	5%	10%	25%	50%	75%	90%	99%	Condition
GLY	24	217	285	413	594	814	700	31	387	728	949	1105	1850	500 - 700	24	282	435	539	576	939	1,170	1,271	1,417	NKHG
VAL	31	55	71	101	141	199	200	42	163	206	276	300	747	180 - 193	75	122	193	231	306	355	505	634	1,056	MSUD
ILE/LEU	34	69	91	123	178	248	300	53	168	275	300	325	484	248 - 300	99	254	315	332	467	694	1,260	1,914	3,490	MSUD
MET	34	12	16	23	34	48	60	52	30	52	66	91	106	48 - 60	23	69	77	99	120	216	487	854	964	HCY
															23	57	60	71	93	115	130	169	193	H-MET
CIT	35	6	8	12	18	30	55	52	21	36	58	77	180	30 - 40	71	35	82	100	138	291	634	969	2,984	CIT-I
															29	19	29	37	51	132	241	352	882	CIT-II
															34	28	34	42	66	100	147	164	240	ASA
PHE	36	33	41	53	71	98	130	53	81	120	132	150	250	98 - 132	604	150	242	271	325	426	572	798	1,590	PKU
															384	112	132	150	176	221	270	333	507	H-PHE
TYR	35	35	50	78	125	201	150	50	112	200	301	400	651	120 - 150	48	70	105	121	146	209	294	389	643	TYR-I
															18	170	211	266	421	533	684	1,034	1,147	TYR-II
ARG	31	3	5	9	17	30	50	43	11	34	50	98	222	30 - 69	7	61	69	80	105	181	268	332	338	ARG
															27	4	7	8	16	31	48	87	152	CIT-II
ASA	14	0.10	0.16	0.28	0.42	0.74	0.40	19	0.06	0.46	1.00	1.84	7.31	0.60 - 0.90	13	0.20	0.41	0.72	1.39	4.03	7.20	85.28	105.7	ASA

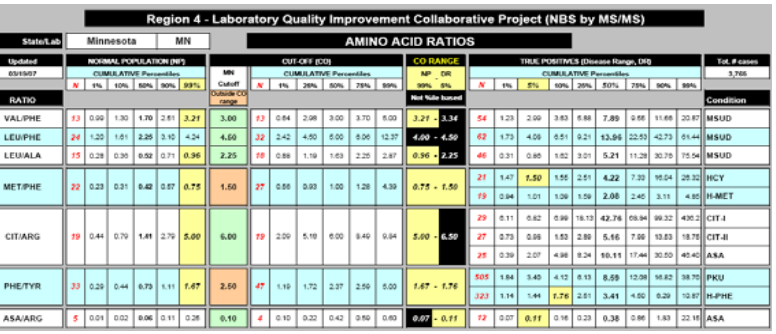
AA Ratios (7)

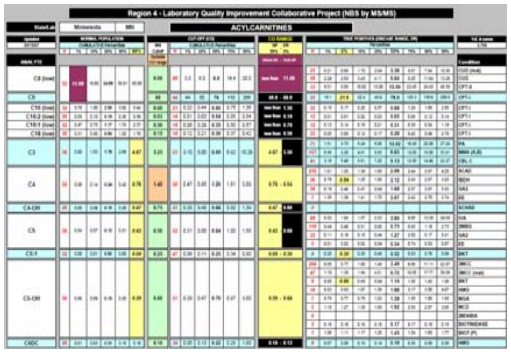
AA (9)

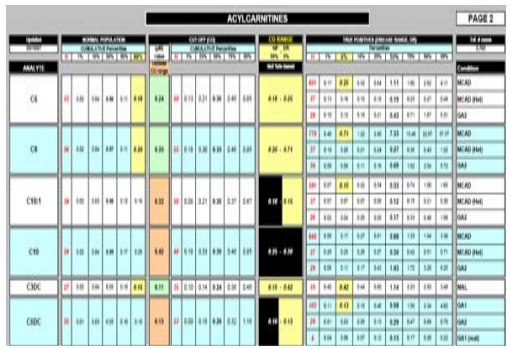
AC (27)

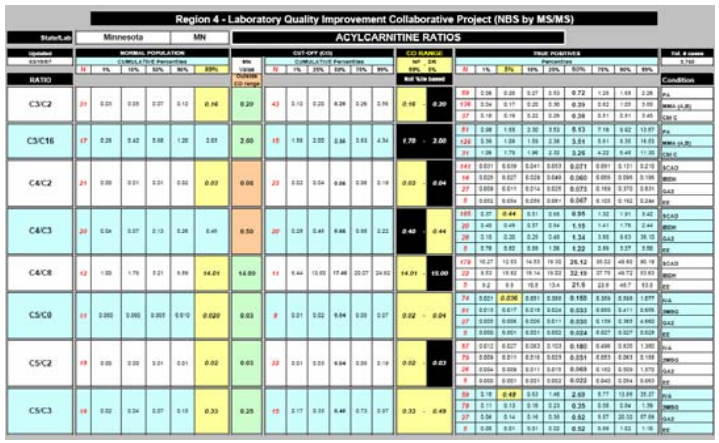
AC Ratios (21)

