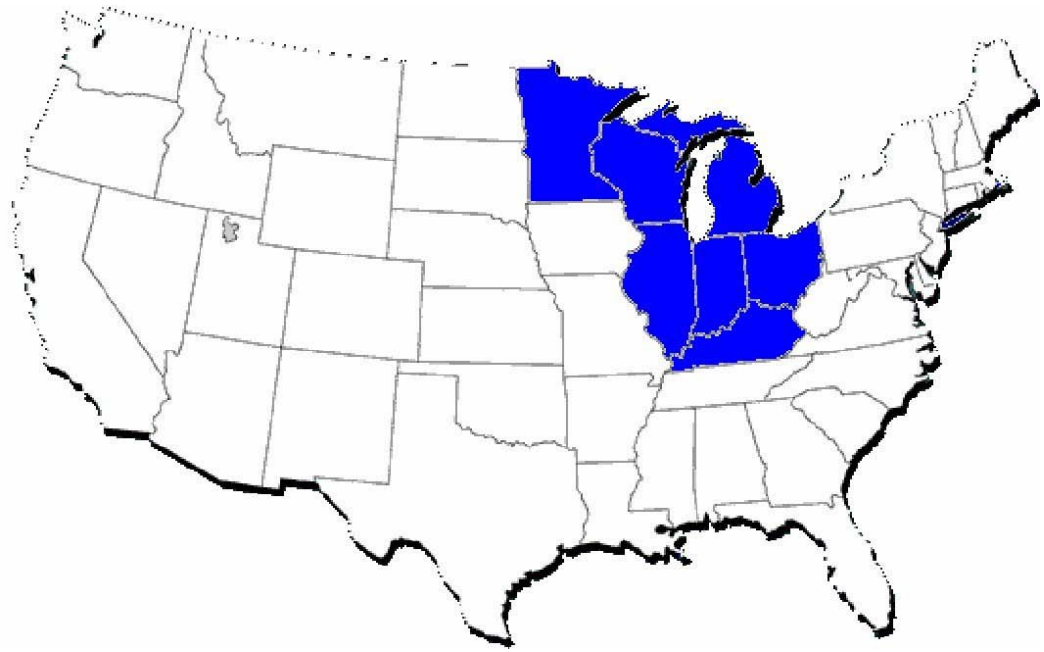
Regional Genetic Service &
Newborn Screening Collaboratives

Region 4 Update

Performance Metrics and Harmonization of Cutoff Values for Newborn Screening by Tandem Mass Spectrometry (MS/MS)

7th Meeting of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC)
February 13th, 2006

A Regional Approach to Improve the Health of Children and Families with Heritable Disorders in Illinois, Indiana, Kentucky, Michigan, Minnesota, Ohio, and Wisconsin (Region 4)



Goals of Regional Collaborative

- **Implement universal screening and confirmatory testing of newborns for inborn errors of amino acid, organic acid, and fatty acid metabolism**
- **Reduce inequities in access to genetic services**
- **Utilize a regional approach to improve public health infrastructure for supporting optimal diagnosis, follow up and management of children with heritable disorders and birth defects**

Objectives of Project 1

- Achieve uniformity of testing panel by MS/MS to maximize detection of affected newborns within the region
- Improve overall analytical performance
- Set and sustain lowest achievable rates of false positive results

HRSA/ACMG Uniform Panel (MS/MS)

UNIFORM PANEL

- Phenylketonuria
- MSUD
- Homocystinuria
- Tyrosinemia type I
- Argininosuccinic acidemia
- Citrullinemia type I
- MCAD deficiency
- VLCAD deficiency
- LCHAD deficiency
- TFP deficiency
- Carnitine uptake defect
- Isovaleric acidemia
- Glutaric acidemia type I
- HMG deficiency
- 3MCC deficiency
- BKT deficiency
- Multiple carboxylase deficiency
- Methylmalonic acidemia (MUT)
- Methylmalonic acidemia (Cbl A,B)
- Propionic acidemia

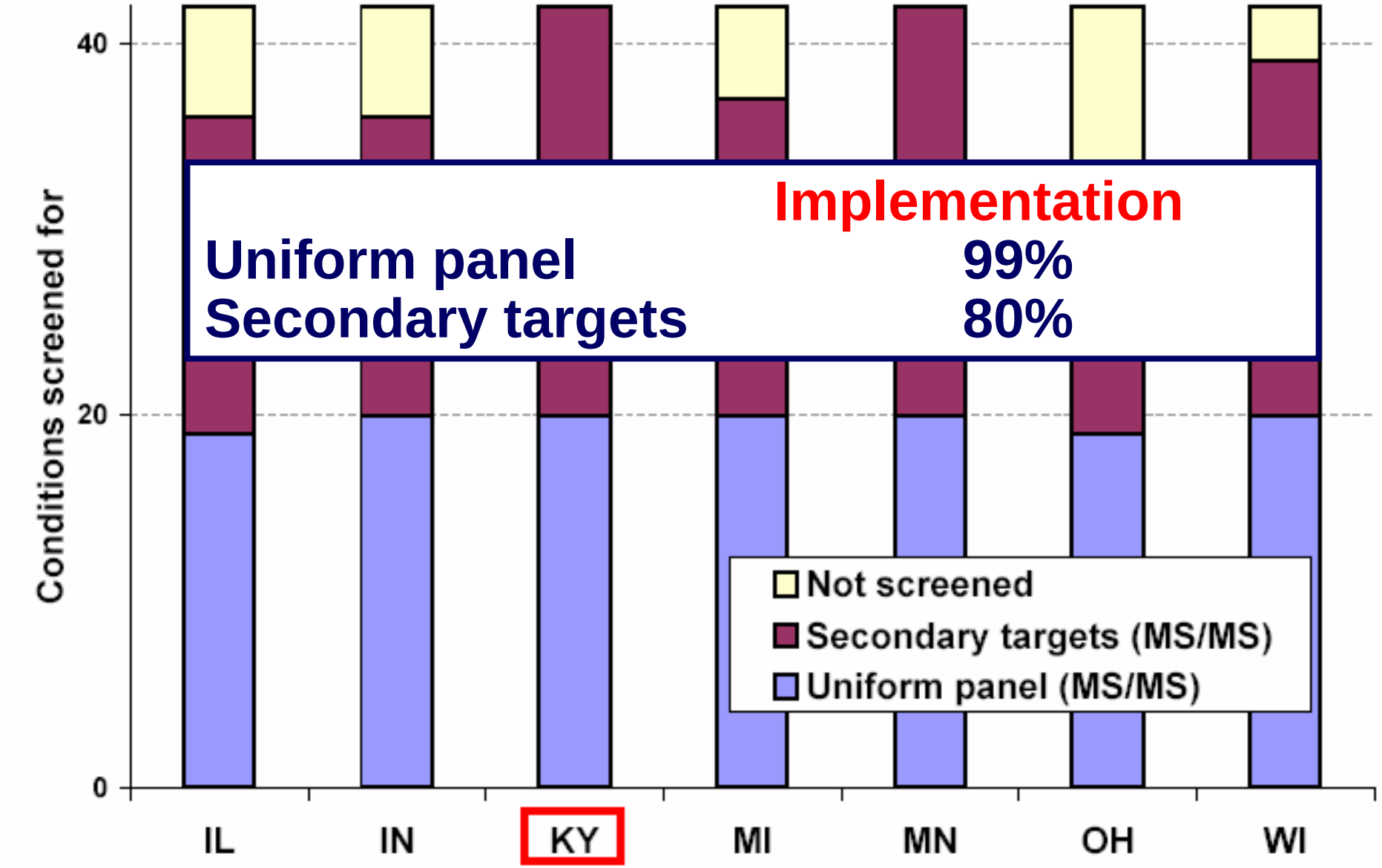
SECONDARY TARGETS

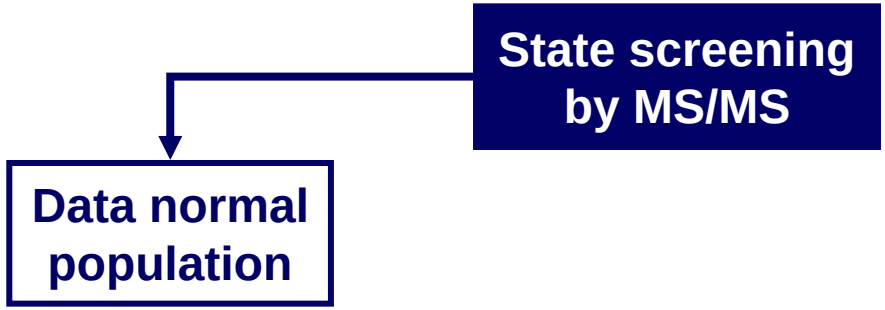
- Hyperphenylalaninemia
- Tyrosinemia type II
- Biopterin defects (Bios)
- Tyrosinemia type III
- Biopterin (Reg)
- Argininemia
- Hypermethioninemia
- Citrullinemia type II
- M/SCHAD deficiency
- SCAD deficiency
- MCKAT deficiency
- CPT-I deficiency
- Glutaric acidemia type II
- CACT deficiency
- Dienoyl red. deficiency
- CPT-II deficiency
- Methylmalonic acidemia (Cbl A,B)
- 2M3HBA deficiency
- IBG deficiency
- 2MBCAD deficiency
- Methylglutaconic acidemia
- Malonic acidemia

20 Primary targets

22 “Secondary” targets

Implementation of UP 2005 (MS/MS) (December 2005)




State screening by MS/MS
Data normal population

Region 4 – "Score Card"

Region 4 - Laboratory Quality Improvement Project

State/Lab	Minnesota	AMINO ACIDS							
Year	2005 (1-12)	Volume	99,525	FPR	0.08	PPV	41%	Detection Rate	1: 2,212

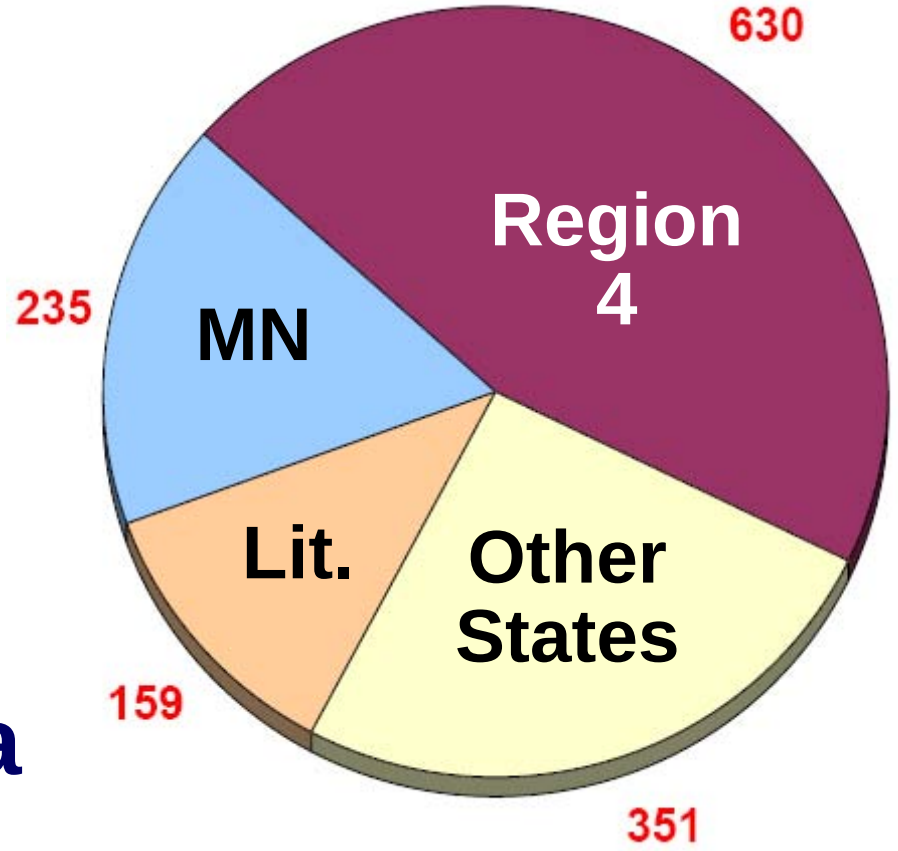
Updated	Tot. # cases
01/26/06	1,345

	NORMAL POPULATION			CUT-OFF (CO)				TRUE POSITIVES									
	Percentiles			(µM)	State	SD	Abn/		5%ile		Percentiles						
ANALYTE	50%	90%	99%	Value	%ile	OFF	10,000	N	<CO	LV	5%	10%	25%	50%	75%	90%	HV	Condition
GLY	184	319	514	700	99.80%	5.1	4.5	8		560	703	846	1,019	1,184	1,265	1,387	1,431	NKHG
VAL	68	95	140	250	99.93%	7.8		23	YES	100	190	199	313	385	472	638	1,029	MSUD
ILE/LEU	104	157	244	300	99.65%	4.3	3.5	30	YES	229	266	296	350	685	1,613	2,579	3,452	MSUD
MET	21	29	49	60	99.47%	3.6	3.2	6		115	151	187	273	570	852	875	888	HCY
								3		112	114	115	120	128	161	181	194	H-MET
CIT	9	13	19	55	99.98%	12.9	0.2	27		97	121	133	207	300	521	683	1,263	CIT-I
								4		61	62	63	66	115	205	281	331	CIT-II
								14	YES	37	47	55	66	94	155	209	232	ASA
PHE	56	74	105	130	99.67%	4.3	2.0	181		145	242	267	325	426	554	812	2,080	PKU
								113		125	145	151	171	204	256	321	578	H-PHE
TYR	69	116	191	150	97.06%	2.1	4.2	10	YES	54	85	115	139	218	226	263	293	TYR-I
								4		220	249	364	430	627	627	949	1,164	TYR-II
ARG	5	9	18	50	99.94%	10.0	2.3	4		93	110	128	180	268	330	335	338	ARG
								10		2.1	3.0	3.9	4.9	5.6	8.3	10.7	25.9	ASA
ASA	0.06	0.13	0.24	0.40	99.85%	6.0	0.1	4		0.58	0.69	0.79	1.11	1.34	2.07	3.28	4.09	ASA


