

## Region 4 Genetics Collaborative Project: Laboratory Quality Improvement of Newborn Screening by MS/MS

Piero Rinaldo, MD, PhD  
Professor of Laboratory Medicine  
T. Denny Sanford Professor of Pediatrics  
Mayo Clinic College of Medicine, Rochester (MN)



MSGRCC (Region 6) 2007 Annual Meeting  
Denver (CO), July 13, 2007

## Objectives

- Understand the criteria for **participation** and **deliverables** of the laboratory quality improvement collaborative project (newborn screening by MS/MS)
- Appreciate the proposed process for an objective definition of cutoff target ranges
- Recognize informative performance metrics and learn how to apply them in clinical practice

## A Regional Approach to Improve the Health of Children and Families with Heritable Disorders in Region 4

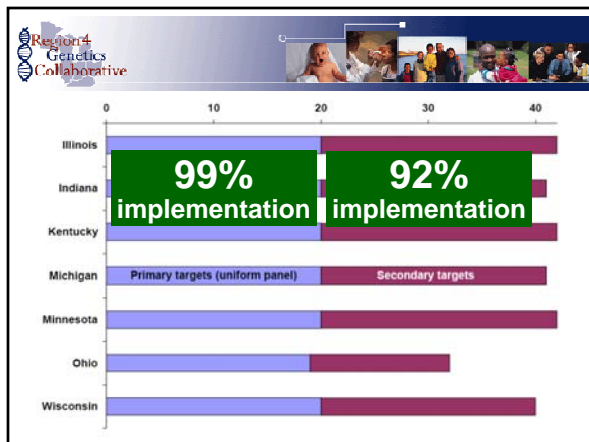


Region4  
Genetics  
Collaborative



## 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

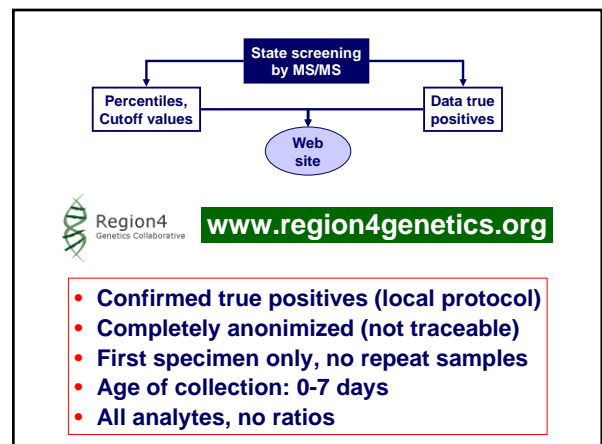
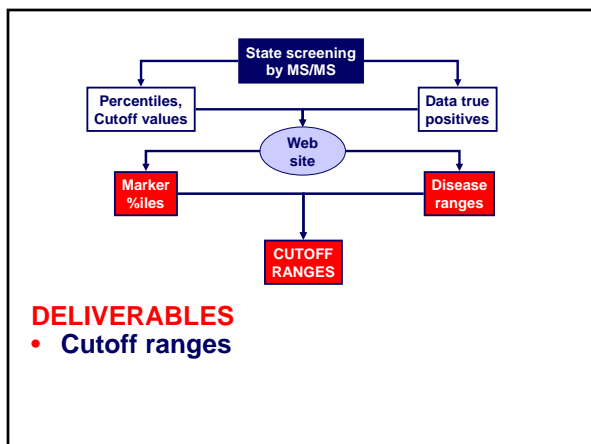
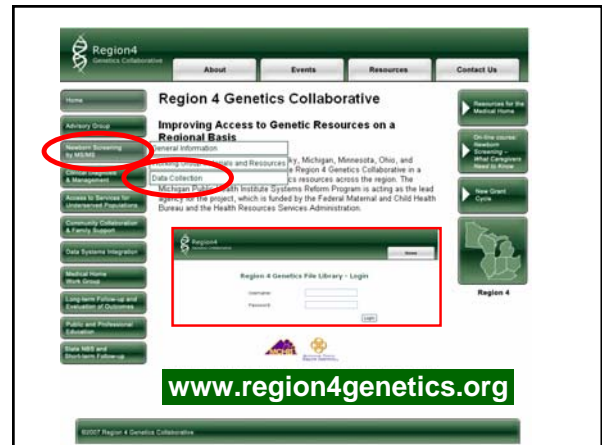
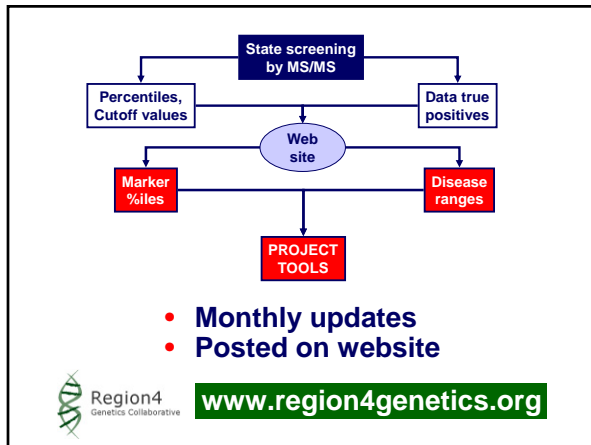
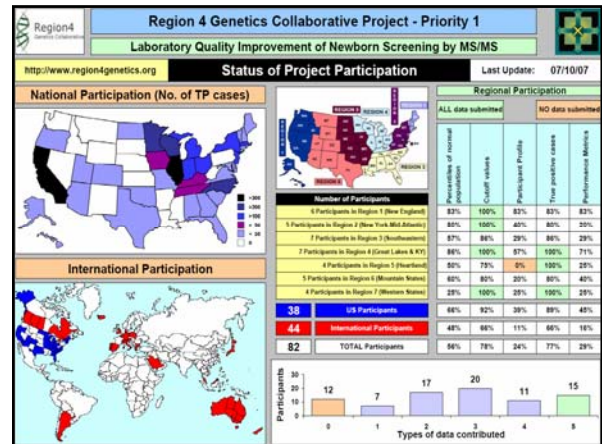


