Analysis of False Positive and False Negative MSUD cases: Using Age Specific Cutoffs to Reduce Both

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Michigan Department of Community Health

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SHORT REPORT

Newborn screening may fail to identify intermediate forms of maple syrup urine disease

K. Bhattacharya · V. Khalili · V. Wiley · K. Carpenter · B. Wilcken

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Maple syrup urine disease: Further evidence that newborn screening may fail to identify variant forms

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Molecular Genetics and Metabolism Reports 1 (2014)

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ELSEVIER

MGM Reports

Case Report

Newborn screening for dihydrolipoamide dehydrogenase deficiency: Citrulline as a useful analyte

Shane C. Quinonez [a,*,1], Andrea H. Seeley [a,1], Mary Seeterlin [b], Eleanor Stanley [b], Ayesha Ahmad [a]

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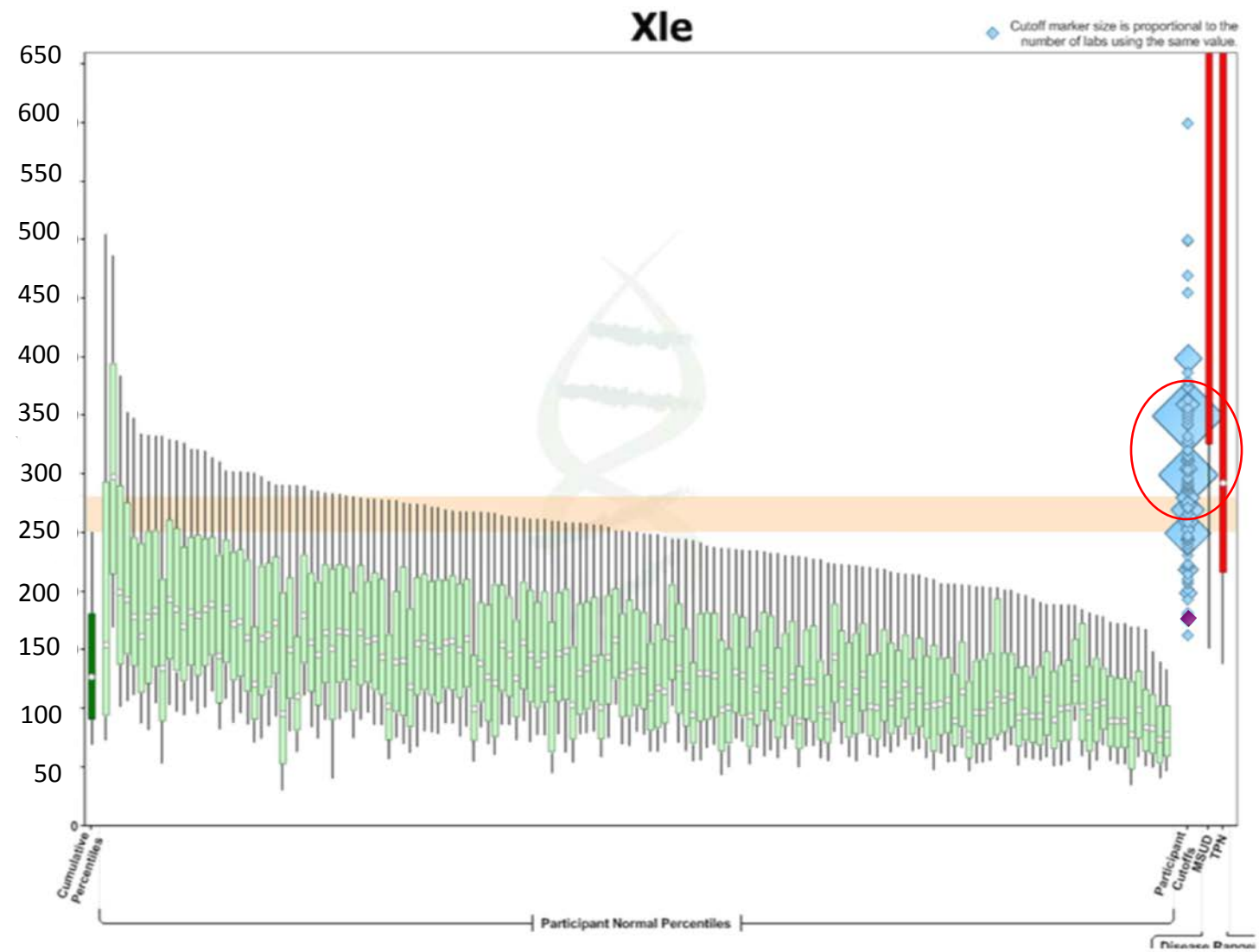
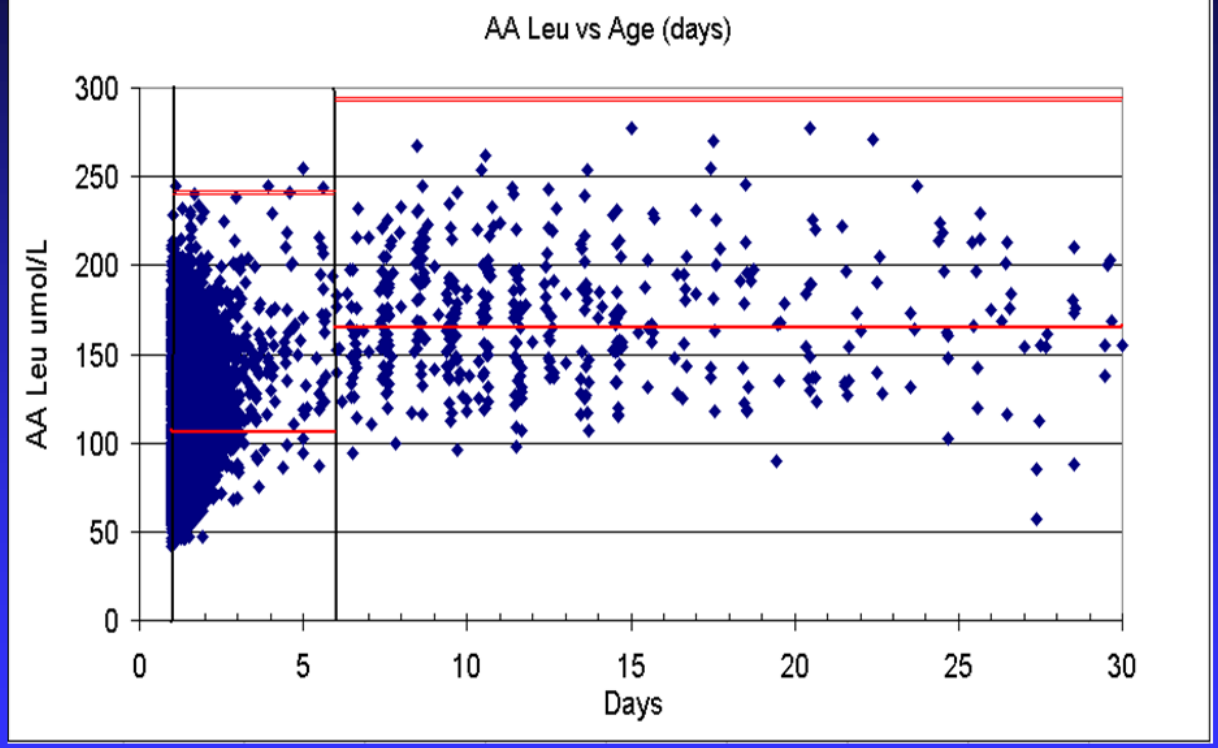