State screening by MS/MS
Data normal population
Data true positives

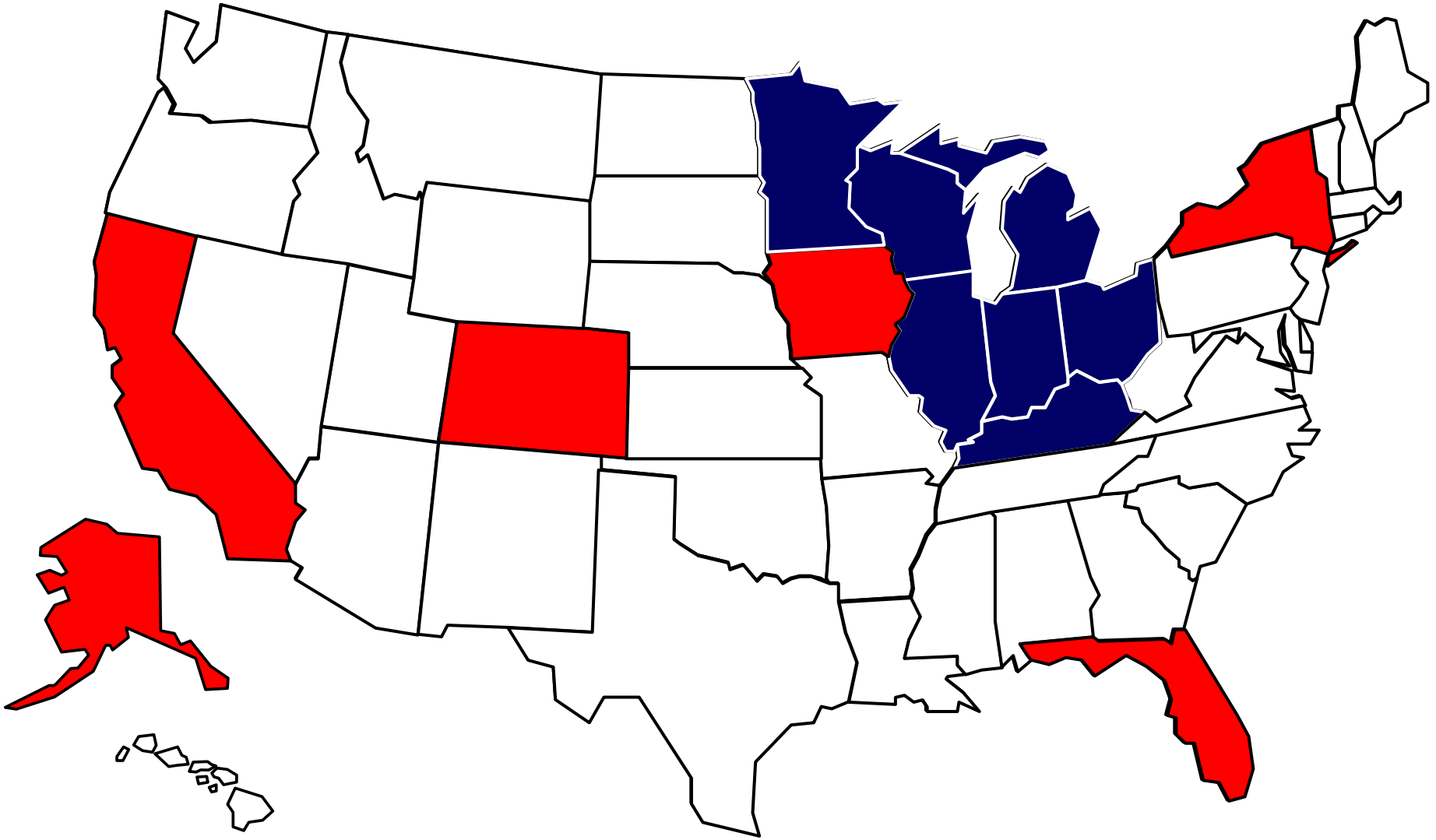
Cumulative Disease Ranges

- **1,375 confirmed cases (as 2/11/06)**
  - **Minnesota**
  - **Region 4**
  - **Other states**
  - **Literature**



- **Anonymized data**
- **Only first specimens (no repeats)**

(Actively) Contributing States



Summary Page

Region 4 MS/MS Working Group

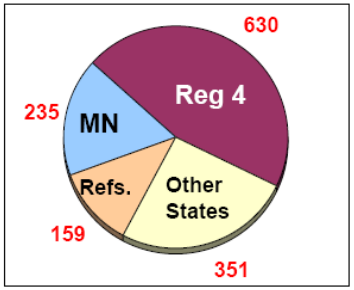
True positive DISEASE RANGE Project

02/11/06 Last Update

True Positives

TOTAL 1,375

				MN	Reg 4	Other States	Refs.
				17%	46%	26%	12%
				235	630	351	159
PRIMARY TARGETS (HRSA/ACMG panel)							
Group	Condition	Code	No. cases				
AA	Phenylketonuria	PKU	182	31	119	32	0
AA	Maple syrup disease	MSUD	30	3	10	13	4
AA	Homocystinuria	HCY	6	0	2	3	1
AA	Citrullinemia type I	CIT 1	28	0	6	7	15
AA	Argininosuccinic acidemia	ASA	14	2	6	5	1
AA	Tyrosinemia type I	TYR 1	11	0	0	6	5
FAO	MCAD deficiency	MCAD	284	25	139	82	38
FAO	(Hetero) MCAD deficiency	MCAD (H)	35	34	0	1	0
FAO	VLCAD deficiency	VLCAD	47	1	18	8	20
FAO	(Hetero) VLCAD deficiency	VLCAD (H)	8	8	0	0	0
FAO	LCHAD deficiency/TFP deficiency	LCHAD/TFP	37	20	7	8	2
FAO	Carnitine uptake defect	CUD	19	7	1	10	1
OA	Isovaleric acidemia	IVA	32	5	18	8	1
OA	Glutaric acidemia type I	GA 1	39	4	10	12	13
OA	3-OH 3-CH3 glutaric aciduria	HMG	4	0	2	2	0
OA	Multiple carboxylase deficiency	MCD	1	0	1	0	0
OA	Methylmalonic acidemia (Mut,A,B)	MUT	58	6	16	34	2
OA	3-MCC deficiency	3MCC	103	13	46	23	21
OA	3-MCC deficiency (maternal)	3MCC (mat)	23	7	5	2	9
OA	Propionic acidemia	PA	34	0	13	18	3
OA	Beta-ketothiolase deficiency	BKT	5	0	3	1	1
SECONDARY TARGETS (HRSA/ACMG panel)							
Group	Condition	Code	No. cases				
AA	Hyperphenylalaninemia	HyperPHE	114	16	87	11	0
AA	Tyrosinemia type II	TYR 2	4	0	2	1	1
AA	Disorders of biopterin biosynthesis	BIOPT (Bio)	1	0	1	0	0
AA	Argininemia	ARG	4	0	1	3	0
AA	Tyrosinemia type III	TYR 3	0	0	0	0	0
AA	Disorders of biopterin regeneration	BIOPT (Reg)	0	0	0	0	0
AA	Hypermethioninemias	MET	3	2	0	1	0
AA	Citrin deficiency (citrullinemia type II)	CIT II	6	2	4	0	0
FAO	SCAD deficiency	SCAD	106	16	66	19	5
FAO	Glutaric acidemia type II	GA-II	10	1	6	3	0
FAO	M/SCHAD deficiency	M/SCHAD	1	0	0	1	0
FAO	MCKAT deficiency	MCKAT	0	0	0	0	0
FAO	CPT-II deficiency	CPT 2	7	1	2	3	1
FAO	Translocase deficiency	CACT	2	0	1	1	0
FAO	CPT-Ia deficiency	CPT 1	26	0	0	22	4
FAO	2,4 Dienoyl reductase deficiency	RED	0	0	0	0	0
OA	Methylmalonic acidemia (Cbl C,D)	Cbl C,D	10	3	1	4	2
OA	Malonic acidemia	MAL	5	1	0	1	3
OA	Isobutyrylglycinuria	IBD	15	4	8	0	3
OA	2-Methyl 3-hydroxy butyric aciduria	2M3HBA	0	0	0	0	0
OA	2-Methylbutyrylglycinuria	SBCAD	42	17	25	0	0
OA	3-Methyl glutaconic aciduria	3MGA	2	0	2	0	0
OTHER CONDITIONS (not included in HRSA/ACMG panel)							
Group	Condition	Code	No. cases				
AA	Non ketotic hyperglycinemia	NKHG	9	1	1	4	3
OA	Biotinidase (partial)	BIOT (P)	5	5	0	0	0
OA	Ethylmalonic encephalopathy	EE	2	0	1	1	0
OA	PC deficiency	PC	1	0	0	1	0



ACMG UNIFORM PANEL 1000

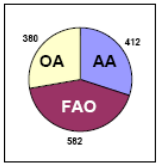
	MN	Reg 4	States	Refs.	Total
AA	36	143	66	26	271
	13%	53%	24%	10%	
FAO	95	165	109	61	430
	22%	38%	25%	14%	
OA	35	114	100	50	299
	8%	27%	23%	12%	

ACMG SECONDARY TARGETS 358

	MN	Reg 4	States	Refs.	Total
AA	20	95	16	1	132
	7%	35%	6%	0%	
FAO	18	75	49	10	152
	4%	17%	11%	2%	
OA	25	36	5	8	74
	6%	8%	1%	2%	

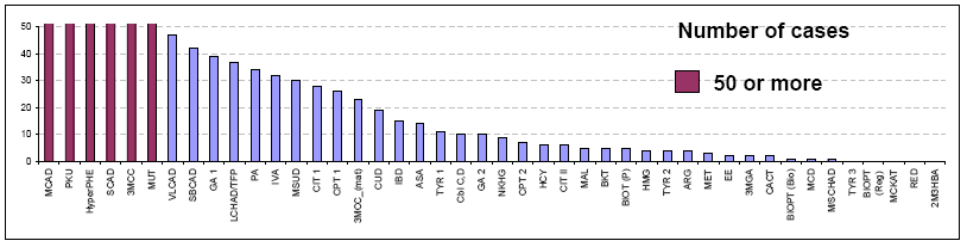
ALL CONDITIONS 1375

	MN	Reg 4	States	Refs.	Total
AA	57	239	86	30	412
	21%	88%	32%	11%	
FAO	113	240	158	71	582
	26%	58%	37%	17%	
OA	65	151	107	58	381
	15%	35%	25%	13%	



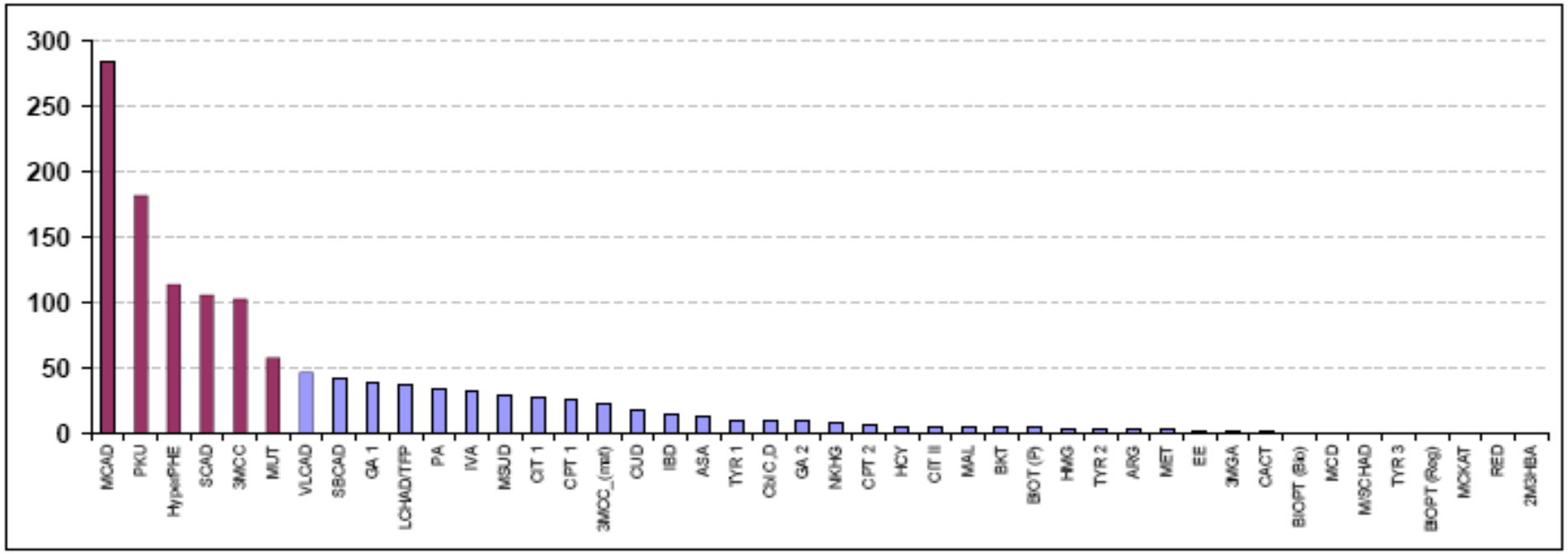
Completeness of data

	Markers	ALL
AA	73%	27%
FAO	64%	48%
OA	70%	29%



Content of Summary

- **Conditions**
- **Uniform panel**
- **Secondary targets**
- **Others**
- **Sorted by group**
  - **AA, FAO, OA**
- **Count**
- **Source**
- **Completeness**


300
250
200
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0
MCAD
PKU
HyperPHE
SCAD
3MCC
MUT
VLCAD
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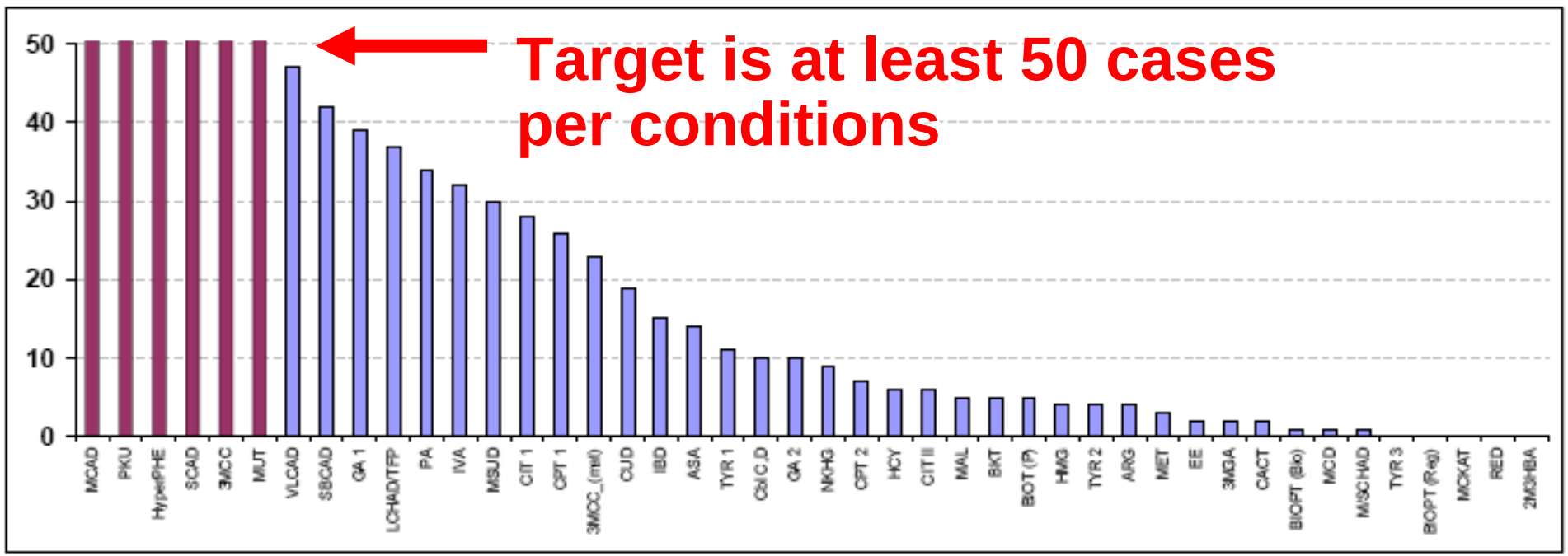
GA 1
LCHAD/TFP
PA
IVA
MSUD
CIT 1
CPT 1
3MCC_(met)
CUD
IBD
ASA
TYR 1
Cbl C,D
GA 2
NKHG
CPT 2
HCY
CIT II
MAL
BKT
BIOT (P)
HMG
TYR 2
ARG
MET
EE
3MGA
CACT
BIOPT (Bio)
MCD
MISCHAD
TYR 3
BIOPT (Reg)
MCKAT
RED
2MSHBA