## Regional 4 Collaborative Project

- Project is based on active participation of NBS labs
- Standardized collection of NBS data (MS/MS only)
- Data collected
  - %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)

# 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



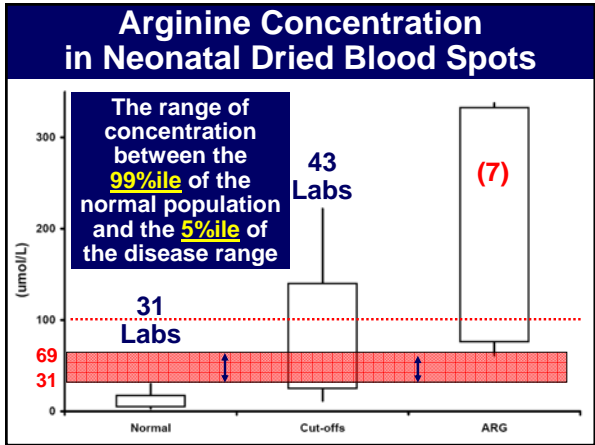
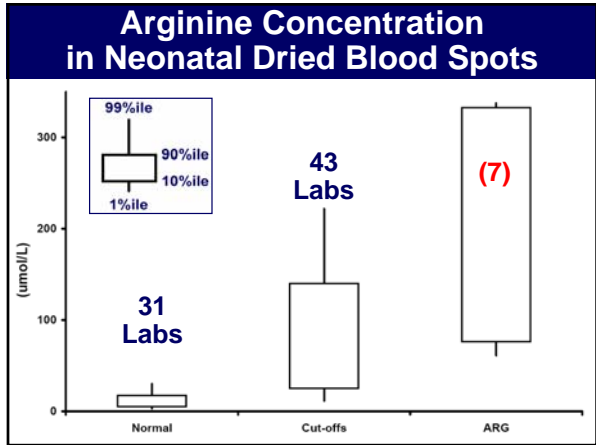
### Project in Numbers