Xle
Cutoff marker size is proportional to the number of labs using the same value.
650
600
550
500
450
400
350
300
250
200
150
100
50
0
Cumulative Percentiles
Participant Normal Percentiles
Participant Cutoffs
MSUD
TPN
© 2004-2014 Region 4 Genetics Collaborative

2005 APHL Presentation

Age-Related Cutoffs for Newborn Screening by Tandem Mass Spectrometry

Leucine



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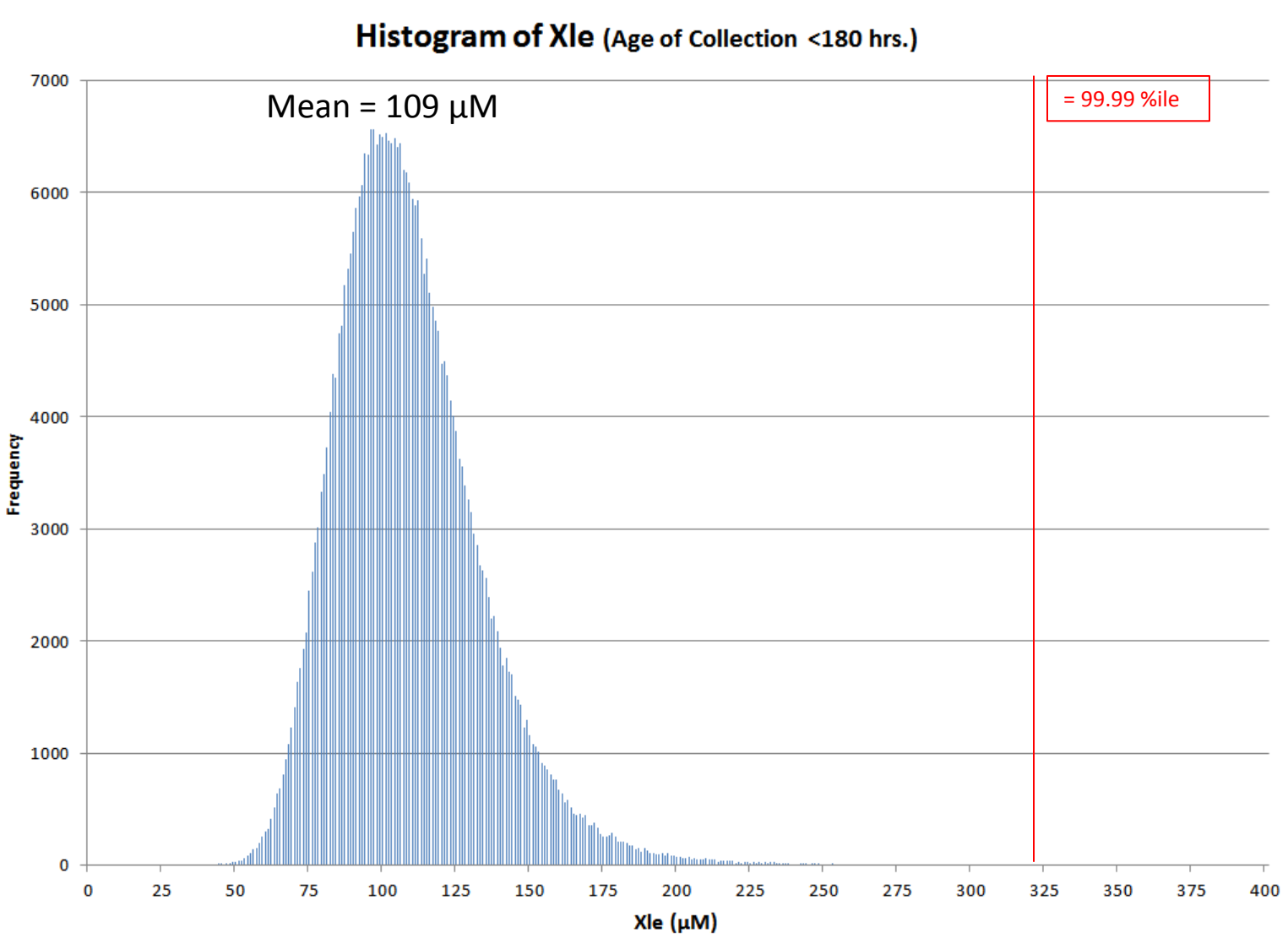
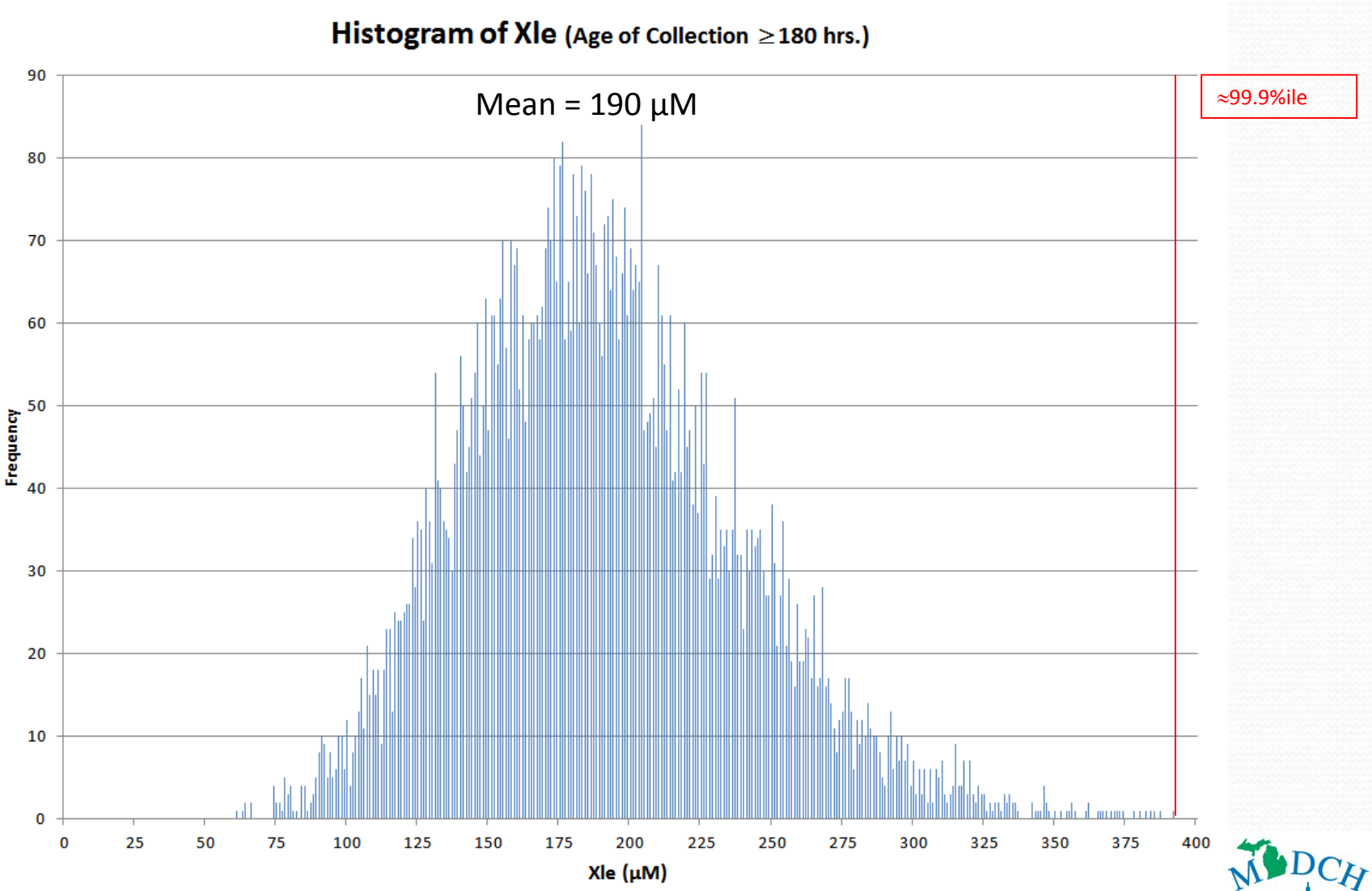