50
40
30
20
10
0
Target is at least 50 cases per conditions
MCAD
PKU
HyperPHE
SCAD
3MCC
MUT
VLCAD
SBCAD
GA 1
LCHAD/TFP
PA
IVA
MSUD
CIT 1
CPT 1
3MCC_(met)
CUD
IBD
ASA
TYR 1
Cbl C,D
GA 2
NKHG
CPT 2
HCY
CIT II
MAL
BKT
BIOT (P)
HMG
TYR 2
ARG
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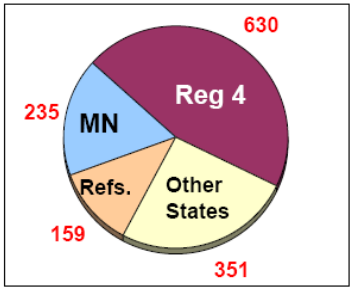

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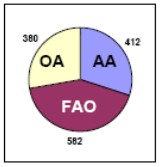

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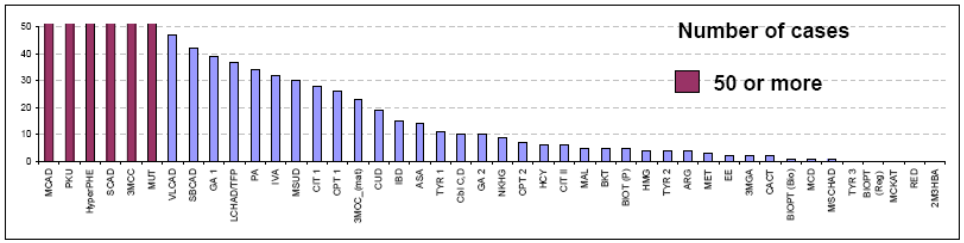
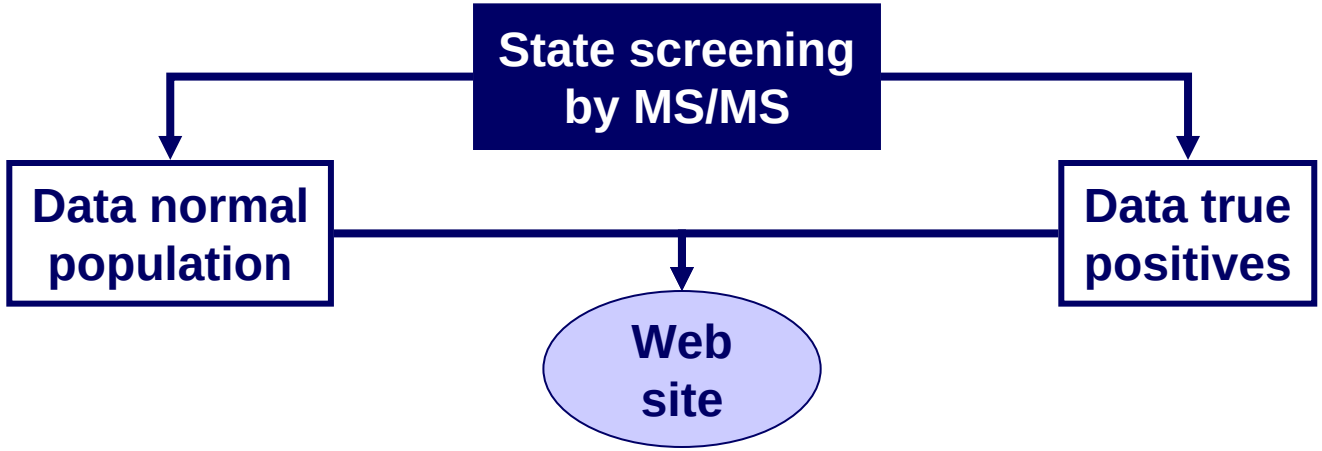


Count by Year (All States)

CONDITION	2	18	142	322	286	579	26	TOTAL
	2000	2001	2002	2003	2004	2005	2006	1375
MCAD	0	4	25	83	55	112	5	284
PKU	0	0	31	47	41	60	3	182
3MCC	0	1	16	15	25	42	4	103
H-PHE	0	0	10	35	29	40	0	114
SCAD	0	2	19	22	23	39	1	106
MMA (A,B)	0	2	9	2	6	39	0	58
SBCAD	0	0	8	9	13	11	1	42
VLCAD	0	1	0	15	4	26	1	47
LCHAD_TFP	0	0	5	8	14	10	0	37
MCAD (H)	0	0	0	0	0	35	0	35
GA1	0	0	1	8	16	10	4	39
PA	0	2	5	6	3	18	0	34
CIT-I	0	0	0	17	3	7	1	28
MSUD	0	0	1	7	5	17	0	30
CPT 1	1	3	0	0	10	12	0	26
IVA	0	0	2	10	4	14	2	32
3MCC (mat)	0	0	3	6	1	13	0	23
CUD	1	0	0	0	5	10	3	19
ASA	0	0	1	2	8	3	0	14
IBD	0	0	1	6	4	4	0	15
CBL C	0	1	2	3	1	3	0	10
TYR-I	0	0	0	1	3	7	0	11
GA-II	0	0	1	1	3	5	0	10
NKHG	0	0	0	3	1	5	0	9
VLCAD (H)	0	0	0	1	0	7	0	8
HCY	0	0	0	2	1	3	0	6
CPT 2	0	1	0	1	0	5	0	7
MAL	0	0	0	3	0	2	0	5
BIOT (P)	0	0	0	0	1	3	1	5
BKT	0	0	0	2	0	3	0	5
CIT-II	0	1	0	1	1	3	0	6
HMG	0	0	0	2	0	2	0	4
TYR 2	0	0	0	1	0	3	0	4
ARG	0	0	0	1	1	2	0	4
MET	0	0	0	0	3	0	0	3
CACT	0	0	0	0	1	1	0	2
EE	0	0	0	1	0	1	0	2
MGA	0	0	2	0	0	0	0	2
BIOPT (bio)	0	0	0	0	1	0	0	1
MCD	0	0	0	1	0	0	0	1
PC	0	0	0	0	0	1	0	1
SCHAD	0	0	0	0	0	1	0	1
2M3HBA	0	0	0	0	0	0	0	0
BIOPT (reg)	0	0	0	0	0	0	0	0
MCKAT	0	0	0	0	0	0	0	0
RED	0	0	0	0	0	0	0	0
TYR 3	0	0	0	0	0	0	0	0

Count by State (All Years)

STATE	1375	MCAD 284	PKU 182	3MCC 103	H-PHE 114	SCAD 105	MMA (A,B) 58	SBCAD 42	VLCAD 47	LCHAD TFP 37	GA1 39	PA 34	CIT-I 28	MSUD 30	IVA 32	3MCC (mut) 23	ASA 14	CUD 19
AL	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AK	22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AZ	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AR	6	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0
CA	75	16	0	6	0	3	8	0	3	4	7	3	3	3	1	0	0	5
CO	8	2	2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
CT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FL	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
HI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ID	10	0	0	0	0	0	0	0	0	0	0	0	0	0	10	0	0	0
IL	210	39	34	9	43	37	6	0	6	3	4	0	2	3	0	1	4	0
IN	78	17	27	9	4	6	1	0	3	1	2	1	0	2	0	0	0	0
IA	44	8	14	3	8	8	1	0	0	0	0	0	0	0	0	0	0	1
KS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
KY	8	1	2	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0
LA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ME	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MD	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
MA	10	2	0	0	0	0	2	0	0	0	0	3	0	0	0	0	0	0
MI	68	22	16	1	13	1	0	1	3	2	0	1	1	3	0	1	1	1
MN	189	24	31	13	16	16	5	17	1	19	4	0	0	3	5	7	2	7
MS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MO	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NV	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NJ	2	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NM	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
NY	80	35	15	13	3	8	2	0	0	2	1	1	1	1	0	0	1	3
NC	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0
ND	6	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0
OH	126	41	28	7	27	1	0	0	5	2	1	4	2	0	0	3	0	0
OK	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
OR	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
PA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PT	4	1	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
RI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SA	41	1	1	0	0	0	13	0	4	1	1	9	2	5	0	0	3	0
SC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TN	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TX	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
UT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
VT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
VI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
VA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
WA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
WV	3	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0
WI	128	20	12	19	0	19	9	24	1	0	3	7	1	2	0	0	1	0
WY	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
LIT	168	38	0	21	0	5	2	0	20	2	14	3	15	4	0	9	1	1
JP	20	0	0	0	0	0	8	0	1	0	1	2	0	4	0	0	0	1
QLD	12	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0


State screening by MS/MS
Data normal population
Data true positives
Web site

Region 4 Genetics Collaborative

Home

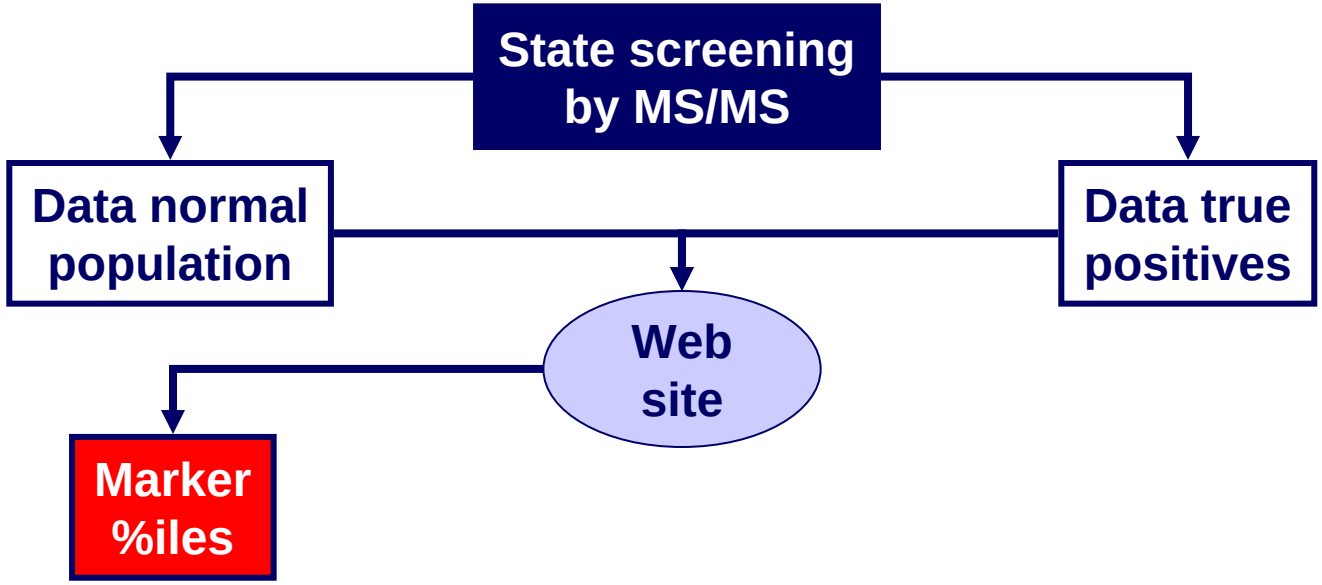
- About the Collaborative
- Events
- State Links
- Resources
- Advisory Group
- Newborn Screening by MS/MS
- Clinical Diagnosis & Management
- Public Health Infrastructure

National Genetics File Libraries

Administration Section

Name	Description	Add File	View Files
True Positives	True Positives	Click Here	Click Here
True Positives - Illinois	True Positives - Illinois	Click Here	Click Here
True Positives - Indiana	True Positives - Indiana	Click Here	Click Here
True Positives - Kentucky	True Positives - Kentucky	Click Here	Click Here
True Positives - Michigan	True Positives - Michigan	Click Here	Click Here
True Positives - Minnesota	True Positives - Minnesota	Click Here	Click Here
True Positives - Ohio	True Positives - Ohio	Click Here	Click Here
True Positives - Wisconsin	True Positives - Wisconsin	Click Here	Click Here
Cutoff Ranges	Cutoff Ranges	Click Here	Click Here
Score Cards	Score Cards	Click Here	Click Here

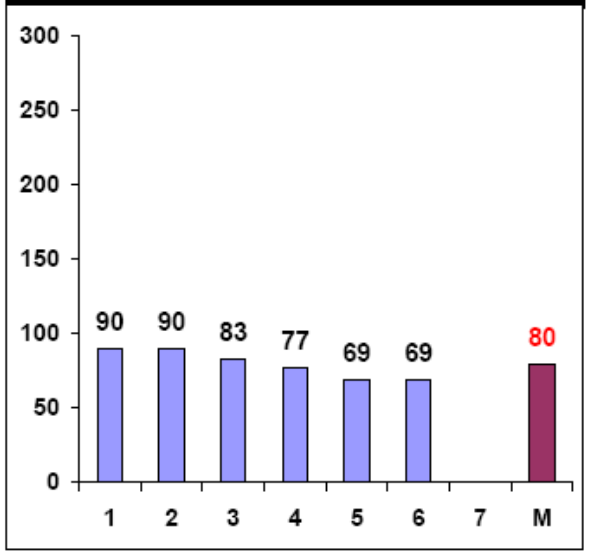
Log Out


State screening by MS/MS
Data normal population
Data true positives
Web site
Marker %iles