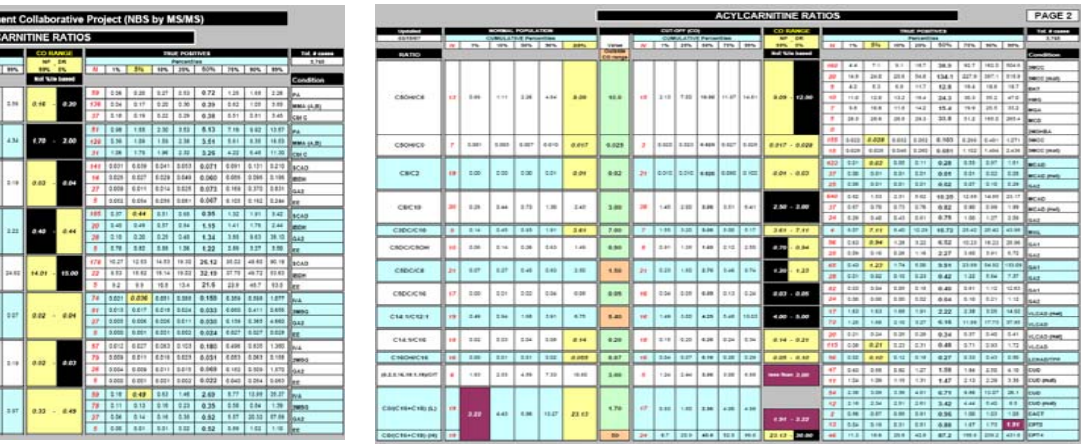


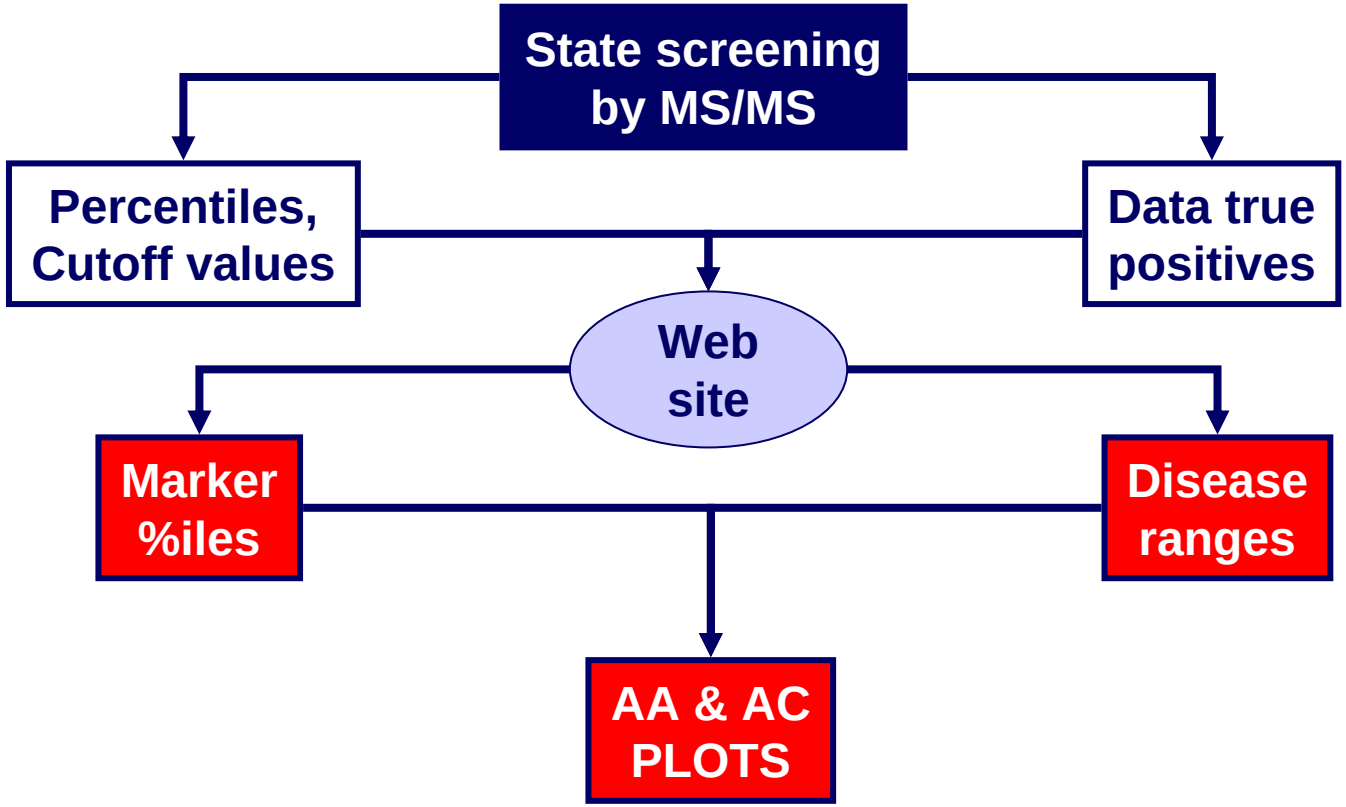











State screening by MS/MS
Percentiles, Cutoff values
Data true positives
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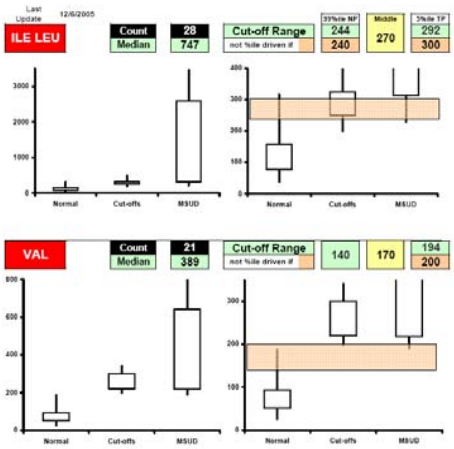
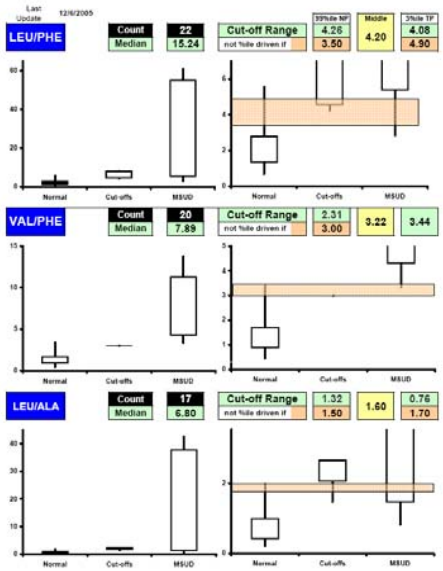
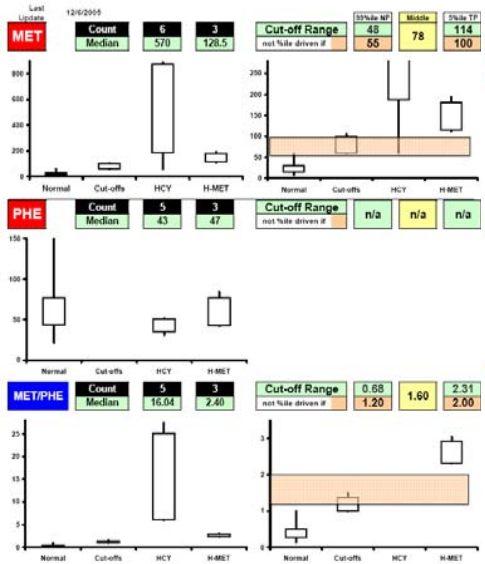
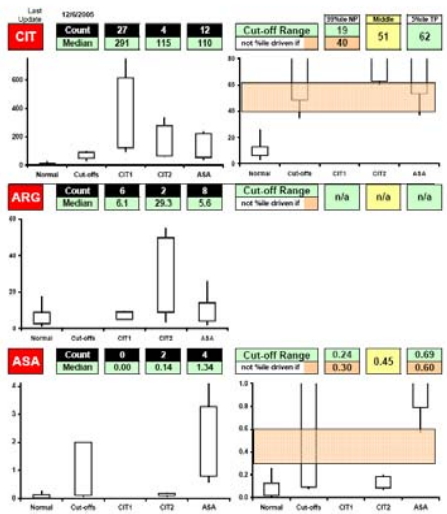
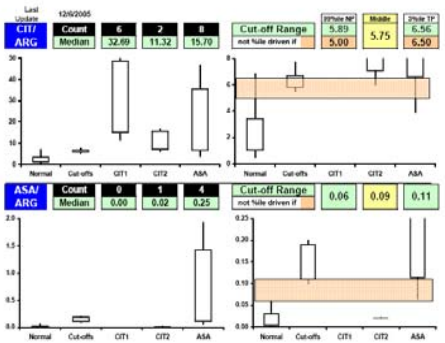
Marker %iles
Disease ranges
AA & AC PLOTS

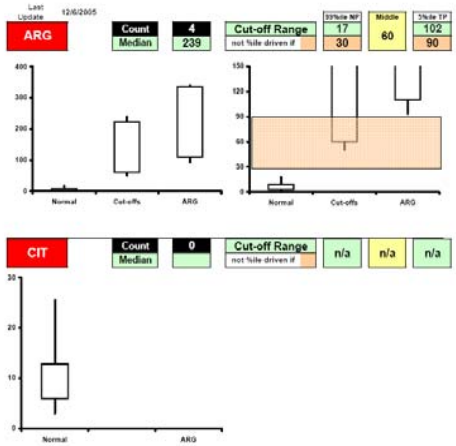

Last Update 12/6/2005
ILE LEU
Count 28
Median 747
Cut-off Range
not %ile driven if
95%ile NP 244 240
Middle 270
5%ile TP 292 300
VAL
Count 21
Median 389
Cut-off Range
not %ile driven if
140 170 194 200
Normal
Cut-offs
MSUD

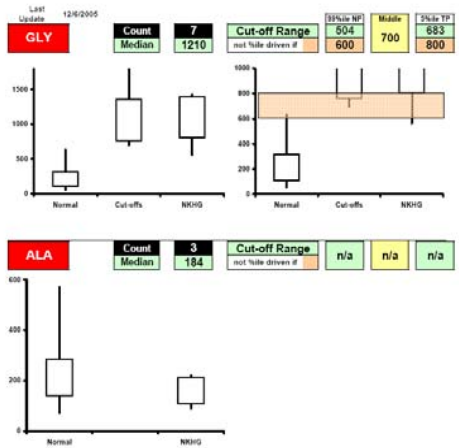

Last Update 12/6/2005
LEU/PHE
Count 22
Median 15.24
Cut-off Range
not %ile driven if
95%ile NP 4.26 3.50
Middle 4.20
5%ile TP 4.08 4.90
VAL/PHE
Count 20
Median 7.89
Cut-off Range
not %ile driven if
2.31 3.00 3.22 3.44
LEU/ALA
Count 17
Median 6.80
Cut-off Range
not %ile driven if
1.32 1.50 1.60 0.76 1.70
Normal
Cut-offs
MSUD

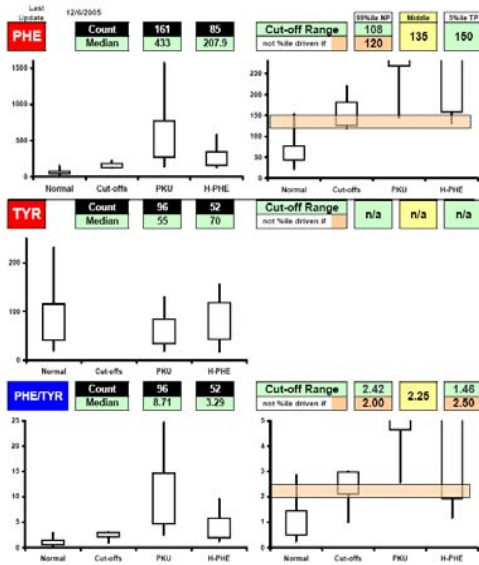

Last Update 12/6/2005
MET
Count 6
Median 570
3
128.5
Cut-off Range
not %ile driven if
95%ile NP 48 55
Middle 78
5%ile TP 114 100
PHE
Count 5
Median 43
3
47
Cut-off Range
not %ile driven if
n/a n/a n/a
MET/PHE
Count 5
Median 16.04
3
2.40
Cut-off Range
not %ile driven if
0.68 1.20 1.60 2.31 2.00
Normal
Cut-offs
HCY
H-MET