Data analyzed: N>350,000 specimens, No NICU, No TPN, Feb. 2011 - Aug. 2014



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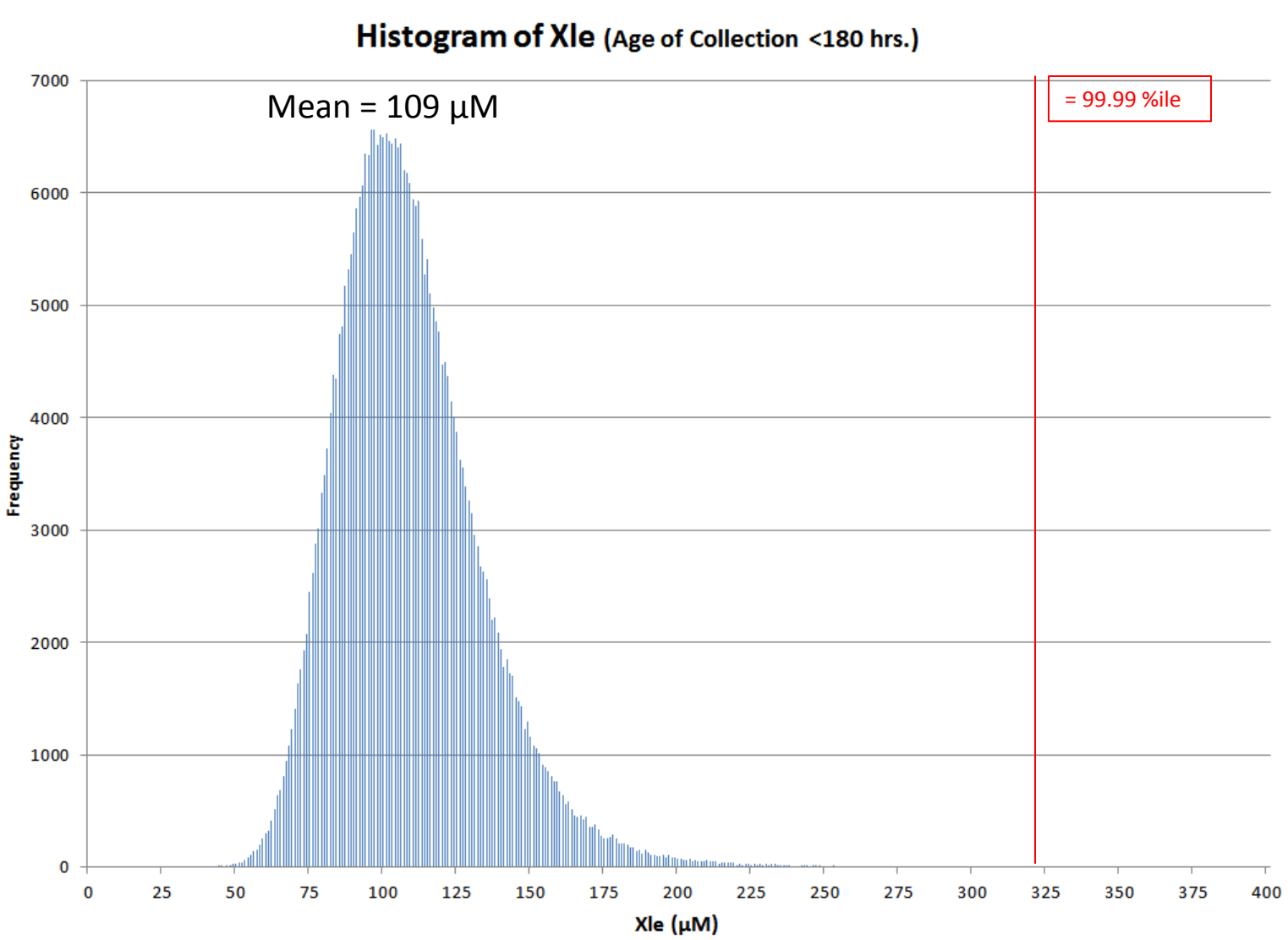
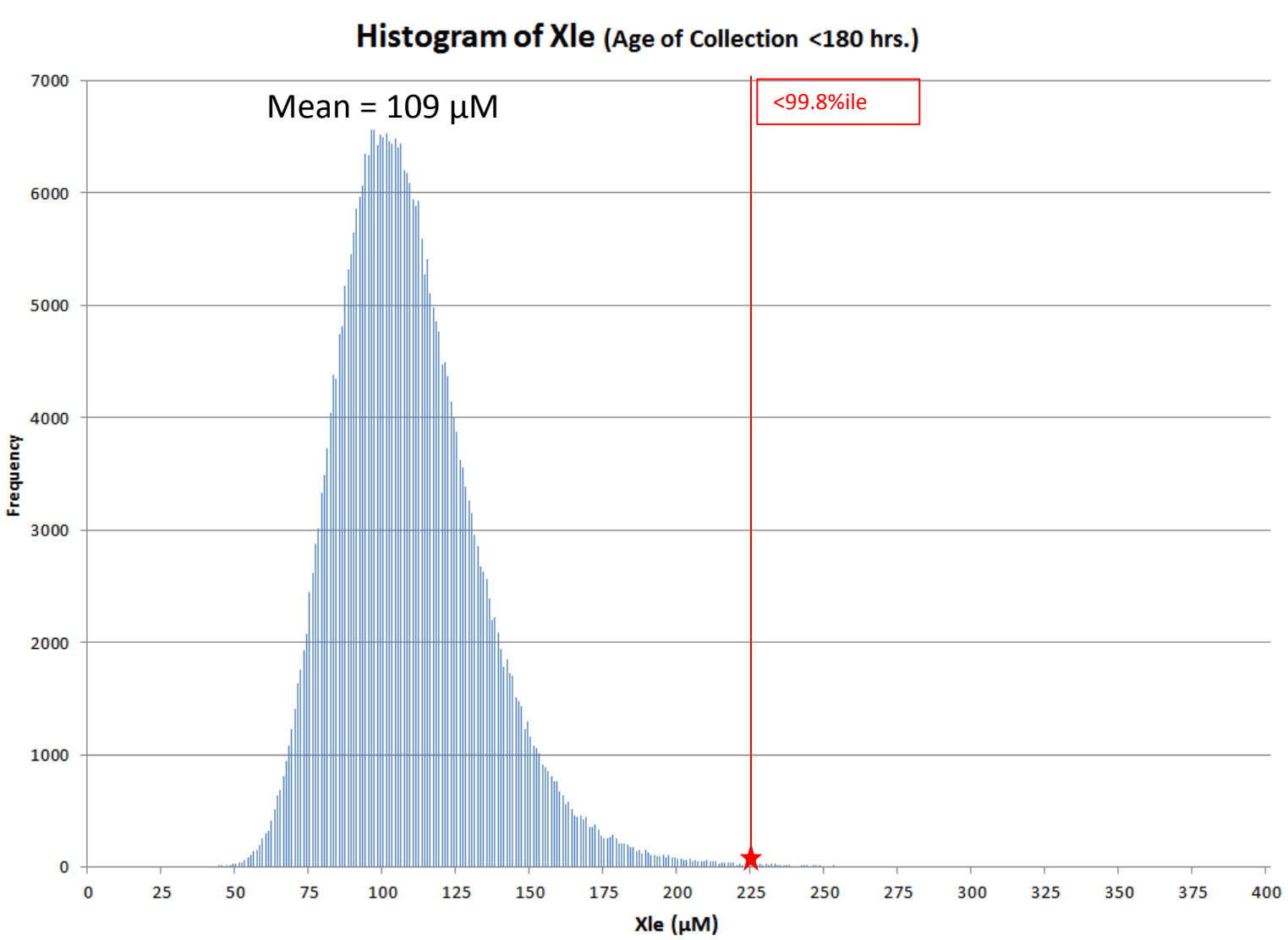
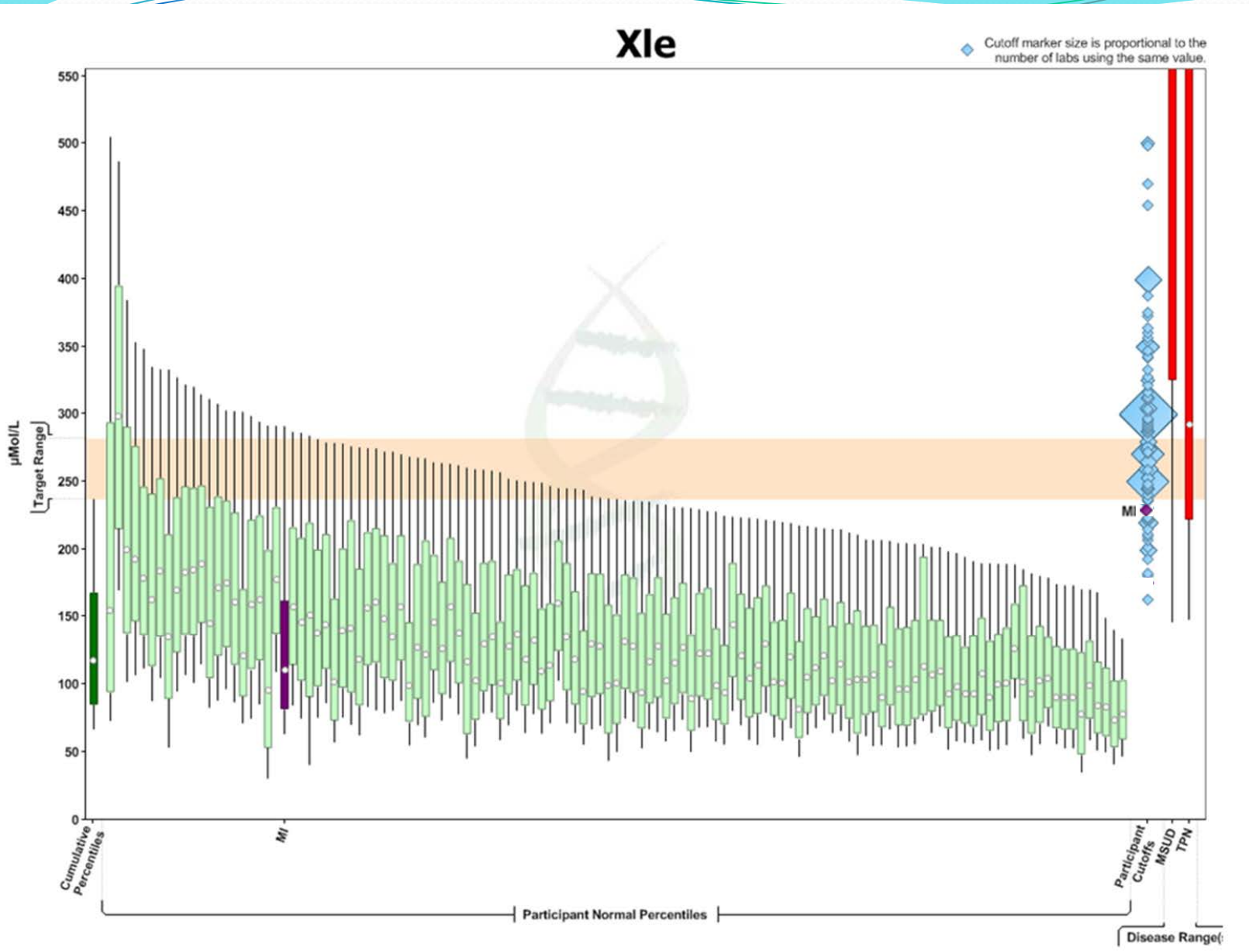