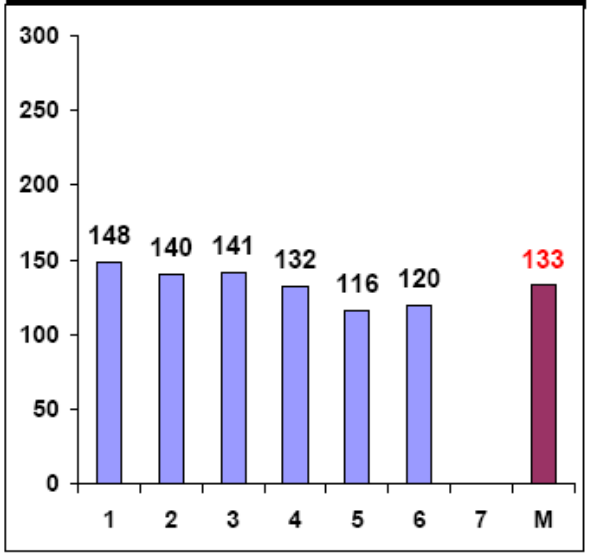
Updated	01/23/06

TYROSINE

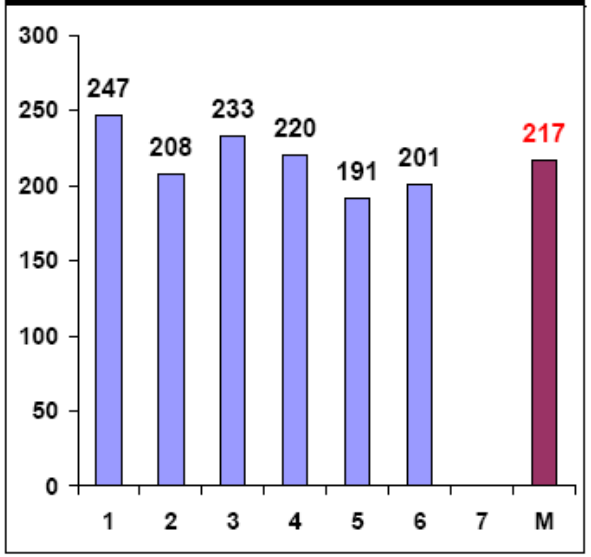
50%ile



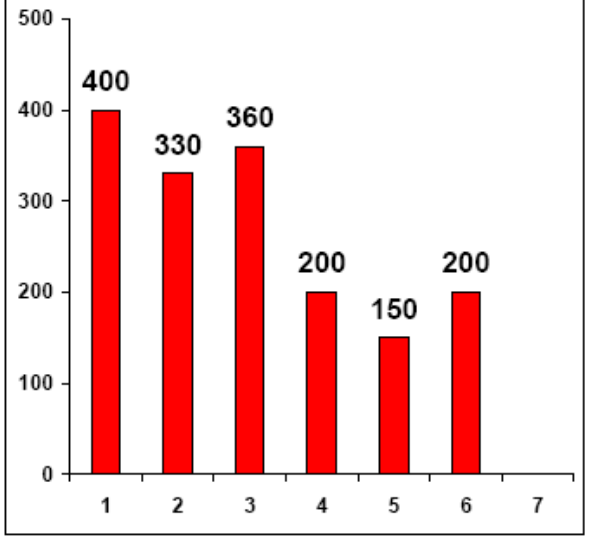
90%ile



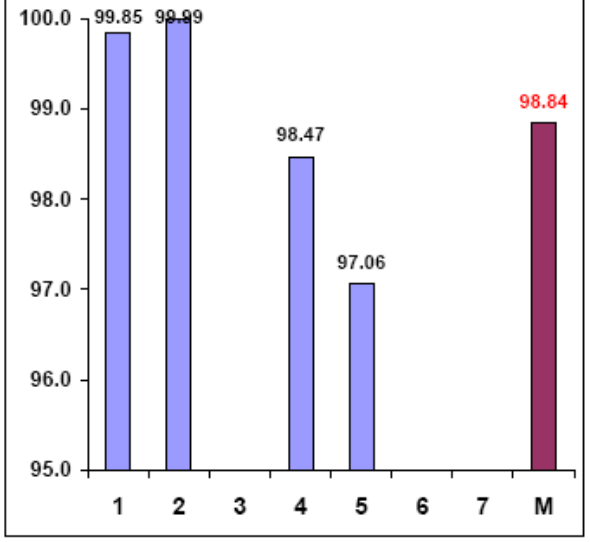
99%ile



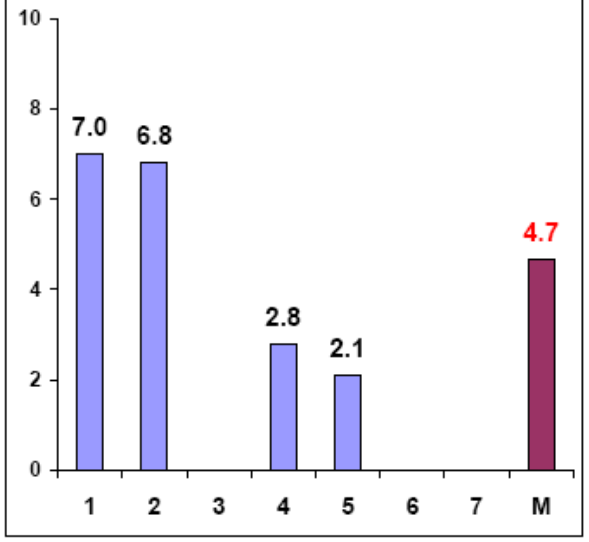
Cutoffs



CO (%ile of controls)



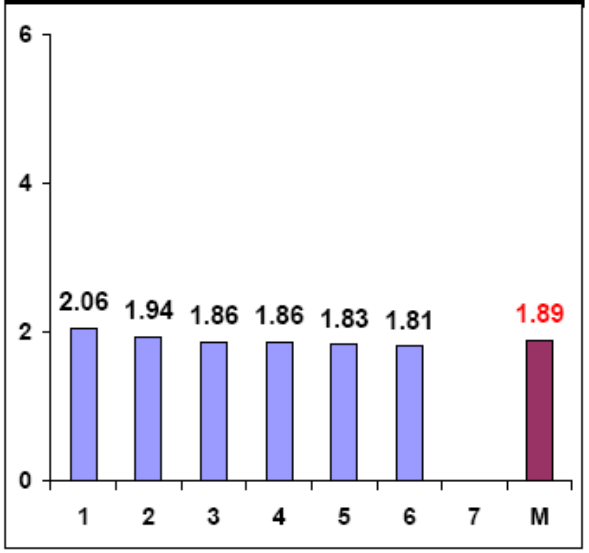
CO (SD above mean)



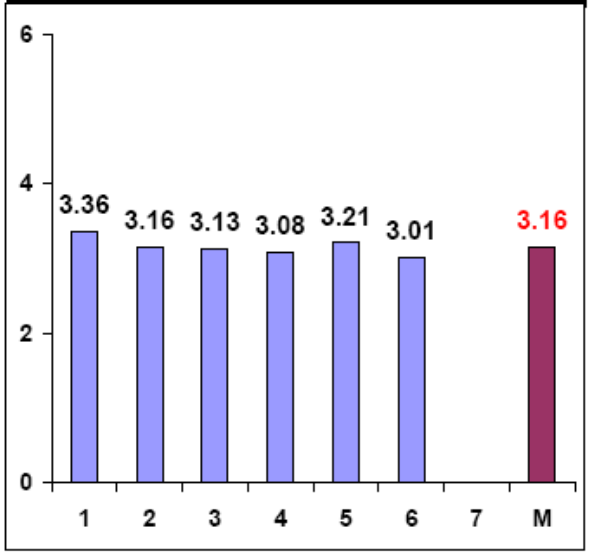
Updated	01/23/06

C3

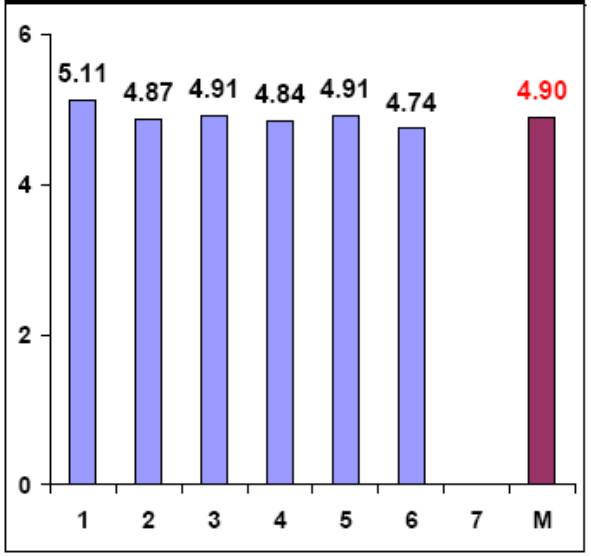
50%ile



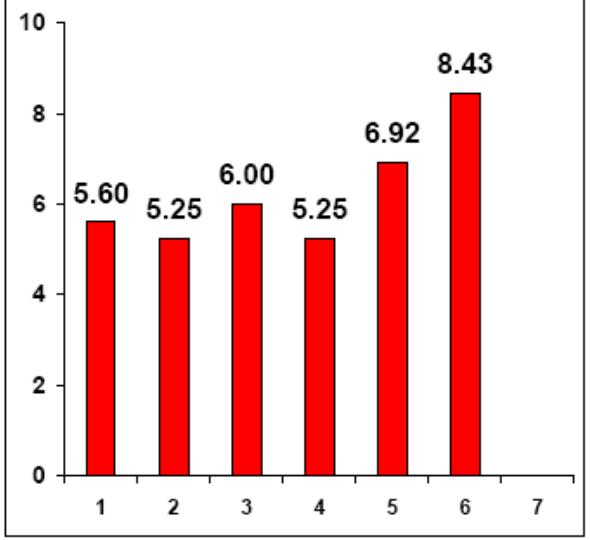
90%ile



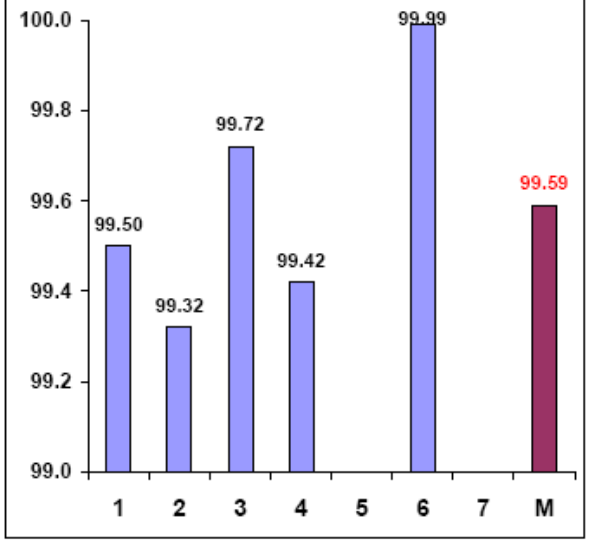
99%ile



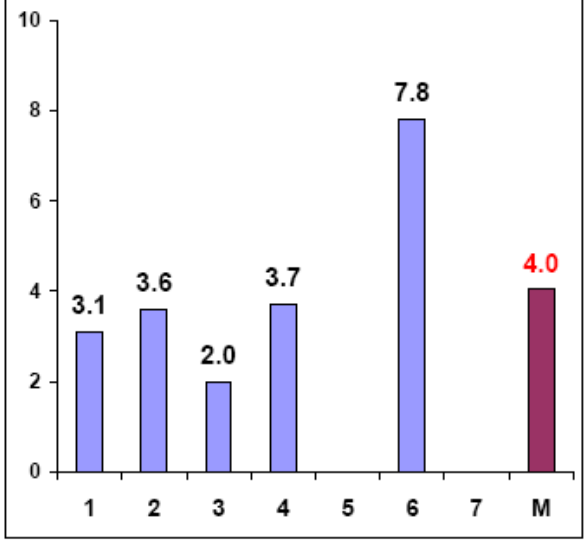
Cutoffs



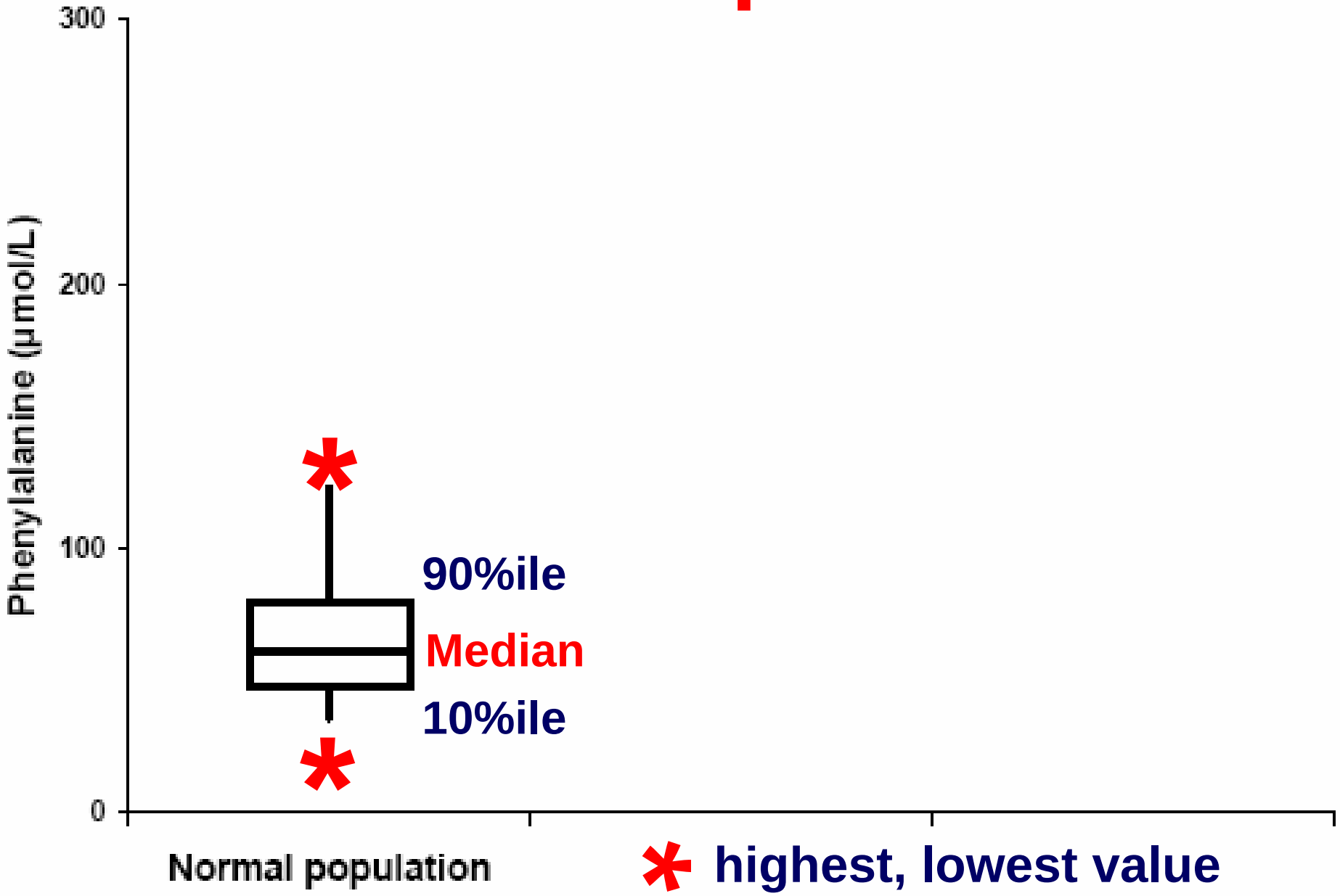
CO (%ile of controls)