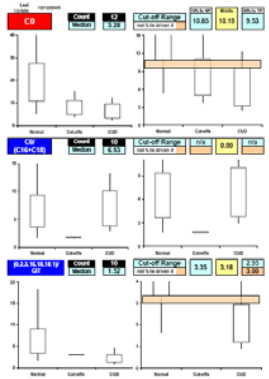
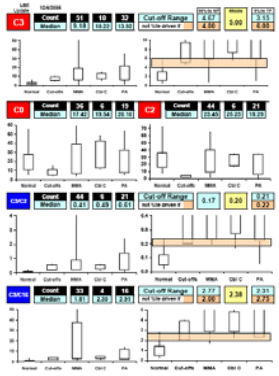
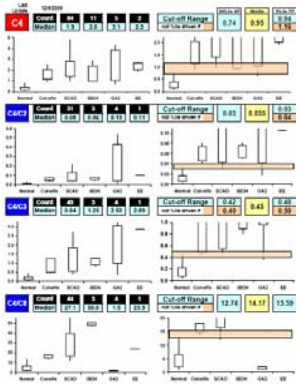
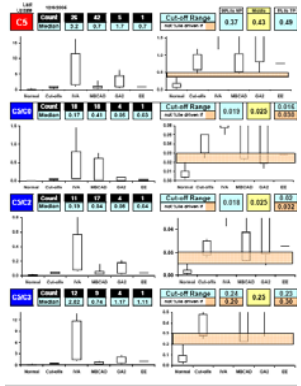
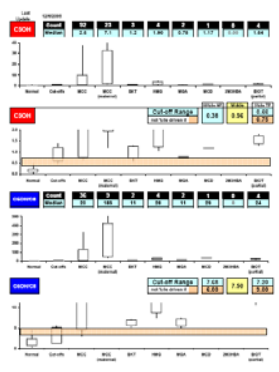
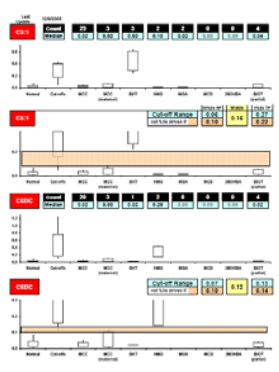
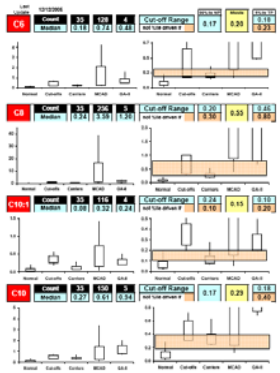
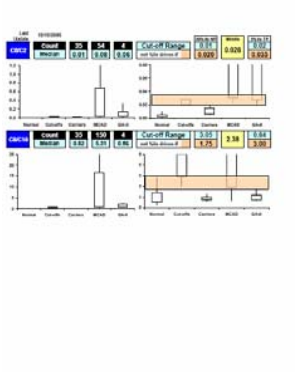
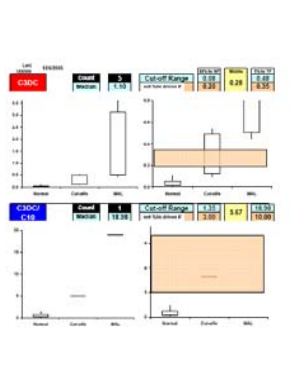
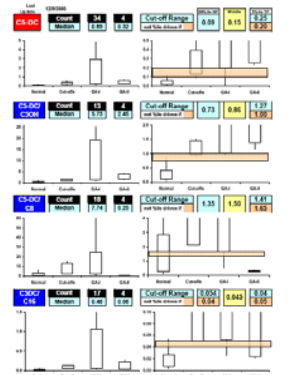
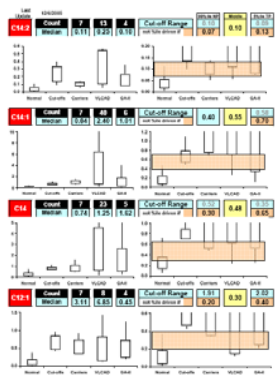
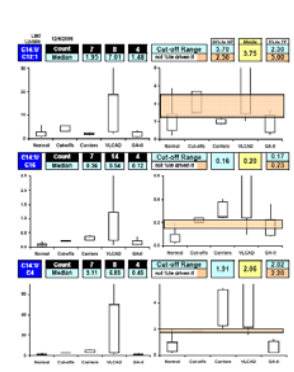
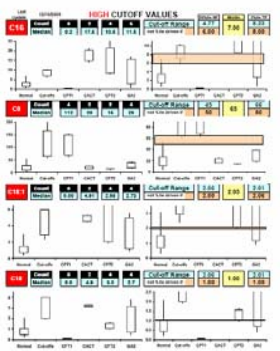
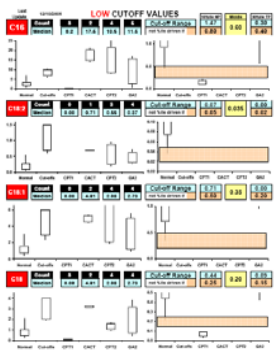
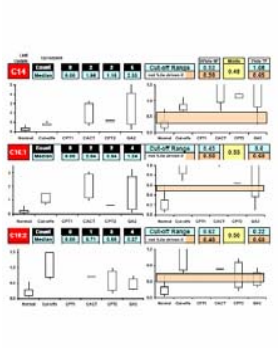
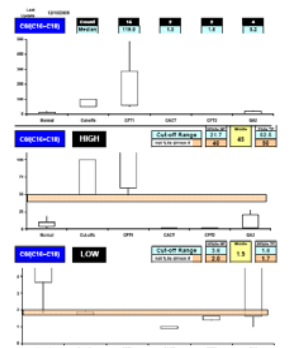
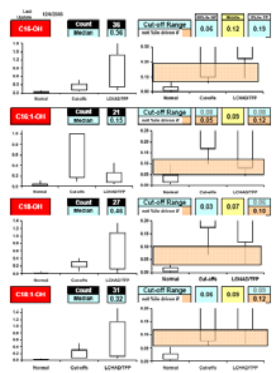
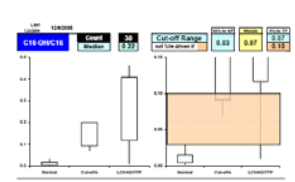

Last Update 12/6/2005
CIT
Count 27
Median 291
4
115
12
110
Cut-off Range
not %ile driven if
95%ile NP 19 40
Middle 51
5%ile TP 62
ARG
Count 6
Median 6.1
2
29.3
8
5.6
Cut-off Range
not %ile driven if
n/a n/a n/a
ASA
Count 0
Median 0.00
2
0.14
4
1.34
Cut-off Range
not %ile driven if
0.24 0.30 0.45 0.69 0.60
Normal
Cut-offs
CIT1
CIT2
ASA

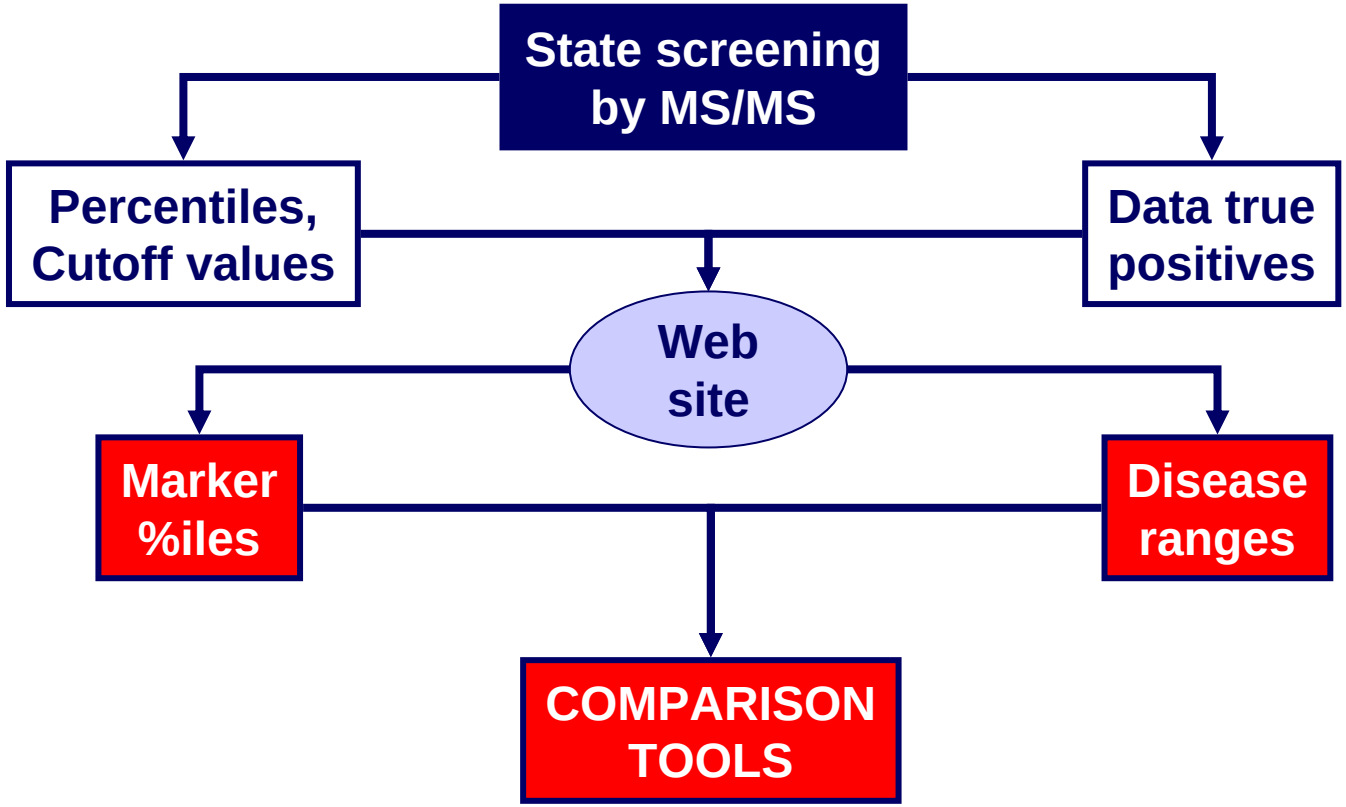

Last Update 12/6/2005
CIT/ ARG
Count 6
Median 32.69
2
11.32
8
15.70
Cut-off Range
not %ile driven if
95%ile NP 5.89 5.00
Middle 5.75
5%ile TP 6.56 6.50
ASA/ ARG
Count 0
Median 0.00
1
0.02
4
0.25
Cut-off Range
not %ile driven if
0.06 0.09 0.11
Normal
Cut-offs
CIT1
CIT2
ASA


Last Update 12/6/2005
ARG
Count 4
Median 239
Cut-off Range
not %ile driven if
95%ile NP 17 30
Middle 60
5%ile TP 102 90
CIT
Count 0
Median
Cut-off Range
not %ile driven if
n/a n/a n/a
Normal
Cut-offs
ARG


Last Update 12/6/2005
GLY
Count 7
Median 1210
Cut-off Range
not %ile driven if
95%ile NP 504 600
Middle 700
5%ile TP 683 800
ALA
Count 3
Median 184
Cut-off Range
not %ile driven if
n/a n/a n/a
Normal
Cut-offs
NKHG


Last Update 12/6/2005
PHE
Count 161
Median 433
85
207.9
Cut-off Range
not %ile driven if
95%ile NP 108 120
Middle 135
5%ile TP 150
TYR
Count 96
Median 55
52
70
Cut-off Range
not %ile driven if
n/a n/a n/a
PHE/TYR
Count 96
Median 8.71
52
3.29
Cut-off Range
not %ile driven if
2.42 2.00 2.25 1.46 2.50
Normal
Cut-offs
PKU
H-PHE

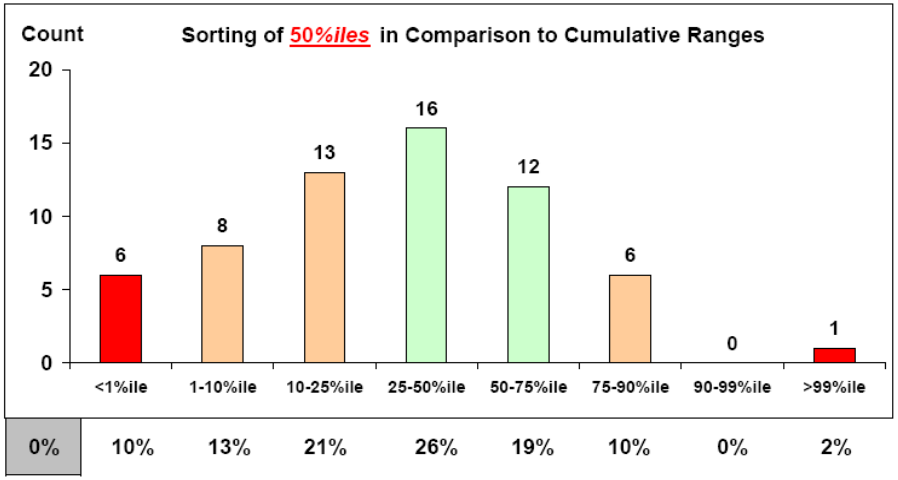

State screening by MS/MS
Percentiles, Cutoff values
Data true positives
Web site
Marker %iles
Disease ranges
COMPARISON TOOLS