Histogram of Xle (Age of Collection <180 hrs.)
Mean = 109 µM
= 99.99 %ile
Frequency
7000
6000
5000
4000
3000
2000
1000
0
0
25
50
75
100
125
150
175
200
225
250
275
300
325
350
375
400
Xle (µM)


Histogram of Xle (Age of Collection <180 hrs.)
Mean = 109 µM
<99.8%ile
Frequency
7000
6000
5000
4000
3000
2000
1000
0
0
25
50
75
100
125
150
175
200
225
250
275
300
325
350
375
400
Xle (µM)



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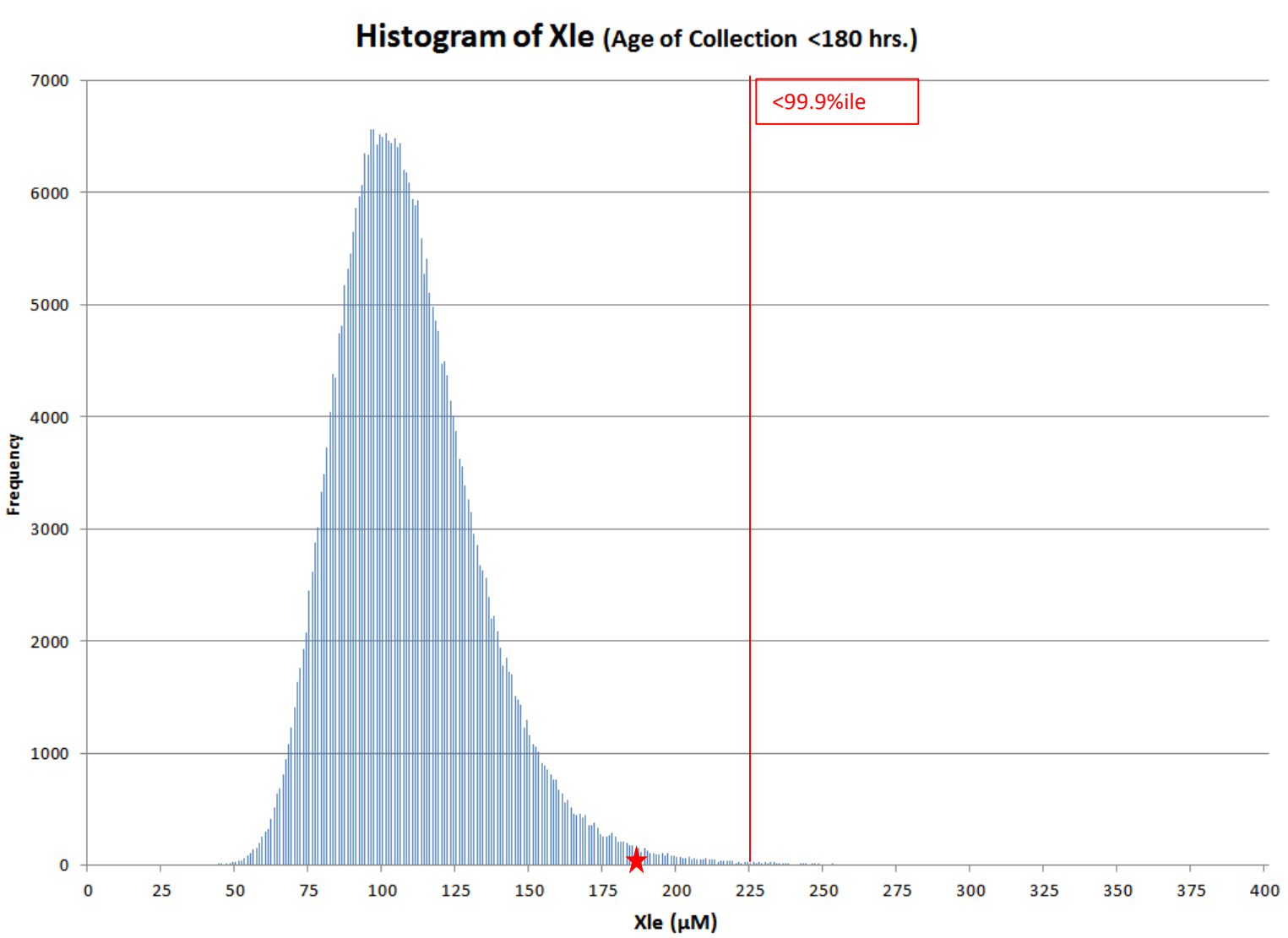
MSUD False Negative Case