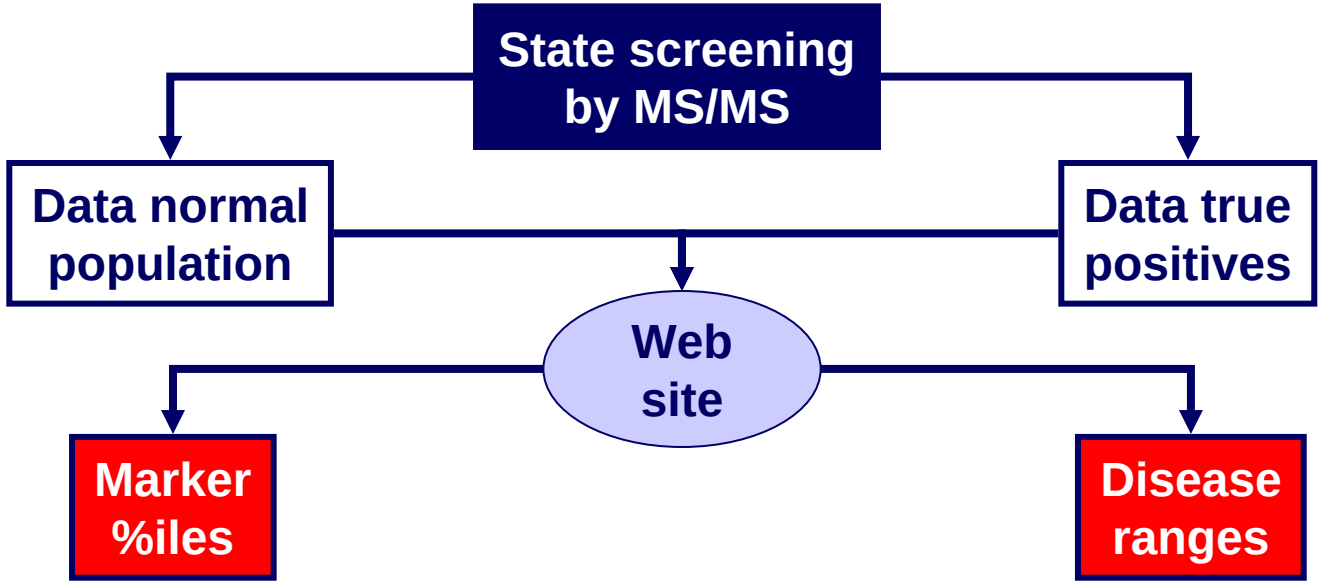


CO (SD below mean)



Normal Population




State screening by MS/MS
Data normal population
Data true positives
Web site
Marker %iles
Disease ranges

Region 4 – "Score Card"

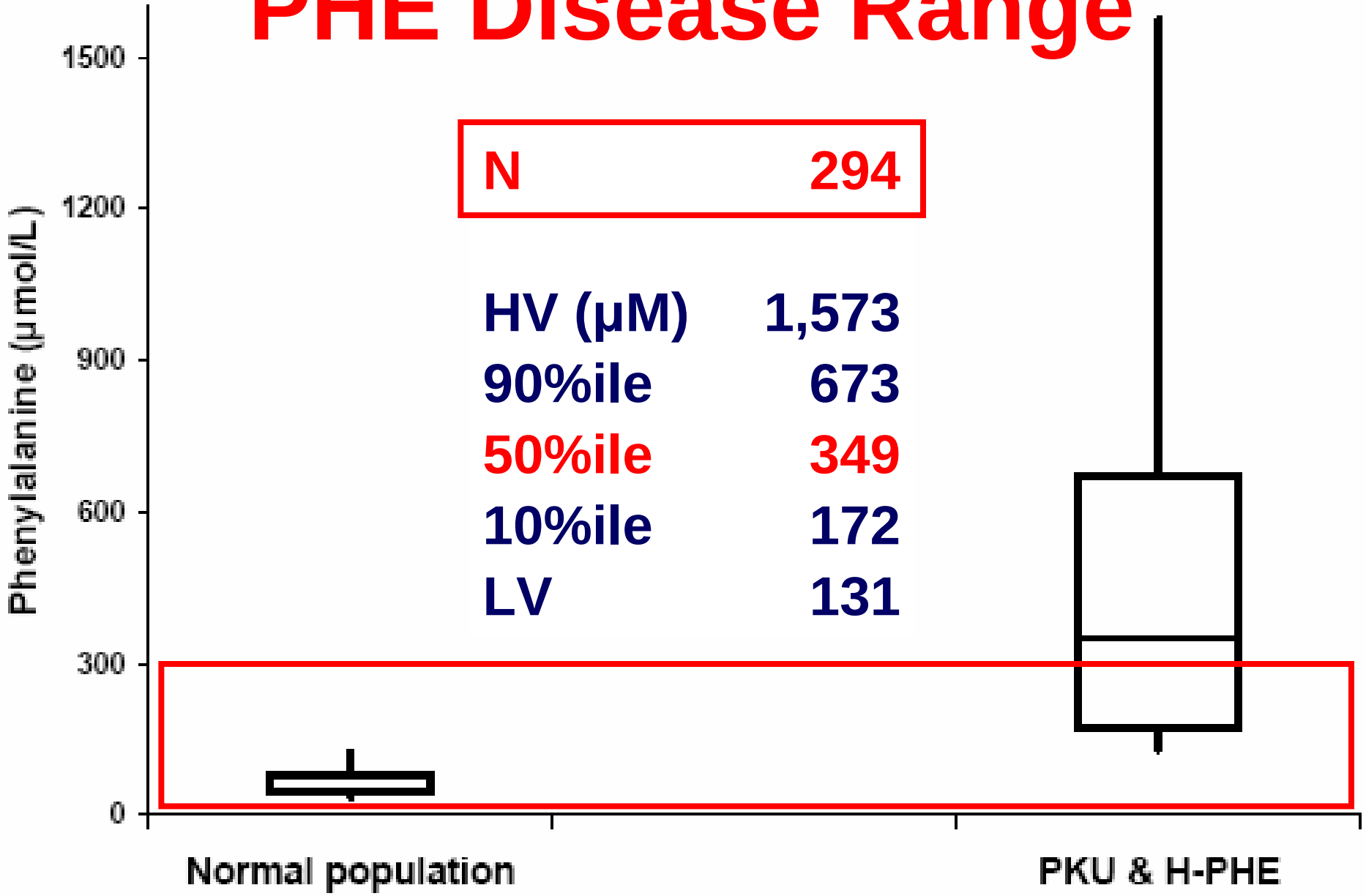
Region 4 - Laboratory Quality Improvement Project

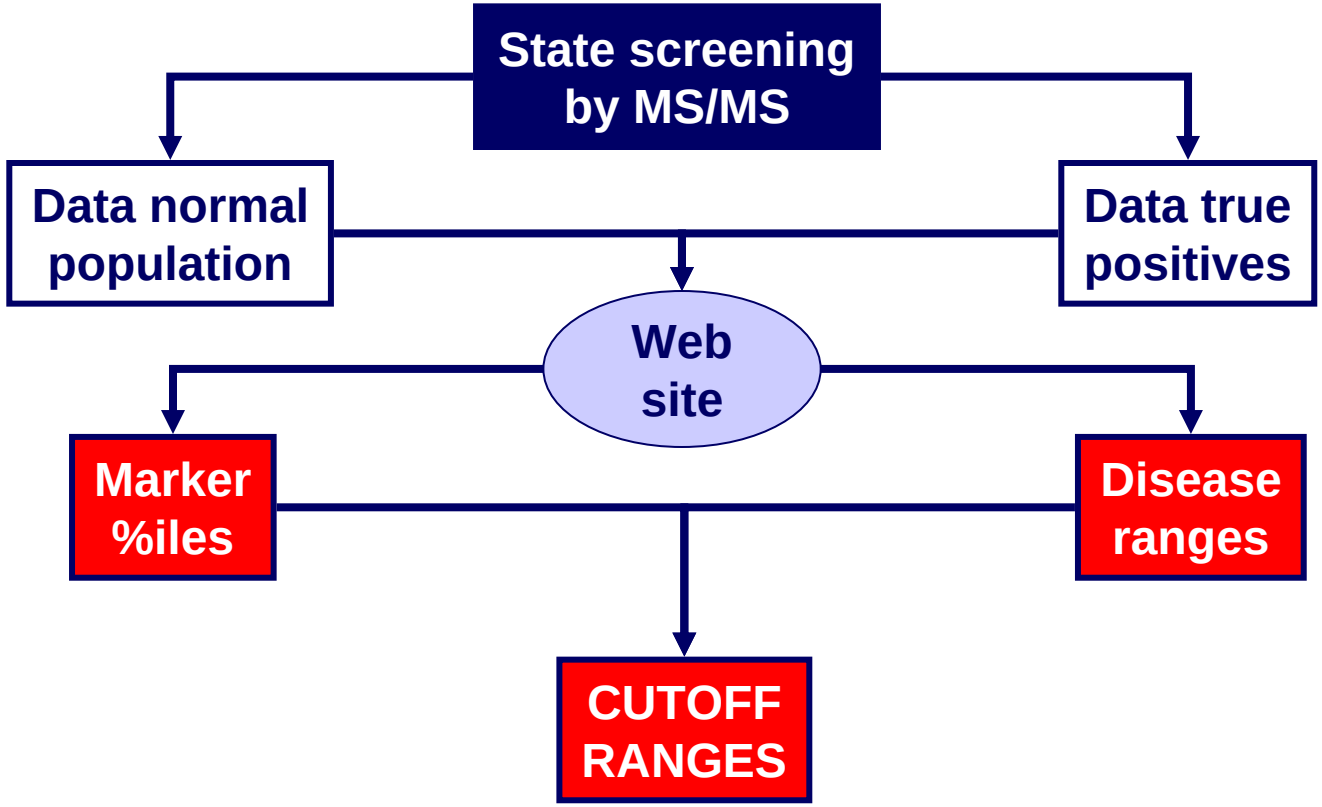
State/Lab	Minnesota	AMINO ACIDS							
Year	2005 (1-12)	Volume	99,525	FPR	0.08	PPV	41%	Detection Rate	1: 2,212

Updated	NORMAL POPULATION			CUT-OFF (CO)				TRUE POSITIVES									Tot. # cases	
01/26/06	Percentiles			(µM)	State	SD	Abn/		5%ile		Percentiles						1,345	
ANALYTE	50%	90%	99%	Value	%ile	OFF	10,000	N	<CO	LV	5%	10%	25%	50%	75%	90%	HV	Condition
GLY	184	319	514	700	99.80%	5.1	4.5	8		560	703	846	1,019	1,184	1,265	1,387	1,431	NKHG
								23	YES	100	190	199	313	385	472	638	1,029	MSUD
								30	YES	229	266	296	350	685	1,613	2,579	3,452	MSUD
								6		115	151	187	273	570	852	875	888	HCY
								3		112	114	115	120	128	161	181	194	H-MET
								27		97	121	133	207	300	521	683	1,263	CIT-I
								4		61	62	63	66	115	205	281	331	CIT-II
								14	YES	37	47	55	66	94	155	209	232	ASA
								181		145	242	267	325	426	554	812	2,080	PKU
								113		125	145	151	171	204	256	321	578	H-PHE
								10	YES	54	85	115	139	218	226	263	293	TYR-I
								4		220	249	364	430	627	627	949	1,164	TYR-II
ARG	5	9	18	50	99.94%	10.0	2.3	4		93	110	128	180	268	330	335	338	ARG
								10		2.1	3.0	3.9	4.9	5.6	8.3	10.7	25.9	ASA
ASA	0.06	0.13	0.24	0.40	99.85%	6.0	0.1	4		0.58	0.69	0.79	1.11	1.34	2.07	3.28	4.09	ASA

- **Number of cases (N)**
- **Lowest value (LV)**
- **Percentiles**
- **Highest value**

PHE Disease Range




State screening by MS/MS
Data normal population
Data true positives
Web site
Marker %iles
Disease ranges
CUTOFF RANGES