50%ile Comparison Tool

Laboratory Quality Improvement Collaborative Project (NBS by MS/MS)

50%ILE Comparison Tool (Lab vs. Range of All Participants)

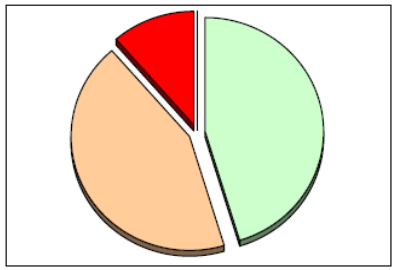
Date	04/28/07	No. of 50%iles	62
State	Minnesota	Submitted	62
Participants	37	Not submitted	0



0%	10%	13%	21%	26%	19%	10%	0%	2%

Within 25-75%ile range	28	45%
Outside 25-75%ile range	34	55%
Outliers	7	11%
Not submitted	0	0%

45% of submitted values



Last update 04/28/07 Version v.003

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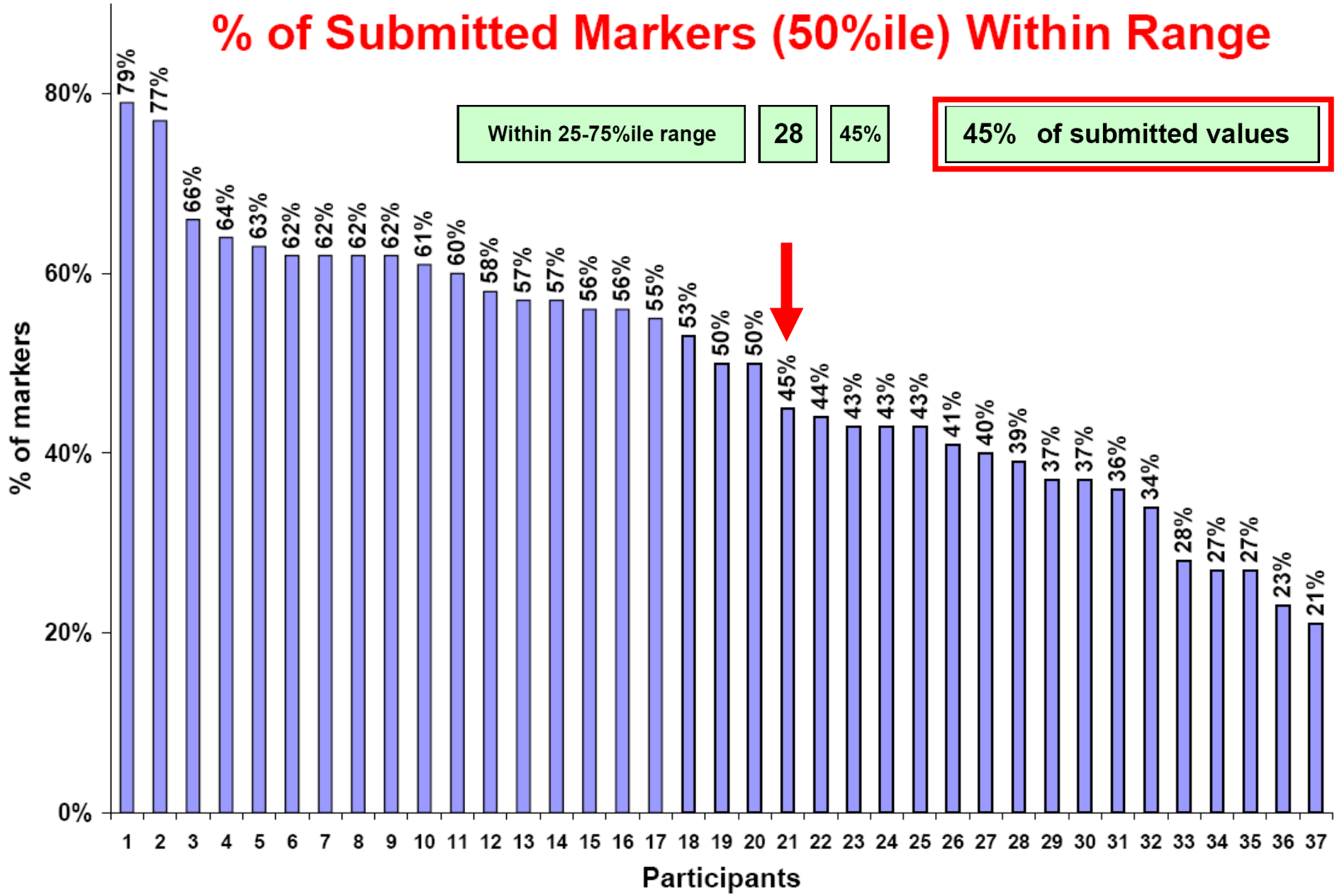
Minnesota 04/28/07

MARKERS & RATIOS	50% ILE	Range of values (NP) 1%	50%	99%	Count	<1%ile	1-10%ile	10-25%ile	25-50%ile	50-75%ile	75-90%ile	90-99%ile	>99%ile
GLY	184	134	382	593	24		184						
VAL	68	62	99	158	32		68						
LEU/ ILE	102	83	123	171	35			102					
MET	21	11	23	30	35				21				
CIT	9	5	12	25	36			9					
PHE	53	38	53	69	37					53			
TYR	71	45	77	106	36				71				
ARG	5	2	9	17	32			5					
ASA	0.06	0.02	0.28	1.35	14		0.06						
PHE/ TYR	0.76	0.46	0.73	0.99	34					0.76			
LEU/ PHE	1.95	1.44	2.23	4.01	26				1.95				
LEU/ ALA	0.45	0.38	0.53	0.79	17			0.45					
VAL/ PHE	1.30	0.80	1.74	2.61	16		1.30						
MET/ PHE	0.41	0.28	0.41	0.52	23				0.41				
CIT/ ARG	1.84	0.41	1.37	2.78	21						1.84		
ASA/ ARG	0.01	0.01	0.06	0.11	6	0.01							
C0	18.04	14.14	24.88	44.06	36		18.04						
C3	2.02	0.92	1.78	2.71	37						2.02		
C4	0.23	0.15	0.24	0.53	35				0.23				
C4-OH	0.15	0.06	0.15	0.24	18					0.15			
C5:1	0.02	0.01	0.02	0.13	34					0.02			
C5	0.12	0.07	0.12	0.21	37				0.12				
C5-OH	0.16	0.08	0.15	0.23	37						0.16		
C6	0.06	0.03	0.06	0.21	34					0.06			
C8	0.07	0.04	0.07	0.18	37				0.07				
C3 DC	0.03	0.03	0.06	0.11	26			0.03					
C10:1	0.05	0.03	0.06	0.11	35				0.05				
C10	0.08	0.05	0.09	0.27	35				0.08				
C5 DC	0.03	0.01	0.05	0.13	36				0.03				
C12:1	0.08	0.03	0.08	0.13	25					0.08			
C6 DC	0.03	0.01	0.06	0.12	25				0.03				
C14:2	0.03	0.02	0.04	0.08	24				0.03				
C14:1	0.14	0.06	0.12	0.29	37					0.14			
C14	0.26	0.15	0.23	0.39	34						0.26		
C16	2.49	1.92	2.50	3.40	37				2.49				
C16:1-OH	0.03	0.01	0.03	0.13	22		0.03						
C16-OH	0.01	0.01	0.03	0.08	37		0.01						
C18:2	0.13	0.10	0.19	0.37	28			0.13					
C18:1	1.04	0.87	1.17	1.56	36				1.04				
C18	0.71	0.52	0.80	0.97	33			0.71					
C18:1-OH	0.01	0.01	0.02	0.07	35			0.01					
C18-OH	0.01	0.01	0.02	0.06	25	0.01							
C3/ C2	0.08	0.06	0.07	0.30	33					0.08			
C3/ C16	0.82	0.57	0.68	1.13	19						0.82		
C4/ C2	0.01	0.01	0.01	0.06	20			0.01					
C4/ C3	0.12	0.10	0.13	0.21	22			0.12					
C4/ C8	3.31	1.82	3.21	4.93	12					3.31			
C5/ C0	0.01	0.00	0.01	0.11	8				0.01				
C5/ C2	0.005	0.00	0.01	0.03	16	0.005							
C5/ C3	0.06	0.04	0.07	0.11	19			0.06					
C5OH /C8	2.32	1.11	2.06	3.56	15					2.32			
C5DC/ C5OH	0.20	0.20	0.26	0.64	11	0.20							
C5DC/ C8	0.45	0.22	0.71	1.97	20			0.45					
C5DC/C16	0.01	0.01	0.02	0.05	18			0.01					
C8/ C2	0.00	0.001	0.00	0.14	12		0.00						
C8/ C10	0.81	0.49	0.73	1.16	31					0.81			
C14:1/C12:1	1.57	0.63	1.66	3.25	21				1.57				
C14:1/ C16	0.06	0.03	0.04	0.08	21						0.06		
C16OH/C16	0.01	0.01	0.01	0.04	19	0.01							
C3DC/ C10	0.38	0.38	0.93	1.30	9	0.38							
AC/ CIT	5.22	4.21	4.59	5.21	6								5.22
(H) FC/ 16+18	26.24	8.65	23.05	71.78	20					26.24			
Total	62					0	6	8	13	16	12	6	0	1
						0%	10%	13%	21%	26%	19%	10%	0%	2%