Sample #	Age (hrs.)	Leu (µM)	Leu/Phe
1	24	184	4.8
2	611	390	9.7


Histogram of Xle (Age of Collection <180 hrs.)
<99.9%ile
Frequency
7000
6000
5000
4000
3000
2000
1000
0
0
25
50
75
100
125
150
175
200
225
250
275
300
325
350
375
400
Xle (µM)

MSUD False Positives (2007-2011)

Age (hrs.)
179
180
56
33
155
234
201
101
288
135
155
280
144
130
79
103

Note: 14/16 Age>72 hrs.

Xle vs. Age of Collection - Data

Age Range (hrs.)	Number of samples	% of samples	Xle Average (µM)	SD	99.0% ile
0-24	77855	24.1	106	23	173
25-47	232522	72.1	106	24	179
48-71	1766	0.5	128	33	229
72-95	520	0.16	154	42	277
96-119	656	0.20	176	47	320
120-143	775	0.24	185	47	325
144-167	833	0.26	190	47	321
168-191	762	0.24	193	46	327
192-215	558	0.17	192	46	316
216-239	415	0.13	193	46	331
240-263	371	0.12	193	50	320
264-287	317	0.10	191	47	311
288-311	304	0.09	196	47	308
312-336	299	0.09	199	46	314