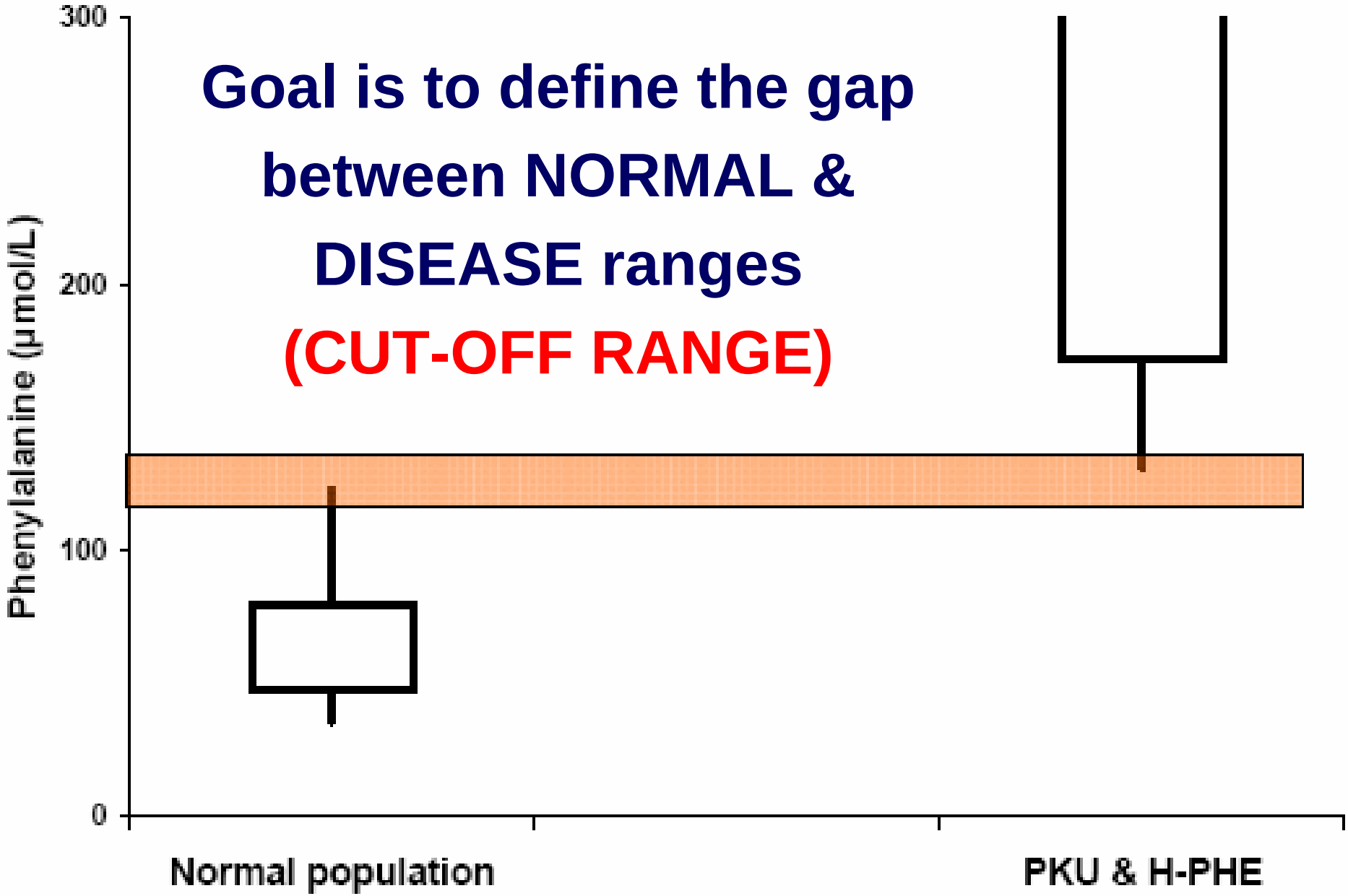
Selection of Cut-Off Value

- **Based on either fixed %ile or $(SD)_n$ above mean of NORMAL population**
- **Increases driven by false positives**
- **Decreases driven by false negatives (usually followed by scores of false positives)**
- **Disconnected from clinical significance**

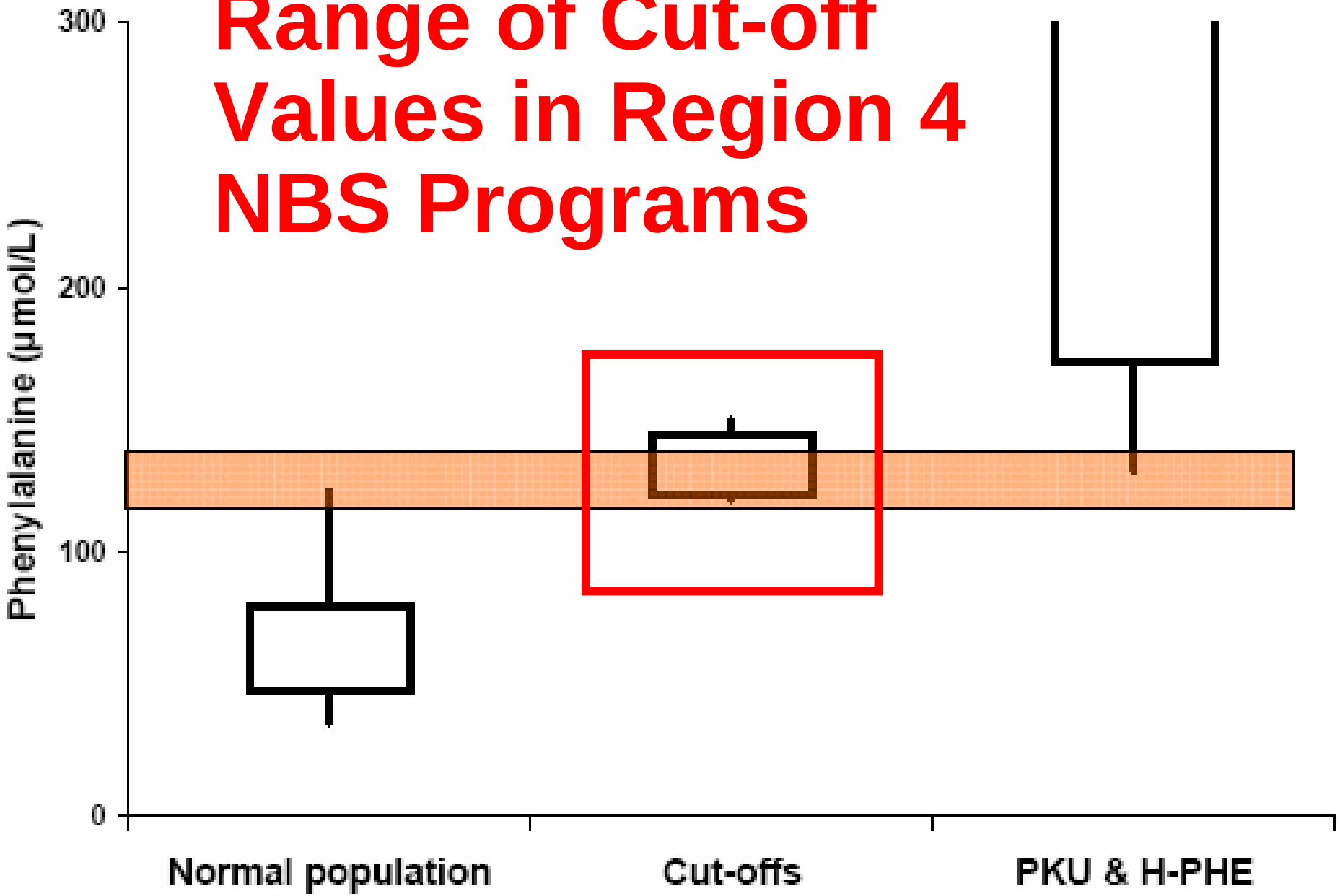
Cut-Off Values

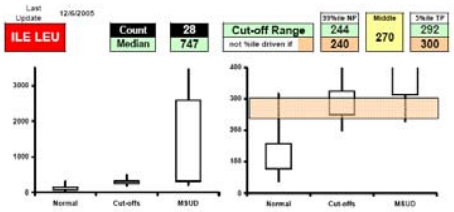
- Value
- State %ile
- SD off mean
- Repeats/10,000 cases (RAR)

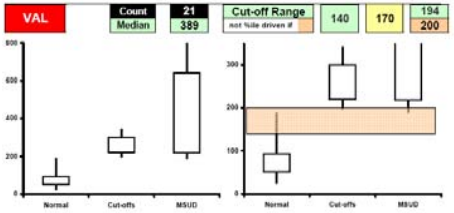
	CUT-OFF (CO) (μM) Value	State %ile	SD OFF	Abn/ 10,000
GLY	800	99.93%	6.4	2.5
VAL	250	99.94%	10.5	0.0
ILE/LEU	300	99.70%	4.9	3.1
(HCY) MET (HMET) MET	60	99.47%	3.5	4.2
(I) CIT (II) CIT (ASA) CIT	55	99.98%	11.9	0.3
(PKU) PHE (HPHE) PHE	130	99.53%	3.8	2.1
(I) TYR	150	96.82%	2.0	5.4
ARG (ASA) ARG	80	99.97%	20.0	3.4
ASA (CIT I) ASA	0.50	99.93%	6.7	0.1

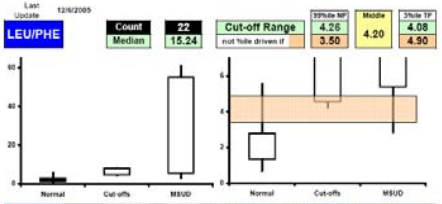

Goal is to define the gap between NORMAL & DISEASE ranges
(CUT-OFF RANGE)
300
200
100
0
Phenylalanine (µmol/L)
Normal population
PKU & H-PHE

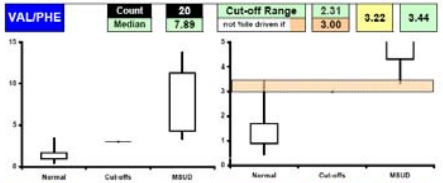
Range of Cut-off Values in Region 4 NBS Programs

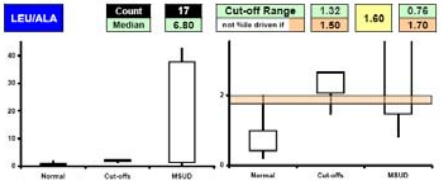


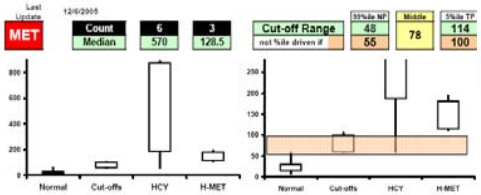

Last Update 12/6/2005
ILE LEU
Count 28
Median 747
Cut-off Range
not %ile driven if
99%ile NP 244
Middle 270
5%ile TP 292
240 300
Normal Cut-offs MSUD

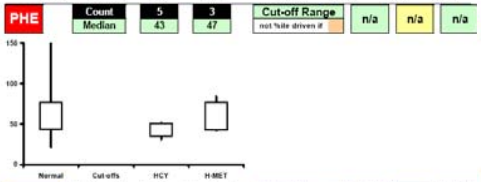

VAL
Count 21
Median 389
Cut-off Range
not %ile driven if
140 170 200
Normal Cut-offs MSUD

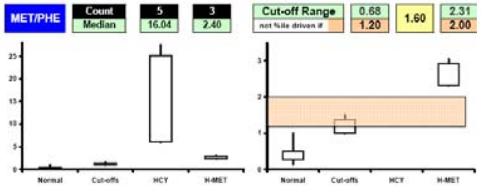

Last Update 12/6/2005
LEU/PHE
Count 22
Median 15.24
Cut-off Range
not %ile driven if
99%ile NP 4.26
Middle 4.20
5%ile TP 4.08
3.50 4.90
Normal Cut-offs MSUD

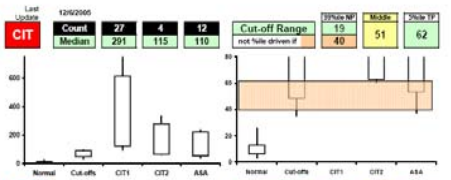

VAL/PHE
Count 20
Median 7.89
Cut-off Range
not %ile driven if
2.31 3.00 3.22 3.44
Normal Cut-offs MSUD

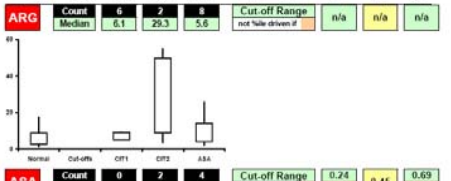

LEU/ALA
Count 17
Median 6.80
Cut-off Range
not %ile driven if
1.32 1.50 1.60 0.76 1.70
Normal Cut-offs MSUD

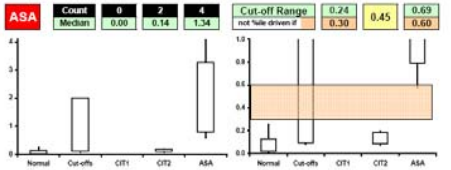

Last Update 12/6/2005
MET
Count 6
Median 570
3 128.5
Cut-off Range
not %ile driven if
99%ile NP 48
Middle 78
5%ile TP 114
55 100
Normal Cut-offs HCY H-MET

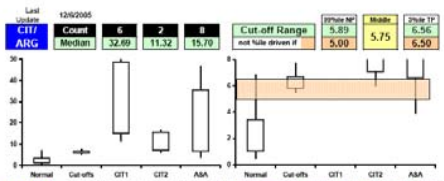

PHE
Count 5
Median 43
3 47
Cut-off Range
not %ile driven if
n/a n/a n/a
Normal Cut-offs HCY H-MET

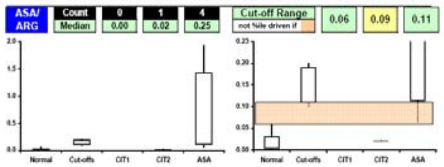

MET/PHE
Count 5
Median 16.04
3 2.40
Cut-off Range
not %ile driven if
0.68 1.20 1.60 2.31 2.00
Normal Cut-offs HCY H-MET

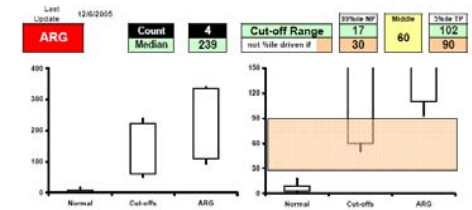

Last Update 12/6/2005
CIT
Count 27
Median 291
4 115
12 110
Cut-off Range
not %ile driven if
99%ile NP 19
Middle 40
5%ile TP 51 62
Normal Cut-offs CIT1 CIT2 ASA

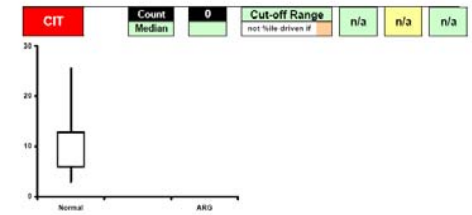

ARG
Count 6
Median 6.1
2 29.3
8 5.6
Cut-off Range
not %ile driven if
n/a n/a n/a
Normal Cut-offs CIT1 CIT2 ASA

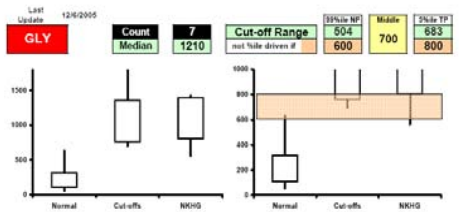

ASA
Count 0
Median 0.00
2 0.14
4 1.34
Cut-off Range
not %ile driven if
0.24 0.30 0.45 0.69 0.60
Normal Cut-offs CIT1 CIT2 ASA

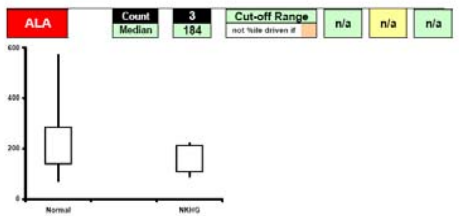

Last Update 12/6/2005
CIT/ ARG
Count 6
Median 32.69
2 11.32
8 15.70
Cut-off Range
not %ile driven if
99%ile NP 5.89
Middle 5.75
5%ile TP 6.56
5.00 6.50
Normal Cut-offs CIT1 CIT2 ASA