	Dec-06	Jul-07	Delta
US participants	30	38	27%
Internat. participants (countries)	28 (16)	44 (25)	25% (57%)
True positive cases	2,950	4,142	40%
Collected data points			
True positive analytes & ratios	149,948	179,340	20%
Informative markers	8,676	12,830	48%
Percentiles (contributors)	3,756 (19)	8,279 (40)	120% (110%)
Cutoff values (contributors)	1,493 (35)	2,450 (59)	57% (63%)
<b>Conditions with &gt;50 cases</b>			
Uniform panel	14/20	14/20	0% (2>40)
Secondary targets	3/22	4/22	0% (3>40)

### Cutoff Target Ranges (AA)

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

State/Lab	Minnesota		MI		AMINO ACIDS										Tot. # cases									
	Normal	Cutoff	Normal	Cutoff	ANALYTE	Normal Population	99%ile	90%ile	10%ile	1%ile	CUMULATIVE Percentile (µM)	CUMULATIVE Percentile (µM)	CO RANGE	TRUE POSITIVES (DISEASE RANGE, DB)		CO RANGE	TRUE POSITIVES (DISEASE RANGE, DB)							
ANALYTE	28	217	250	382	330	340	750	23	104	721	949	1050	1045	500 - 700	23	204	440	540	580	969	1,107	1,201	1,410	Condition
GLY	23	30	70	101	141	160	200	44	100	274	300	370	477	177 - 390	43	60	171	271	281	347	450	620	1,047	MSUD
VAL	27	80	90	120	177	247	300	50	170	270	300	350	347	160	107	207	303	307	407	494	1,230	1,947	5,442	MSUD
ILE/LEU	27	12	16	23	34	47	60	55	30	51	66	90	119	47 - 62	20	30	60	94	110	130	200	347	507	HCT
MET	27	12	16	23	34	47	60	55	30	51	66	90	119	47 - 62	20	30	60	94	110	130	200	347	507	H-MET
CIT	28	6	8	12	16	20	25	55	20	30	40	70	110	30 - 40	70	30	60	100	100	201	310	440	2,740	CIT-A
															20	10	20	37	51	112	241	302	302	CIT-B
															30	20	34	44	60	97	140	211	250	ASA
PHE	29	33	41	62	70	88	130	50	84	120	133	150	240	80 - 132	630	100	240	271	300	424	570	704	1,046	PKU
															300	110	132	160	177	221	270	331	362	H-PHE
TYR	28	30	40	77	120	160	150	54	110	200	301	400	447	120 - 150	40	50	100	121	140	200	204	300	440	TPR
															10	11	214	273	400	530	600	1,020	1,147	TPR-B
ARG	25	3	5	8	11	17	21	30	43	51	70	90	121	31 - 40	7	44	69	90	100	181	200	300	340	ARG
															27	4	7	8	10	31	40	67	102	CIT-C
ASA	14	0.10	0.10	0.20	0.40	0.74	0.40	0.0	0.00	0.00	1.04	1.00	1.00	0.00 - 0.00	13	0.00	0.41	0.72	1.00	4.00	1.20	10.20	100.00	ASA