% of Submitted Markers (50%ile) Within Range
Within 25-75%ile range
28
45%
45% of submitted values
% of markers
80%
60%
40%
20%
0%
79%
77%
66%
64%
63%
62%
62%
62%
62%
61%
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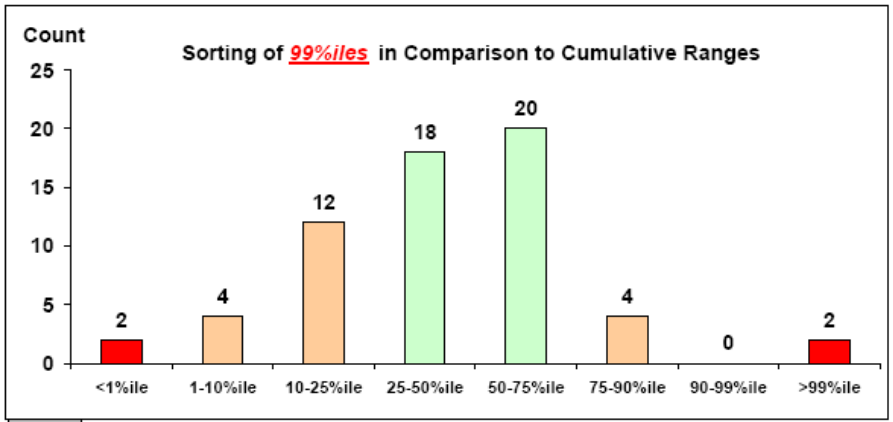
37%
36%
34%
28%
27%
27%
23%
21%
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37
Participants

99%ile Comparison Tool

Laboratory Quality Improvement Collaborative Project (NBS by MS/MS)

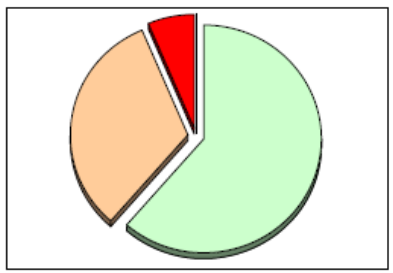
99%ILE **Comparison Tool (Lab vs. Range of All Participants)**

Date	03/11/07	No. of 99%iles	62
State	Minnesota	Submitted	62
Participants	33	Not submitted	0



Within 25-75%ile range	38	61%
Outside 25-75%ile range	24	39%
Outliers	4	6%
Not submitted	0	0%

61% of submitted values



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Minnesota 03/11/07

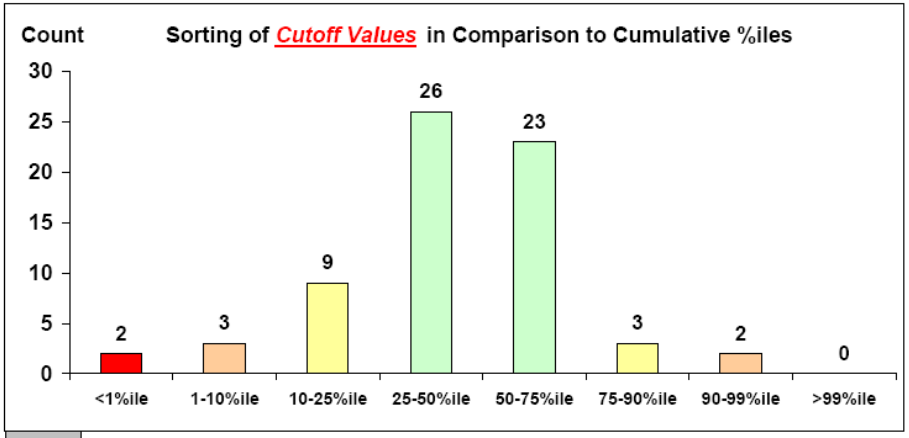
MARKERS & RATIOS	99% ILE	Range of values (NP) 1%	50%	99%	Count	<1%ile	1-10%ile	10-25%ile	25-50%ile	50-75%ile	75-90%ile	90-99%ile	>99%ile
GLY	505	304	840	1979	22			505					
VAL	141	140	199	313	28		141						
LEU/ ILE	237	142	247	340	31				237				
MET	52	27	48	70	31					52			
CIT	20	13	30	70	32			20					
PHE	101	63	97	121	33					101			
TYR	190	112	201	268	33				190				
ARG	19	11	30	86	29			19					
ASA	0.25	0.07	0.77	3.48	13		0.25						
PHE/ TYR	2.10	1.01	1.67	2.08	31								2.10
LEU/ PHE	4.32	2.07	4.18	6.80	23					4.32			
LEU/ ALA	1.17	0.81	0.98	1.69	14						1.17		
VAL/ PHE	2.43	2.45	3.17	3.94	12	2.43							
MET/ PHE	0.75	0.47	0.75	1.00	21					0.75			
CIT/ ARG	5.82	2.83	5.00	8.35	17					5.82			
ASA/ ARG	0.07	0.08	0.26	0.42	4	0.07							
C0	45.69	40.10	59.88	106.38	32			45.69					
C3	5.19	2.92	4.66	7.28	33					5.19			
C4	0.76	0.44	0.75	1.44	31					0.76			
C4-OH	0.40	0.17	0.47	0.69	20				0.40				
C5:1	0.06	0.03	0.10	0.51	29				0.06				
C5	0.46	0.24	0.43	1.39	33					0.46			
C5-OH	0.40	0.20	0.38	0.60	33					0.40			
C6	0.18	0.10	0.18	0.47	30					0.18			
C8	0.22	0.12	0.20	0.45	33					0.22			
C3 DC	0.08	0.07	0.15	0.40	25		0.08						
C10:1	0.20	0.09	0.19	0.36	31					0.20			
C10	0.24	0.16	0.29	0.58	31				0.24				
C5 DC	0.09	0.05	0.14	0.27	32			0.09					
C12:1	0.39	0.14	0.32	0.48	23						0.39		
C6 DC	0.09	0.04	0.16	0.39	23				0.09				
C14:2	0.11	0.05	0.14	0.30	24				0.11				
C14:1	0.43	0.17	0.37	1.14	33					0.43			
C14	0.61	0.36	0.50	0.94	30					0.61			
C16	5.03	4.59	5.52	7.42	33				5.03				
C16:1-OH	0.08	0.05	0.10	0.46	22		0.08						
C16-OH	0.05	0.05	0.10	0.28	32			0.05					
C18:2	0.59	0.38	0.56	1.53	26					0.59			
C18:1	2.05	1.77	2.37	3.69	32			2.05					
C18	1.50	1.32	1.70	2.18	30			1.50					
C18:1-OH	0.05	0.03	0.08	0.27	31				0.05				
C18-OH	0.03	0.02	0.06	0.39	23			0.03					
C3/ C2	0.18	0.13	0.16	0.26	28					0.18			
C3/ C16	2.87	1.41	2.03	3.38	16					2.87			
C4/ C2	0.03	0.02	0.03	0.10	20				0.03				
C4/ C3	0.41	0.24	0.44	0.69	19				0.41				
C4/ C8	13.69	6.25	13.88	21.47	11				13.69				
C5/ C0	0.02	0.01	0.02	0.05	10						0.02		
C5/ C2	0.02	0.01	0.02	0.05	18					0.02			
C5/ C3	0.31	0.15	0.33	0.71	17				0.31				
C5OH /C8	8.92	4.01	9.09	15.51	11				8.92				
C5DC/ C5OH	0.69	0.68	1.36	2.58	9			0.69					
C5DC/ C8	1.49	0.63	2.00	4.75	20				1.49				
C5DC/C16	0.05	0.03	0.08	0.18	16			0.05					
C8/ C2	0.01	0.006	0.01	0.40	18				0.01				
C8/ C10	3.37	1.11	2.49	5.93	27					3.37			
C14:1/C12:1	6.41	1.18	6.75	15.31	18				6.41				
C14:1/ C16	0.17	0.07	0.15	0.27	17						0.17		
C16OH/C16	0.03	0.03	0.06	0.25	15				0.03				
C3DC/ C10	1.51	1.25	3.41	4.93	8			1.51					
AC/ CIT	13.19	9.17	10.16	13.10	5								13.19
(H) FC/ 16+18	26.09	8.61	22.87	71.77	19					26.09			
Total	62					0	2	4	12	18	20	4	0	2
						0%	3%	6%	19%	29%	32%	6%	0%	3%

Cutoff Comparison Tool

Laboratory Quality Improvement Collaborative Project (NBS by MS/MS)

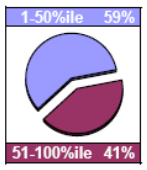
CUTOFF Comparison Tool (Lab vs. Range of All Participants)

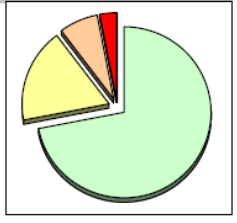
Date	04/30/07	Markers & ratios	68
State	Minnesota	In use	68
Participants	55	Not used	0



0%	3%	4%	13%	38%	34%	4%	3%	0%
NOT USED								

CO within target ranges	37	of 68	54%	54% of all markers
CO values within the target range AND the 25-75%ile of all participant values	37 of 68 = 54%			These are the CO values that MEET THE GOAL of the project!
CO >25%ile & <75%ile	49	72%		
CO <25%ile & >75%ile	12	18%		
CO <10%ile & >90%ile	5	7%		
CO <1%ile & >99%ile	2	3%		





Last update 04/30/07 Version v.002

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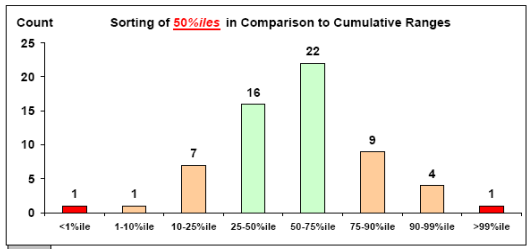
Minnesota 04/30/07