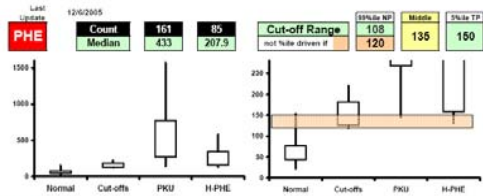

ASA/ ARG
Count 0
Median 0.00
1 0.02
4 0.25
Cut-off Range
not %ile driven if
0.06 0.09 0.11
Normal Cut-offs CIT1 CIT2 ASA

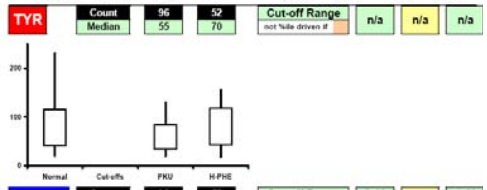

Last Update 12/6/2005
ARG
Count 4
Median 239
Cut-off Range
not %ile driven if
99%ile NP 17
Middle 30 60
5%ile TP 102
90
Normal Cut-offs ARG

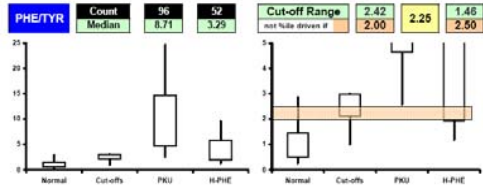

CIT
Count 0
Median
Cut-off Range
not %ile driven if
n/a n/a n/a
Normal ARG

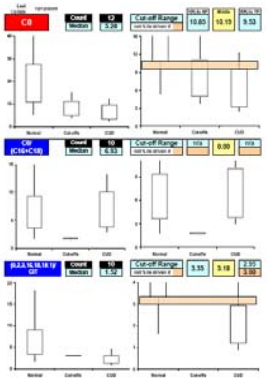
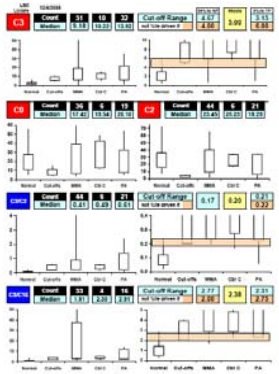
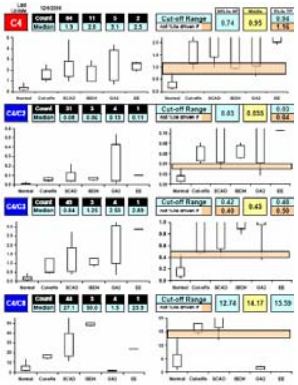
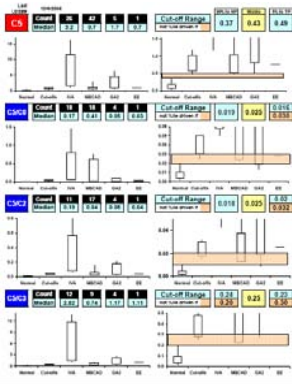
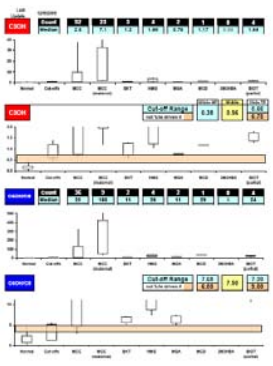
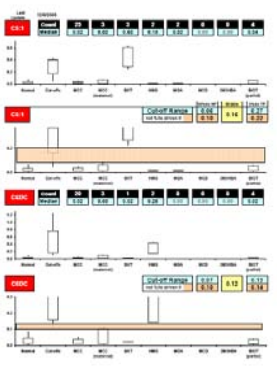
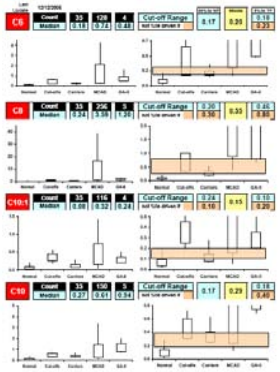
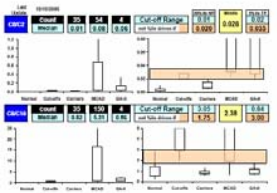
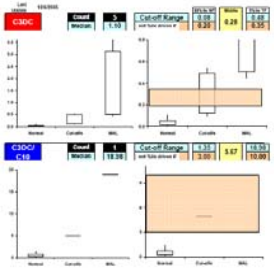
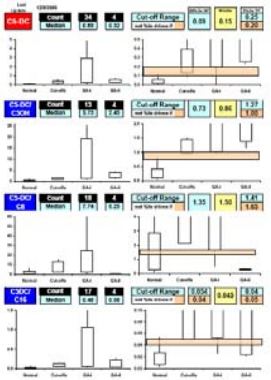
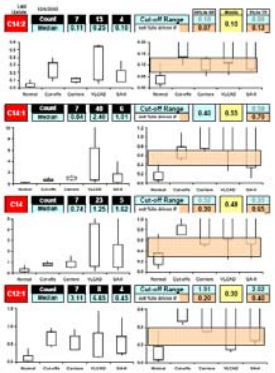
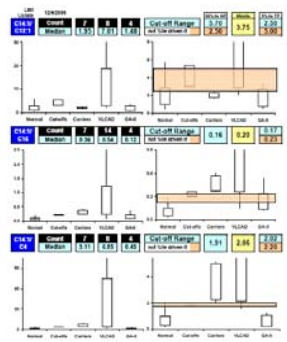
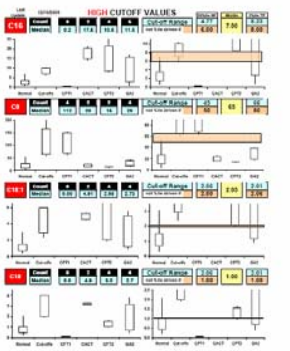
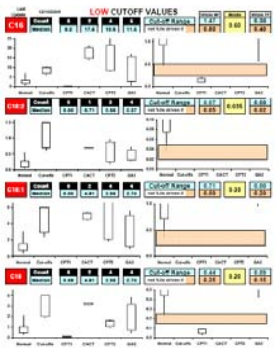
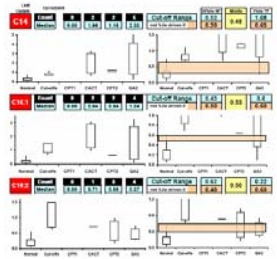
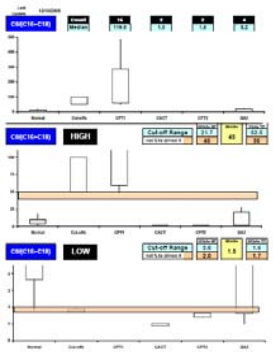
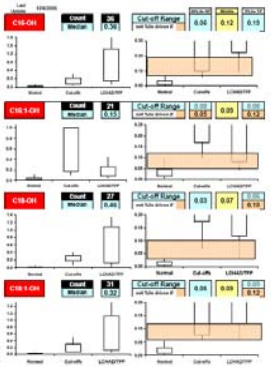
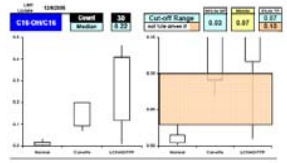

Last Update 12/6/2005
GLY
Count 7
Median 1210
Cut-off Range
not %ile driven if
99%ile NP 504
Middle 700
5%ile TP 683
600 800
Normal Cut-offs NKHG

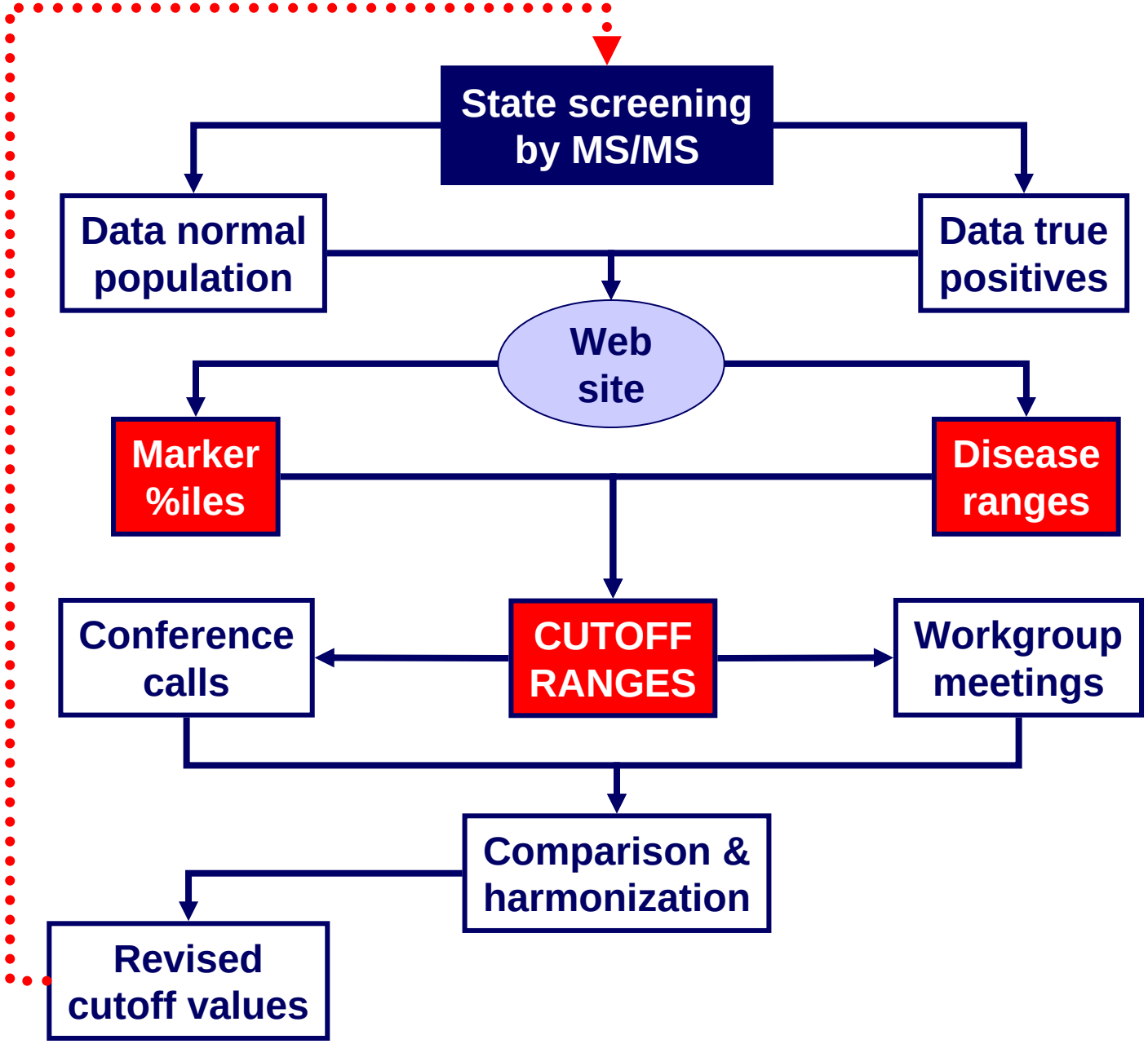

ALA
Count 3
Median 184
Cut-off Range
not %ile driven if
n/a n/a n/a
Normal NKHG


Last Update 12/6/2005
PHE
Count 161
Median 433
85 207.9
Cut-off Range
not %ile driven if
99%ile NP 108
Middle 120 135
5%ile TP 150
Normal Cut-offs PKU H-PHE

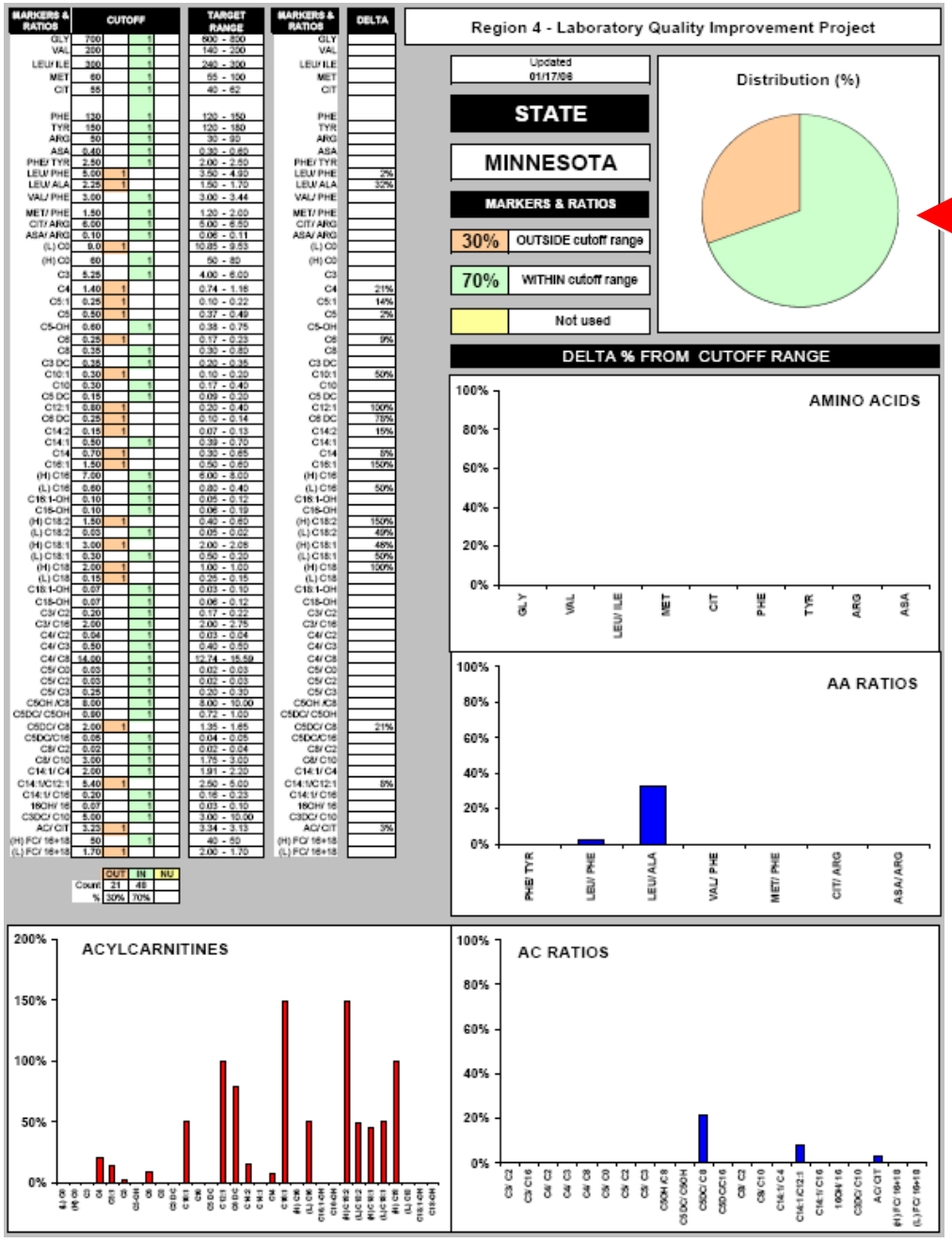

TYR
Count 96
Median 55
52 70
Cut-off Range
not %ile driven if
n/a n/a n/a
Normal Cut-offs PKU H-PHE