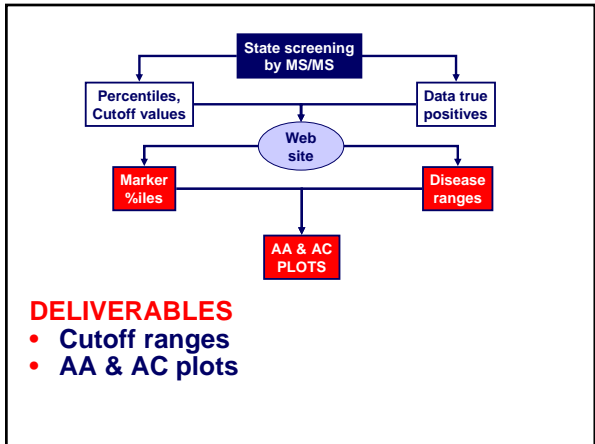


### AA Ratios (7)

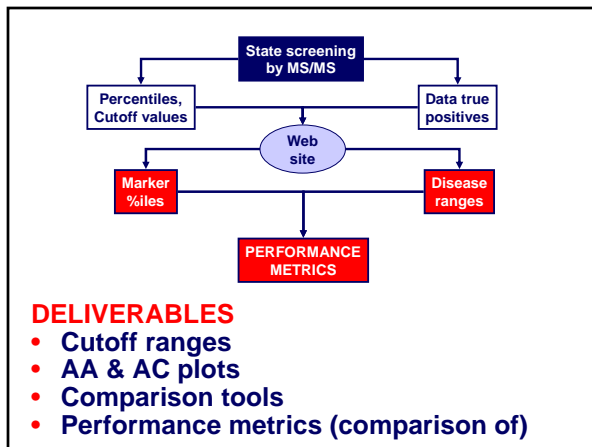
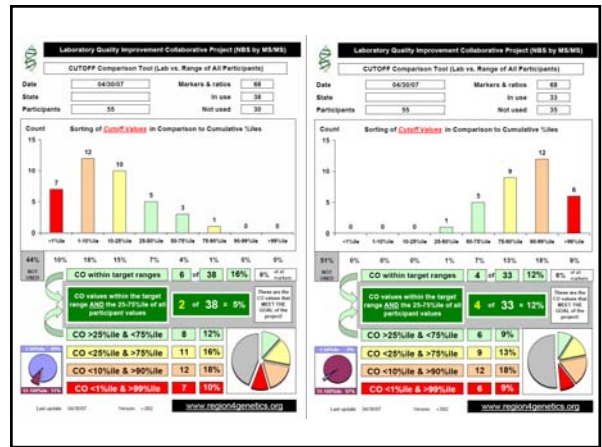
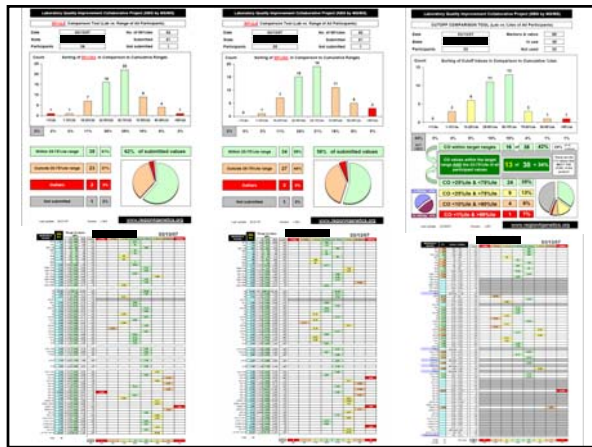
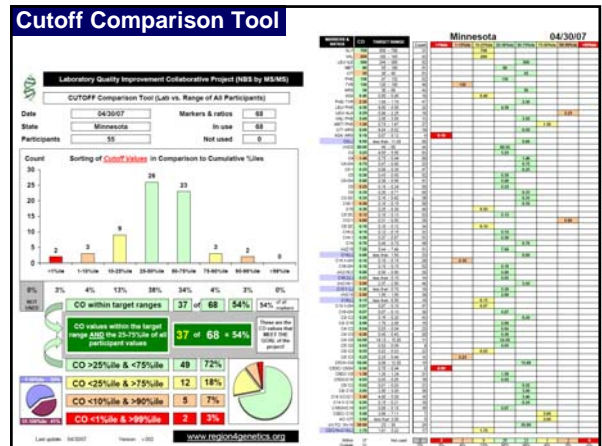
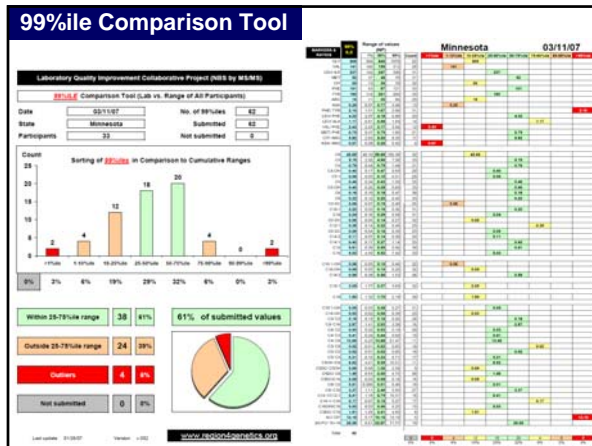
AA (9)