MARKERS & RATIOS	CO	TARGET RANGE	Count	<1%ile	1-10%ile	10-25%ile	25-50%ile	50-75%ile	75-90%ile	90-99%ile	>99%ile
GLY	700	500 - 700	31			700					
VAL	200	180 - 193	42			200					
LEU/ ILE	300	248 - 300	52					300			
MET	60	55 - 100	51				60				
CIT	55	30 - 40	51					55			
PHE	130	97 - 132	52				130				
TYR	150	120 - 150	49		150						
ARG	50	30 - 69	43					50			
ASA	0.40	0.00 - 0.90	18			0.40					
PHE/ TYR	2.50	1.68 - 1.76	47					2.50			
LEU/ PHE	4.50	4.00 - 4.50	32				4.50				
LEU/ ALA	2.25	0.99 - 2.25	18							2.25	
VAL/ PHE	3.00	3.00 - 3.50	13					3.00			
MET/ PHE	1.50	0.75 - 1.47	27						1.50		
CIT/ ARG	6.00	4.84 - 6.82	19					6.00			
ASA/ ARG	0.10	0.07 - 0.12	4	0.10							
C0(L)	9.00	less than 11.08	50					9.00			
(H)C0	60.00	40 - 60	44				60.00				
C3	5.25	4.65 - 5.50	53				5.25				
C4	1.40	0.75 - 0.94	50					1.40			
C4-OH	0.75	0.47 - 0.80	23					0.75			
C5:1	0.25	0.09 - 0.30	47					0.25			
C5	0.50	0.43 - 0.60	52				0.50				
C5-OH	0.60	0.38 - 0.66	51				0.60				
C6	0.25	0.18 - 0.24	50				0.25				
C8	0.35	0.20 - 0.71	55					0.35			
C3 DC	0.35	0.16 - 0.42	36					0.35			
C10:1	0.30	0.10 - 0.15	50					0.30			
C10	0.30	0.25 - 0.30	48			0.30					
C5 DC	0.15	0.10 - 0.13	53				0.15				
C12:1	0.80	0.31 - 0.50	28							0.80	
C6 DC	0.10	0.10 - 0.12	34			0.10					
C14:2	0.15	0.12 - 0.15	31				0.15				
C14:1	0.50	0.37 - 0.67	51				0.50				
C14	0.70	0.49 - 0.70	46					0.70			
(H)C16	7.00	5.44 - 7.48	51				7.00				
C16(L)	0.60	less than 1.50	23					0.60			
C16:1-OH	0.10	0.10 - 0.15	26		0.10						
C16-OH	0.10	0.10 - 0.15	52				0.10				
(H)C18:2	0.60	0.50 - 0.60	28				0.60				
C18:2(L)	0.03	less than 0.10	14				0.03				
(H)C18:1	3.00	2.37 - 2.50	48					3.00			
C18:1 (L)	0.30	less than 0.70	19				0.30				
(H)C18	2.00	1.50 - 1.60	39				2.00				
C18(L)	0.15	less than 0.50	18			0.15					
C18:1-OH	0.07	0.07 - 0.10	47			0.07					
C18-OH	0.07	0.07 - 0.10	30				0.07				
C3/ C2	0.20	0.16 - 0.20	43					0.20			
C3/ C16	2.00	1.70 - 2.00	15				2.00				
C4/ C2	0.04	0.03 - 0.04	23				0.04				
C4/ C3	0.50	0.40 - 0.43	20				0.50				
C4/ C8	14.00	14.13 - 15.00	11				14.00				
C5/ C0	0.03	0.02 - 0.04	9				0.03				
C5/ C2	0.03	0.02 - 0.03	22			0.03					
C5/ C3	0.25	0.33 - 0.49	15		0.25						
C5OH /C8	10.00	9.09 - 12.00	15					10.00			
C5DC/ C5OH	0.90	0.70 - 0.94	8	0.90							
C5DC/ C8	1.50	1.20 - 1.24	21				1.50				
C5DC/C16	0.05	0.03 - 0.05	16				0.05				
C8/ C2	0.02	0.01 - 0.03	21					0.02			
C8/ C10	3.00	2.50 - 3.00	38					3.00			
C14:1/C12:1	5.40	4.00 - 5.00	16					5.40			
C14:1/ C16	0.20	0.15 - 0.21	18					0.20			
C16OH/C16	0.07	0.06 - 0.10	16				0.07				
C3DC/ C10	5.00	3.69 - 7.11	7						5.00		
AC/ CIT	3.00	less than 3.00	5						3.00		
(H) FC/ 16+18	50.00	23 - 30	24					50.00			
C0/C16+C18(L)	1.70	1.91 - 3.22	17			1.70					
Within	37	Not used	0	2	3	9	26	23	3	2	0
Outside	31		0%	3%	4%	13%	38%	34%	4%	3%	0%

Laboratory Quality Improvement Collaborative Project (NBS by MS/MS)

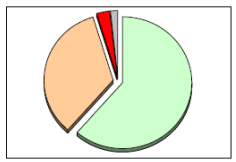
50%ILE Comparison Tool (Lab vs. Range of All Participants)

Date	03/13/07	No. of 99%iles	62
State	[redacted]	Submitted	61
Participants	36	Not submitted	1



2%	2%	2%	11%	26%	35%	15%	6%	2%

Within 25-75%ile range	38	61%	62% of submitted values
Outside 25-75%ile range	23	37%	
Outliers	2	3%	
Not submitted	1	2%	



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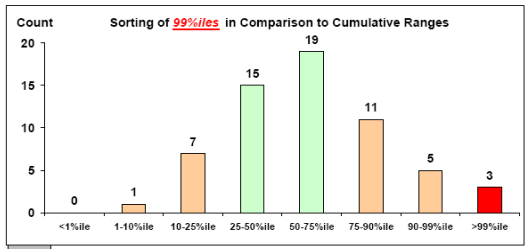
Laboratory Quality Improvement Collaborative Project (NBS by MS/MS)

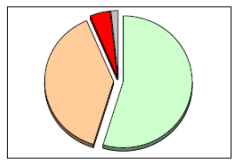
99%ILE Comparison Tool (Lab vs. Range of All Participants)

Date	03/13/07	No. of 99%iles	62
State	[redacted]	Submitted	61
Participants	35	Not submitted	1



2%	0%	2%	11%	24%	31%	18%	8%	5%

Within 25-75%ile range	34	55%	56% of submitted values
Outside 25-75%ile range	27	44%	
Outliers	3	5%	
Not submitted	1	2%	



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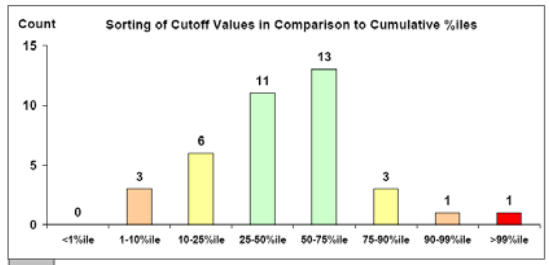
Laboratory Quality Improvement Collaborative Project (NBS by MS/MS)

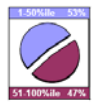
CUTOFF COMPARISON TOOL (Lab vs.%iles of All Participants)

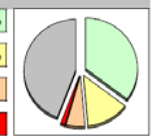
Date	03/13/07	Markers & ratios	68
State	[redacted]	In use	38
Participants	55	Not used	30



44% NOT USED	0%	4%	9%	16%	19%	4%	1%	1%

CO within target ranges	16 of 38	42%	24% of all markers
CO values within the target range AND the 25-75%ile of all participant values	13 of 38 = 34%		These are the CO values that MEET THE GOAL of the project!
CO >25%ile & <75%ile	24	35%	
CO <25%ile & >75%ile	9	13%	
CO <10%ile & >90%ile	4	6%	
CO <1%ile & >99%ile	1	1%	





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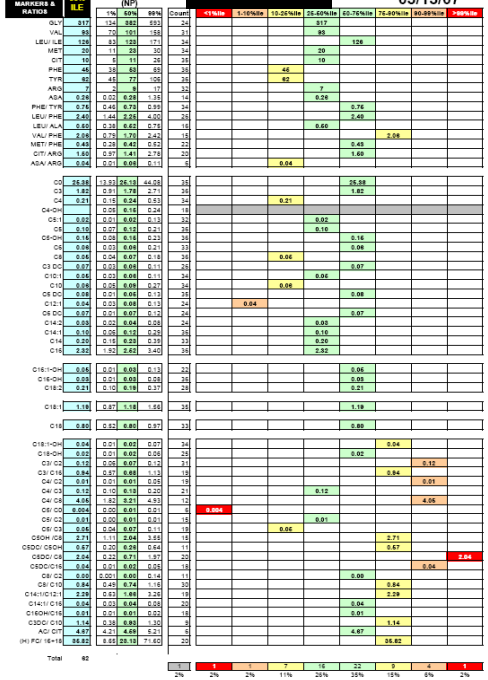
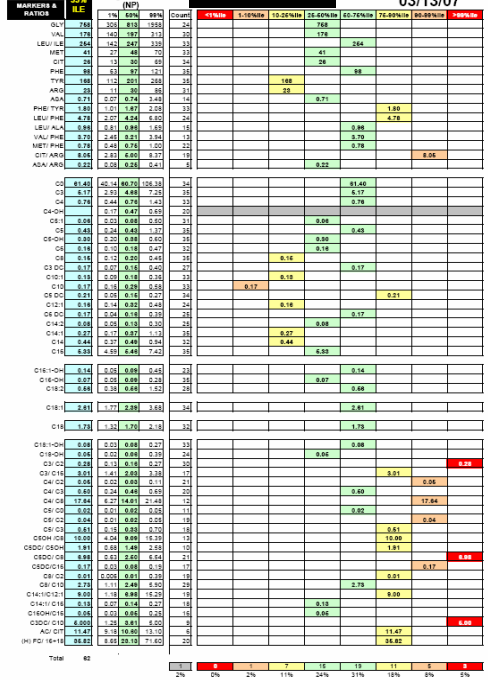
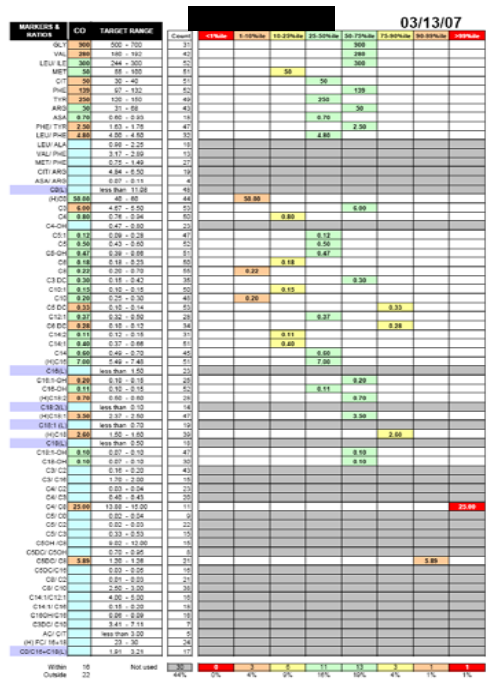