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
Data normal population
Data true positives
Web site
Marker %iles
Disease ranges
Conference calls
CUTOFF RANGES
Workgroup meetings
Comparison & harmonization
Revised cutoff values

MS/MS “Quality” Report Card

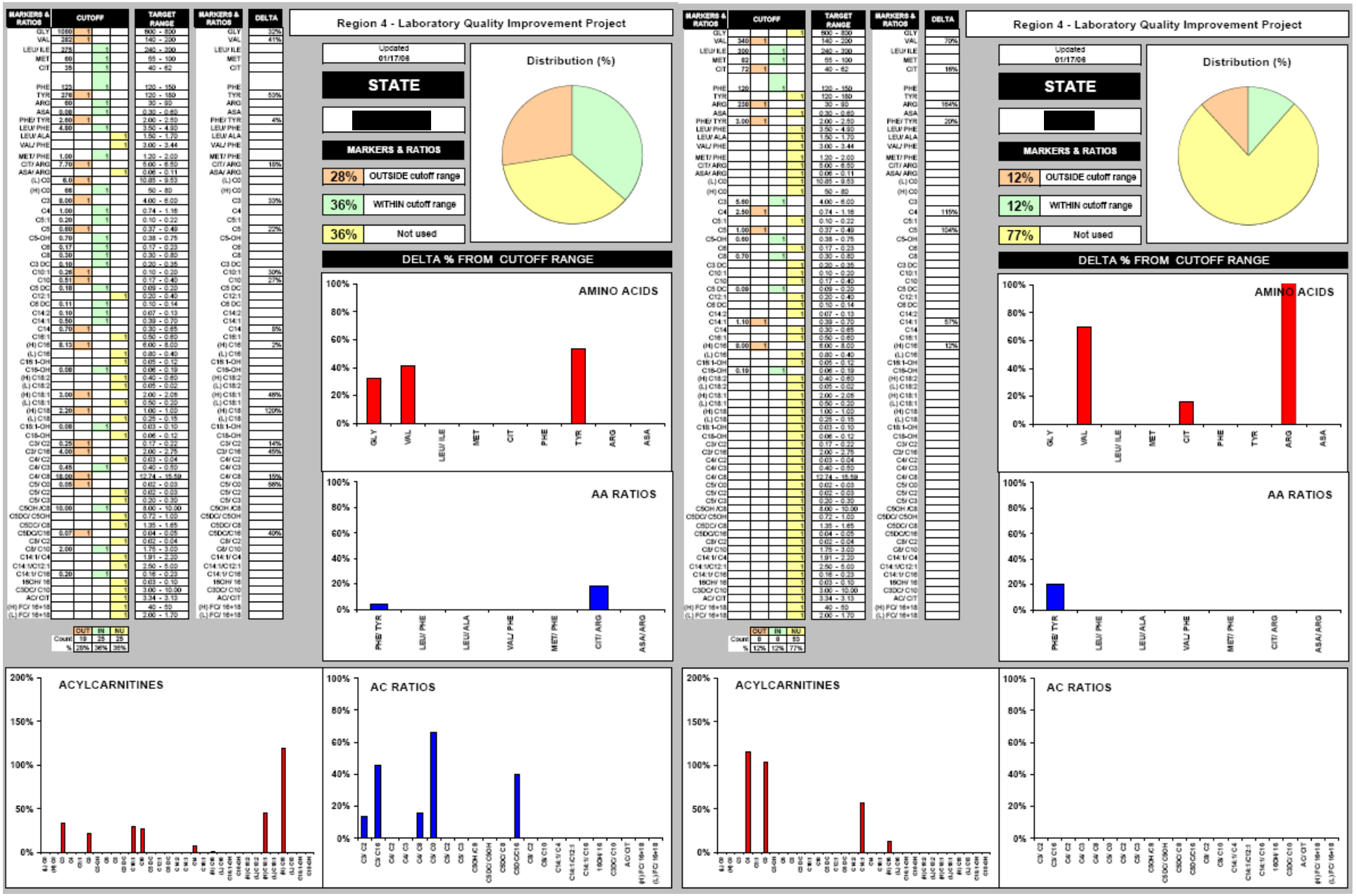


Cutoff OUTSIDE target range

Cutoff WITHIN target range

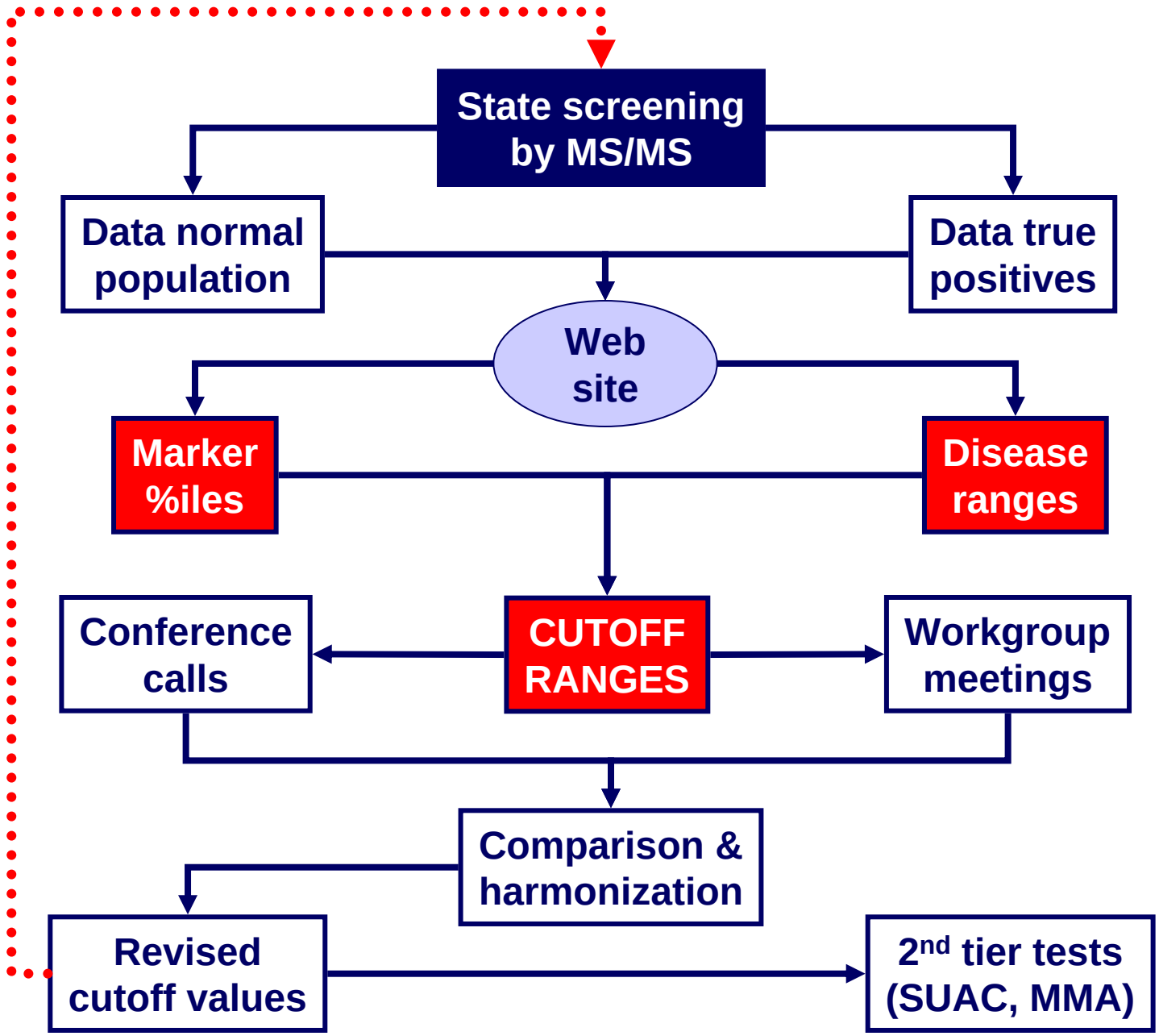
Parameter NOT USED

MS/MS “Quality” Report Card



Status of Cutoff Ranges (as 01/31/06, N=69)

Region 4	Median	Range
Adequate	29%	12% - 71%
Not adequate	34%	12% - 58%
Not used	41%	0% - 77%


State screening by MS/MS
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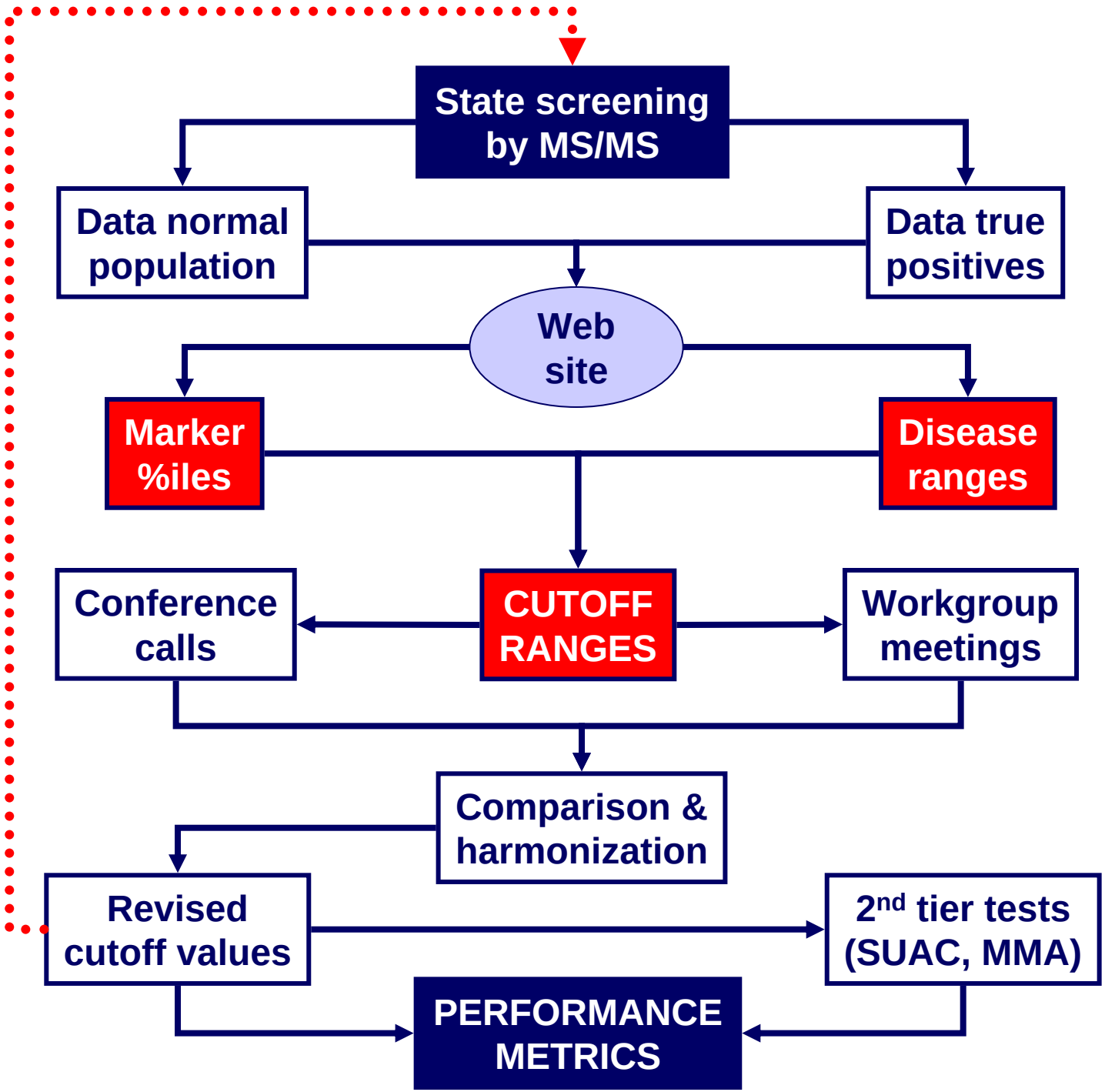
Revised cutoff values
2nd tier tests (SUAC, MMA)

Implementation of 2nd Tier Tests (as 02/11/06)

Region 4	SUAC	MMA	HCY	CAH
Illinois	(*)	-	-	-
Indiana	-	-	-	-
Kentucky	+	+	+	+
Michigan	+	(±)	-	(+)
Minnesota	+	+	+	+
Ohio	+	-	-	-
Wisconsin	-	-	-	-
Other states	(+)	(±)	(±)	+

(*) in house; (±) sporadic use; (+) under implementation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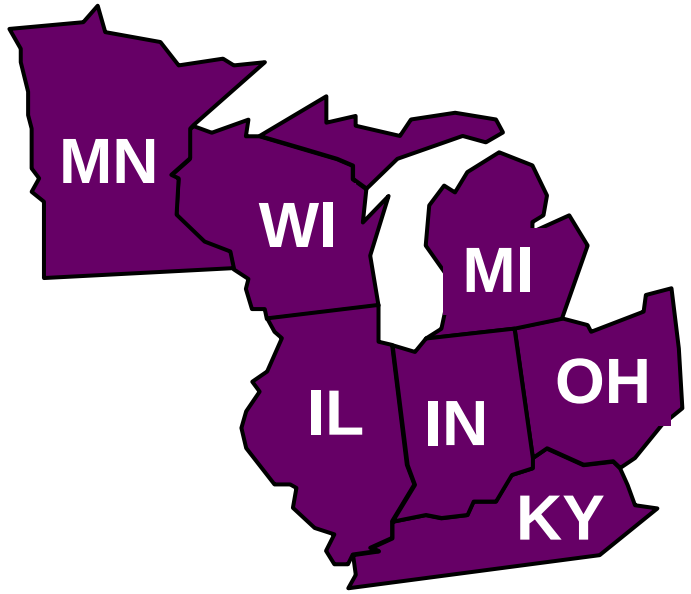
2nd tier tests (SUAC, MMA)
PERFORMANCE METRICS

Region 4 Collaborative Project: Performance TARGETS



Is this a true measure of SUCCESS?

FPR <0.30%

PPV >20%

Detect. rate <1:3,000

“Defining your criteria for success is easier when you suck. As you get better, it becomes harder. The steps are smaller.”

Bode Miller

***Newsweek*, January 23, 2006 (p. 44)**