AC (27)

AC Ratios (21)







## Region 4 Collaborative Project: Performance TARGETS

False positive rate	<0.30%
Pos. predict. value	>20%
Detection rate	<1:3,000

MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES  
RESEARCH REVIEW 13, 201-207 (2008)

**MAKING THE CASE FOR OBJECTIVE PERFORMANCE METRICS IN NEWBORN SCREENING BY TANDEM MASS SPECTROMETRY**

Piero Risoldi,<sup>1</sup> Saba Zafari, Silvia Torronelli, and Dietrich Mann  
Biomedical Genetic Laboratory, Division of Laboratory Genetics, Department of Laboratory Medicine,<sup>1</sup> Mount Zion College of Medicine, Biotech Research

**DETECTION RATE**  
The detection rate of a newborn screening program is expressed as the number of neonates that on average needs to be tested to detect one affected patient.

**FALSE POSITIVE RATE**  
The false positive rate of a newborn screening program is expressed as the proportion of positive tests in subjects proven by follow up evaluation not to have one of the conditions targeted by a given screening program

**POSITIVE PREDICTIVE VALUE**  
The positive predictive value of a test is the probability that the patient has the disease when restricted to those patients who test positive

The number of tandem screening programs to include results...  
1,000 g/L in different conditions. The use of tandem screening by MS/MS has a sensitivity greater than the tandem...  
The false positive rate of a given screening program is expressed as the proportion of positive tests in subjects proven by follow up evaluation not to have one of the conditions targeted by a given screening program...  
The positive predictive value of a test is the probability that the patient has the disease when restricted to those patients who test positive...  
All diagnostic programs...  
The link between...  
The number of tandem screening programs to include results...  
1,000 g/L in different conditions. The use of tandem screening by MS/MS has a sensitivity greater than the tandem...  
The false positive rate of a given screening program is expressed as the proportion of positive tests in subjects proven by follow up evaluation not to have one of the conditions targeted by a given screening program...  
The positive predictive value of a test is the probability that the patient has the disease when restricted to those patients who test positive...

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

**PERFORMANCE METRICS**

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

STATUS

	Affected	Not affected	TOTAL
POSITIVE	0	0	0
NEGATIVE	0	0	0
TOTAL	0	0	0 Population

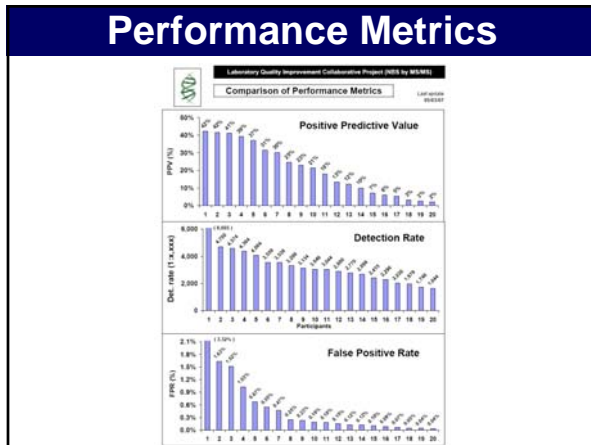
www.region4genetics.org

	A	B	TP	FP
C	D	FN	TN	

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



- Conclusions**
- The number of participants continues to grow (82), strong international component
  - Collection of data is progressing faster than