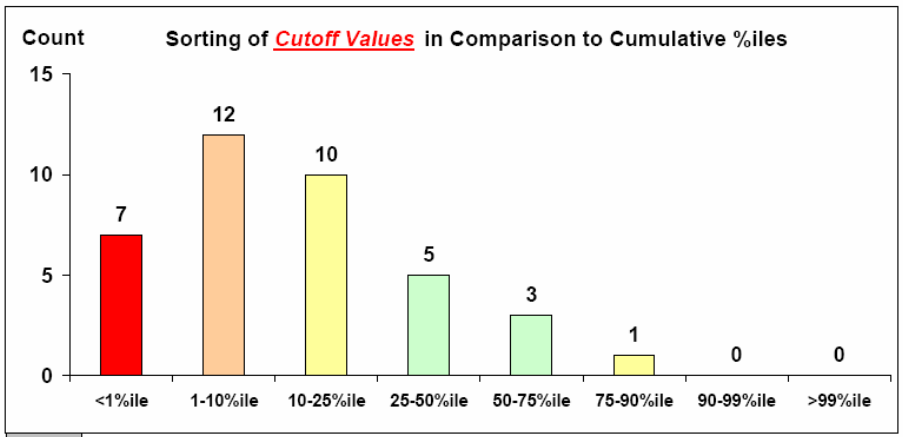




Laboratory Quality Improvement Collaborative Project (NBS by MS/MS)

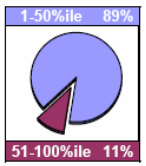
CUTOFF Comparison Tool (Lab vs. Range of All Participants)

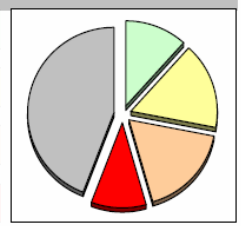
Date	04/30/07	Markers & ratios	68
State		In use	38
Participants	55	Not used	30



44%	10%	18%	15%	7%	4%	1%	0%	0%
NOT USED								

CO within target ranges	6 of 38	16%	9% of all markers	
CO values within the target range AND the 25-75%ile of all participant values	2 of 38 = 5%			These are the CO values that MEET THE GOAL of the project!
CO >25%ile & <75%ile	8	12%		
CO <25%ile & >75%ile	11	16%		
CO <10%ile & >90%ile	12	18%		
CO <1%ile & >99%ile	7	10%		





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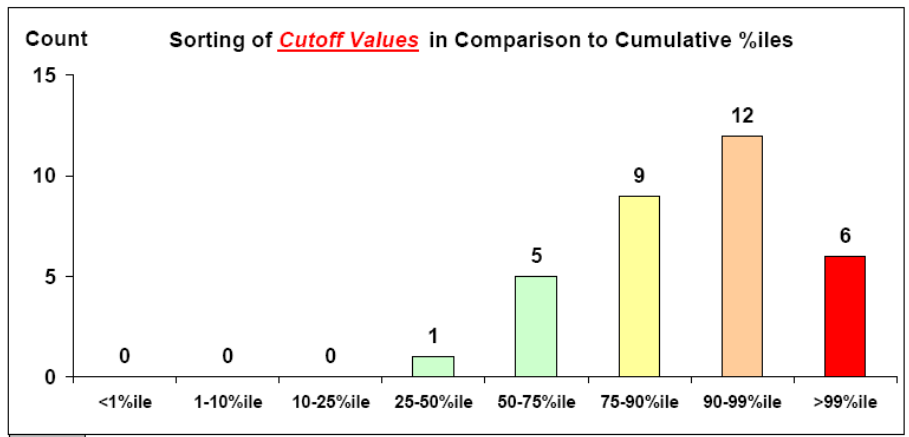
Laboratory Quality Improvement Collaborative Project (NBS by MS/MS)

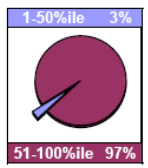
CUTOFF Comparison Tool (Lab vs. Range of All Participants)

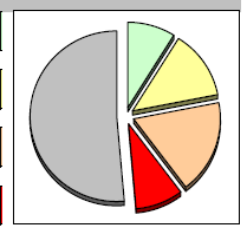
Date	04/30/07	Markers & ratios	68
State		In use	33
Participants	55	Not used	35



51%	0%	0%	0%	1%	7%	13%	18%	9%
NOT USED								

CO within target ranges	4 of 33	12%	6% of all markers	
CO values within the target range AND the 25-75%ile of all participant values	4 of 33 = 12%			These are the CO values that MEET THE GOAL of the project!
CO >25%ile & <75%ile	6	9%		
CO <25%ile & >75%ile	9	13%		
CO <10%ile & >90%ile	12	18%		
CO <1%ile & >99%ile	6	9%		





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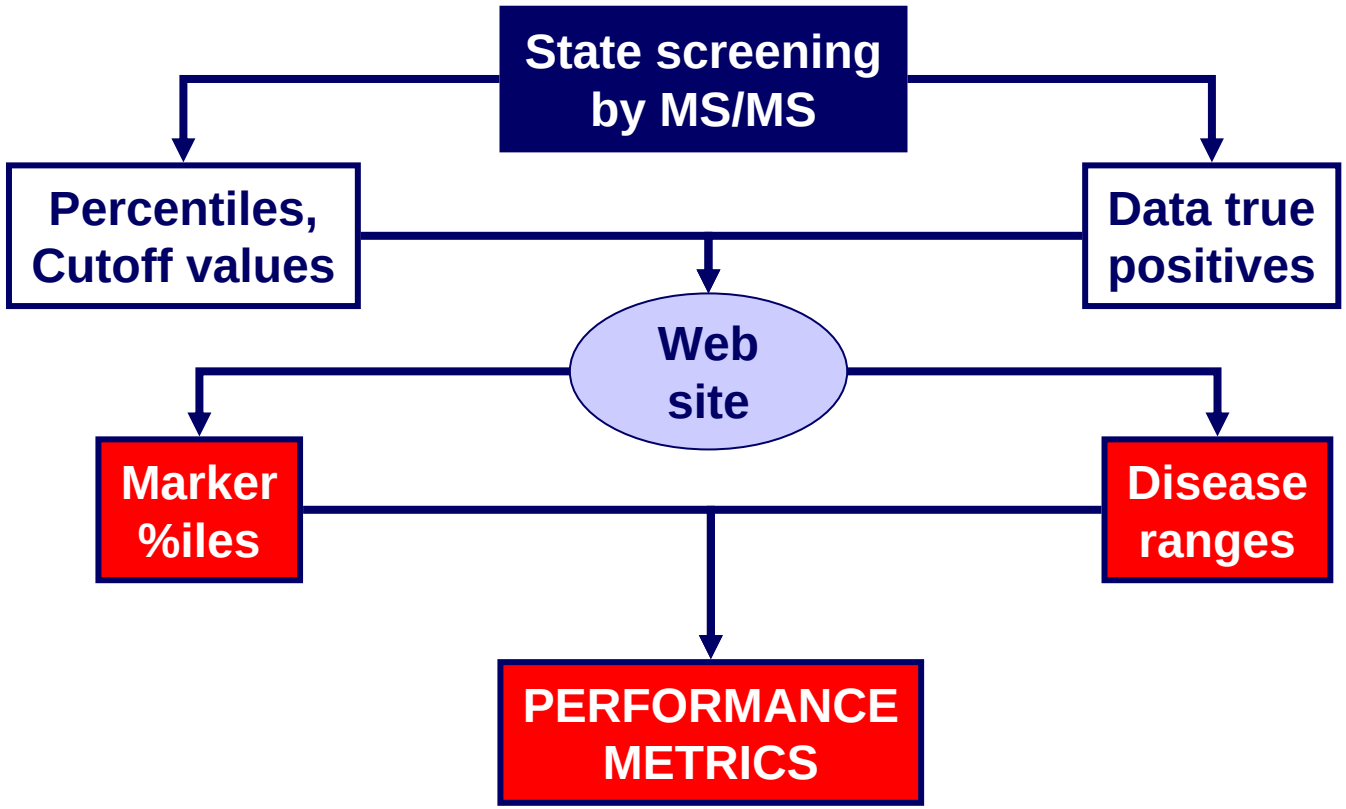
State screening by MS/MS
Percentiles, Cutoff values
Data true positives
Web site
Marker %iles
Disease ranges
PERFORMANCE METRICS

MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS 12: 255–261 (2006)

Making the Case for Objective Performance Metrics in Newborn Screening by Tandem Mass Spectrometry

Piero Rinaldo,* Saba Zafari, Silvia Tortorelli, and Dietrich Mater

Biochemical Genetics Laboratory, Division of Laboratory Genetics, Department of Laboratory Medicine a
Mayo Clinic College of Medicine, Rochester, Minnesota

The expansion of newborn screening programs to include multiplex testing by tandem mass spectrometry requires understanding and close monitoring of performance metrics. This is not done consistently because of lack of defined targets, and interlaboratory comparison is almost nonexistent. Between July 2004 and April 2006 ($N = 176,185$ cases), the overall performance metrics of the Minnesota program, limited to MS/MS testing, were as follows: detection rate 1:1,816, positive predictive value 37% (54% in 2006 till date), and false positive rate 0.09%. The repeat rate and the proportion of cases with abnormal findings actually been reported are new metrics proposed here as an objective mean to express the overall noise in a program, where noise is defined as the total number of abnormal results obtained using a given set of cut-off values. On the basis of our experience, we propose the following targets as evidence of adequate analytical and postanalytical performance: detection rate 1:3,000 or higher, positive predictive value >20%, and false positive rate <0.3%.
MRDD Research Reviews 2006;12:255–261.

Key Words: tandem mass spectrometry; detection rate; positive predictive value; false positive rate

Of all cooperative enterprises, public health is the most important and gives the greatest returns

(William J. Mayo, MD)

Tandem mass spectrometry (MS/MS) allows for the rapid analysis of individual compounds in complex mixtures, and provides an excellent analytical methodology for newborn screening [Chace et al., 2003; Rinaldo et al., 2004; Chace and Kalas, 2005]. The use of a multiplex platform of this nature, however, is challenging and requires not only analytical, but also significant postanalytical skills for proper interpretation of complex metabolite profiles, some of which could involve as many as 15 different markers and ratios in the same profile (Fig. 1). Variability is also significant at the quantitative level, where the concentration of informative findings could span over four orders of magnitude (0.1 to

*Correspondence to: Piero Rinaldo, Biochemical Genetics La
Department of Laboratory Medicine and Pathology, 200 First
Minnesota 55905. E-mail: rinaldo@mayo.edu
Received 10 October 2006; Accepted 11 October 2006
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/mrdd.20130

DETECTION RATE

The detection rate of a newborn screening program is expressed as the

The expansion of newborn screening programs to include multiplex testing by tandem mass spectrometry requires understanding and close monitoring of performance metrics. This is not done consistently because of lack of defined targets, and interlaboratory comparison is almost nonexistent. Between July 2004 and April 2006 ($N = 176,185$ cases), the overall performance metrics of the Minnesota program, limited to MS/MS testing, were as follows: detection rate 1:1,816, positive predictive value 37% (54% in 2006 till date), and false positive rate 0.09%. The repeat rate and the proportion of cases with abnormal findings actually been reported are new metrics proposed here as an objective mean to express the overall noise in a program, where noise is defined as the total number of abnormal results obtained using a given set of cut-off values. On the basis of our experience, we propose the following targets as evidence of adequate analytical and postanalytical performance: detection rate 1:3,000 or higher, positive predictive value >20%, and false positive rate <0.3%.
MRDD Research Reviews 2006;12:255–261.

patients who test positive

Laboratory Quality Improvement Collaborative Project (NBS by MS/MS)

PERFORMANCE METRICS

STATE/LAB		
PERIOD		(mm/yr to mm/yr; for example, 01/05 - 12/06)
VOLUME		(no.of newborns tested, should match the "population" total listed below)

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TEST		STATUS: Affected	STATUS: Not affected	TOTAL	
	POSITIVE			0	
	NEGATIVE			0	
	TOTAL	0	0	0	Population

A	B	TP	FP
C	D	FN	TN

SENSITIVITY	#DIV/0!	A/(A+C)	TP/(TP+FN)
SPECIFICITY	#DIV/0!	D/(B+D)	TN/(FP+TN)
PPV	#DIV/0!	A/(A+B)	TP/(TP+FP)
NPV	#DIV/0!	D/(C+D)	TN/(FN+TN)

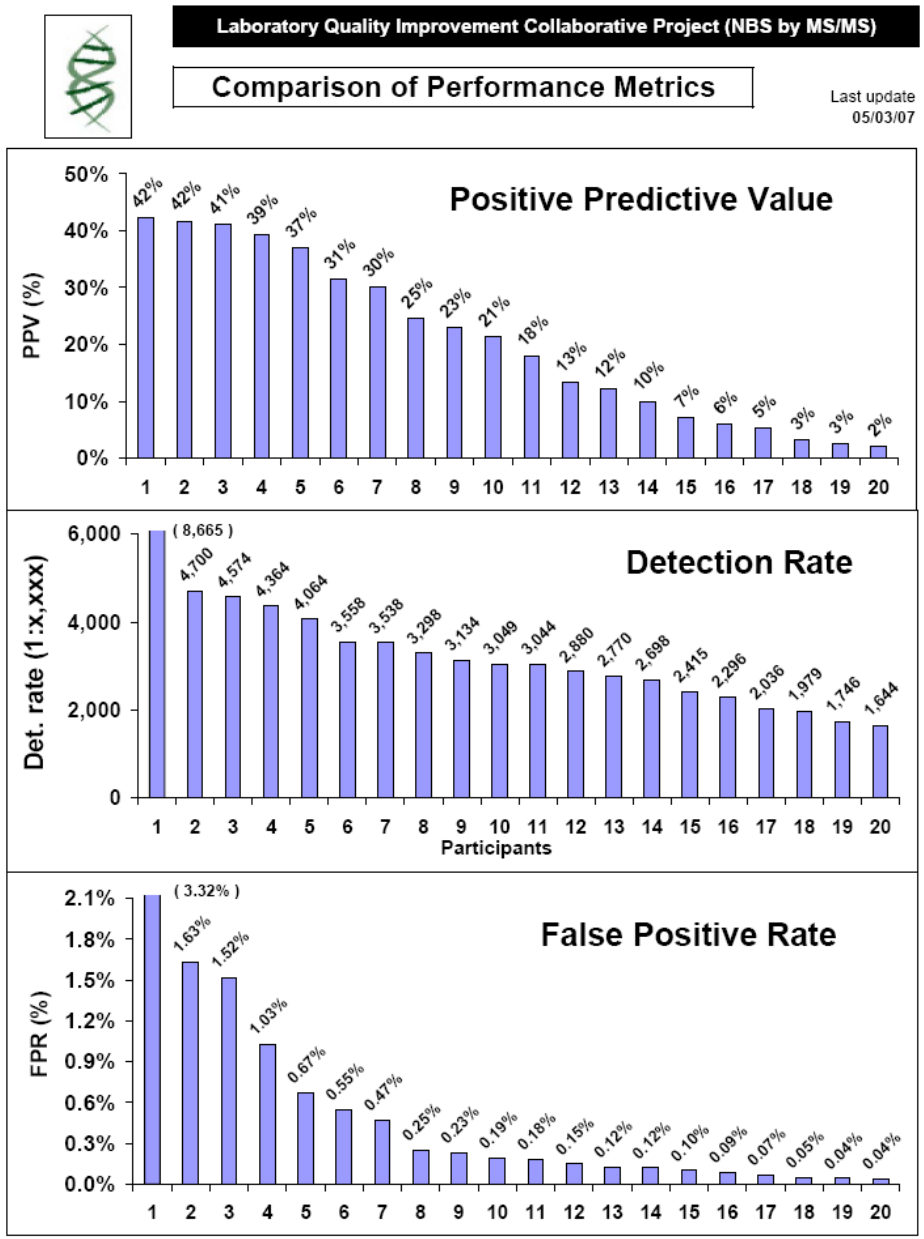
Pos detection rate	1 : #DIV/0!	(Prevalence)
False positive rate	#DIV/0!	FP/Population

Instructions

Only colored cells are accessible
Enter state, period, and volume
Enter the volumes of the 4 groups (TP, FP, FN, TN)
Save as (state) Performance metrics (date)
Example: **MN Performance metrics 01-11-07**
Post file on the website (your state folder)

Updated 01/11/07

Performance Metrics



Sample Exchange

Stephanie Mayfield, MD

Kentucky

Targets of the Program

1. 100% correlation of TP cases with threshold of 95%
2. 90% of primary analyte(s) values within 20% of submitters corresponding values
3. 100% active participation from all states within Region 4 in the exchange process
4. Increase participation from at least three states outside of Region 4

100% Correlation of TP Cases (threshold of 95%)

- As of May 3, 2007
  - 138 cases
  - 119 completed, 19 pending
  - 97% correlation
- 3 discrepancies
  - VLCAD
  - GA I
  - Maternal CUD

Training Courses

REGIONAL COLLABORATIVE PROJECT - PRIORITY 1

TRAINING PROGRAM IN NEWBORN SCREENING BY MS/MS

Biochemical Genetics Laboratory, Mayo Clinic College of Medicine - Rochester (MN), June 25-29, 2007

BGL Personnel	Title
Piero Rinaldo, MD, PhD	Project coordinator, lab director
Dietrich Matern, MD	Lab director
Slivia Tortorelli, MD, PhD	Lab director
Dimitar Gavrilov, MD, PhD	Lab director
James Lim, PhD	Fellow
Amy Barthel	MS/MS supervisor
Mark Magera	Development coordinator

Practical | Presentation

Participants	State
Bonifacio Dy	Florida
Erin Strovel	Maryland
Tanya McCallister	Oklahoma
Alfredo Chardon	Puerto Rico
Shelly Lawson	South Carolina
Robin Porter	South Carolina
Christine McKeever	Tennessee

Flex time | Other

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
8:00	Overview of program, flex time planning, tour	REVIEW of daily results and REPORTING	REVIEW of daily results and REPORTING (including CAH)	REVIEW of daily results (participants alone)	Pediatrics Grand Rounds (NBS related)
8:30					
9:00	Observation of PRE-ANALYTICAL AND ANALYTICAL processing			REVIEW of daily results and REPORTING (including CAH)	REVIEW of daily results (participants are the PRIMARY REVIEWERS) and REPORTING
9:30					
10:00					
10:30	Introduction to MS/MS analysis and AA/AC profile interpretation				
11:00					
11:30		Review 2nd tier test results (CAH, MMA/HCY, BCAA)			
12:00					BGL Case conference
12:30			Break (lunch)		
13:00	Break (lunch)	Break (lunch)		Break (lunch)	Break (lunch)
13:30			MN NBS conference call		
14:00	Examples of profile interpretation and testing algorithms	Overview of databases and tools of the collaborative project	Discussion of participants' panels, cutoffs, %iles, and performance metrics	FLEX TIME, topic to be chosen by participants (options listed below)	FLEX TIME
14:30					
15:00					
15:30					
16:00	REVIEW of daily results and REPORTING	REVIEW of daily results and REPORTING	REVIEW of daily results and REPORTING	REVIEW of daily results and REPORTING	REVIEW of daily results and REPORTING
16:30					
17:00					
17:30					
18:00					

FLEX TIME OPTIONS				
	2nd tier tests **(sample prep)**	2nd tier tests **(analytical)**	Confirmatory testing	TP cases review
	Review of participants' own data, cases (if requested)		MS/MS troubleshooting	Tools customization
	MS/MS calibration, tuning	QC/QA process & procedures	Quiet time (at last)	Shopping

Collaborative Project

(The sequel: 2007-2012)

Project Objectives (2007)

- Development and implementation in screening practice of clinically validated cut-off values and post-analytical tools
- Training course at Mayo in small groups
- Development of customized software to manage data collection, analysis, and reporting of NBS data
- Collection, compilation and monitoring of performance metrics, with definition of targets of acceptable performance
- Monthly conference calls and bi-annual face-to-face meetings
- Continuing clinical validation of 2nd tier tests
- Round robin sample exchange

Project Objectives (2007)

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Operating Principles

- **Web-based access, password protected, large (100-200) number of total users with the expectation of multiple simultaneous log-ins**
- **Peripheral data submission (participants enter own data, not done centrally)**
- **Automation of administrative functions (e-mail reminders, monthly posting of general updates)**
- **On demand, user-driven production of project tools (score cards, plots)**
- **Easy generation of customize reports (comparison tools of own data vs. cumulative data)**
- **Flexibility to add new conditions and markers (with potential applicability beyond MS/MS panel), and to query the database to generate novel reports**

Of all cooperative enterprises, public health is the most important and gives the greatest return

Charles J. Mayo, MD