Data analyzed: N>350,000 specimens, No NICU, No TPN, Feb. 2011 - April. 2014

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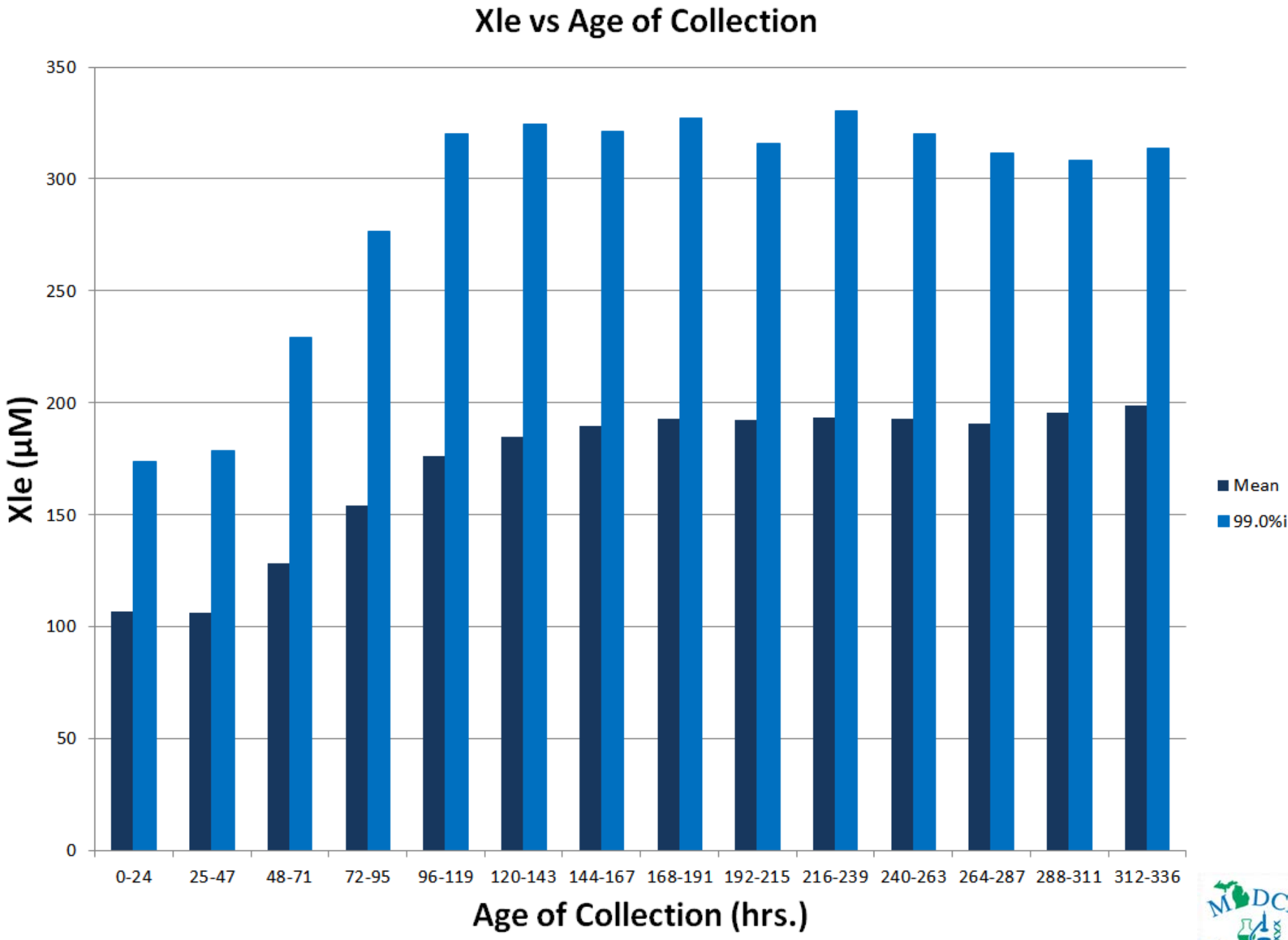
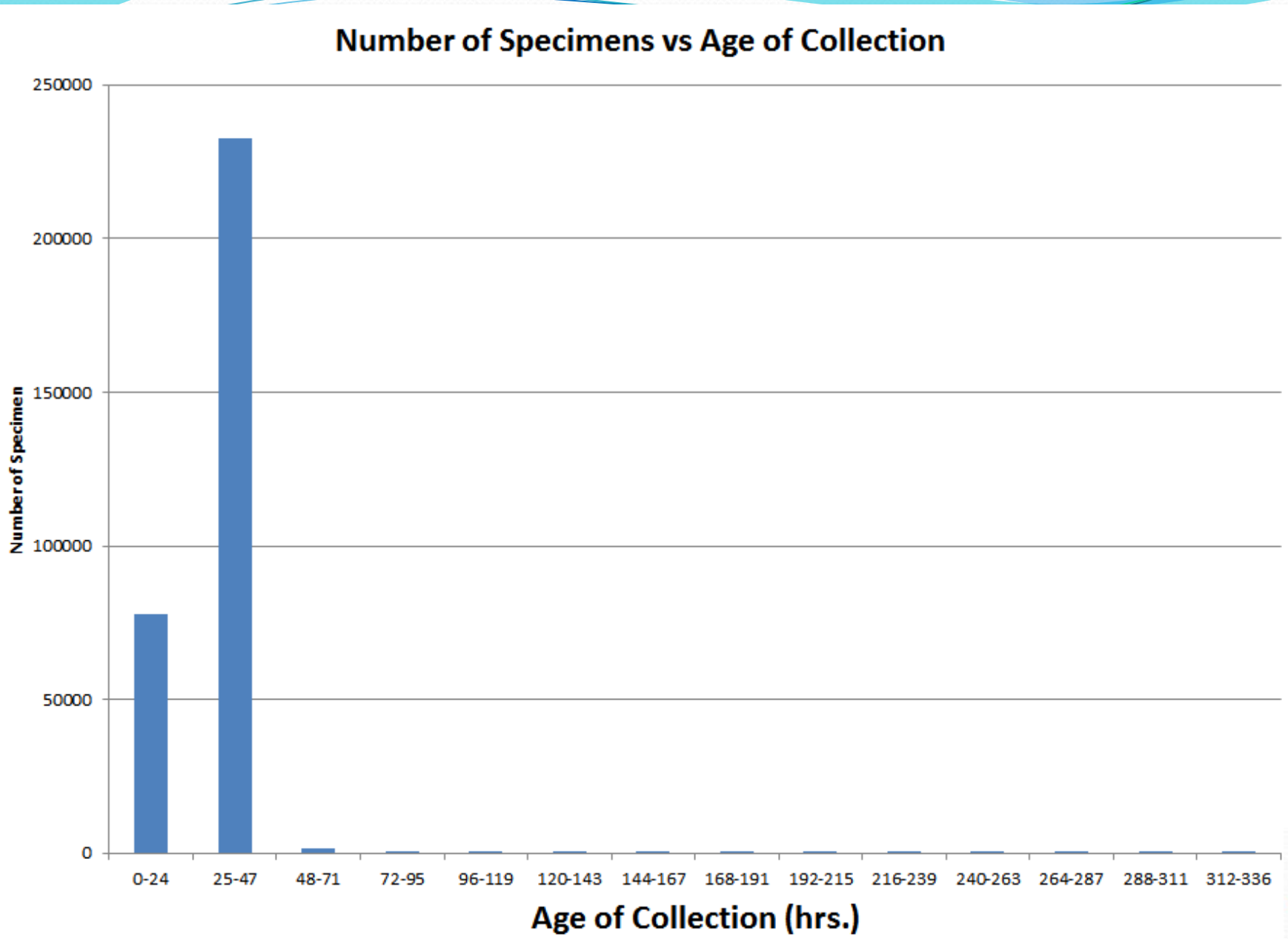
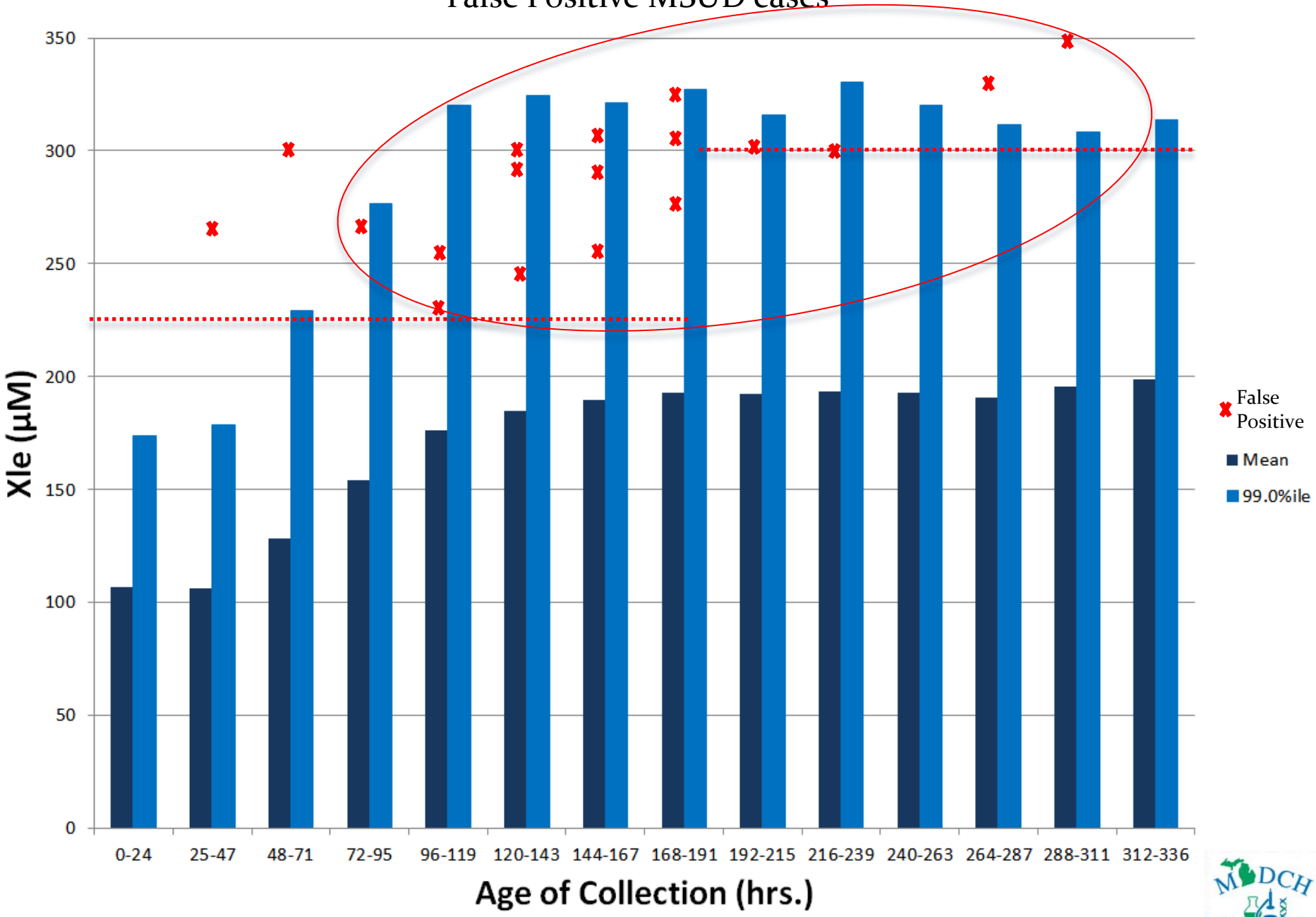
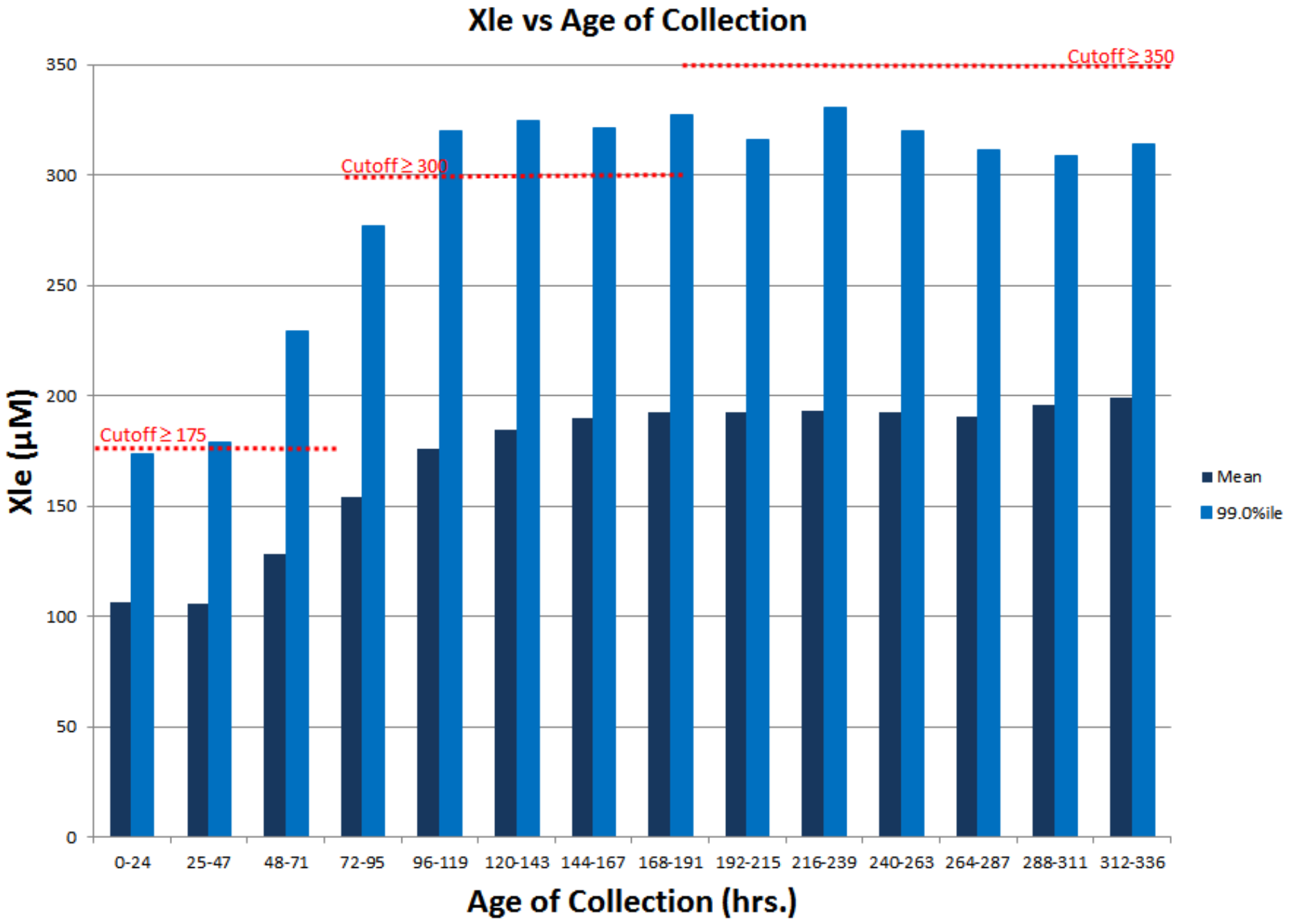
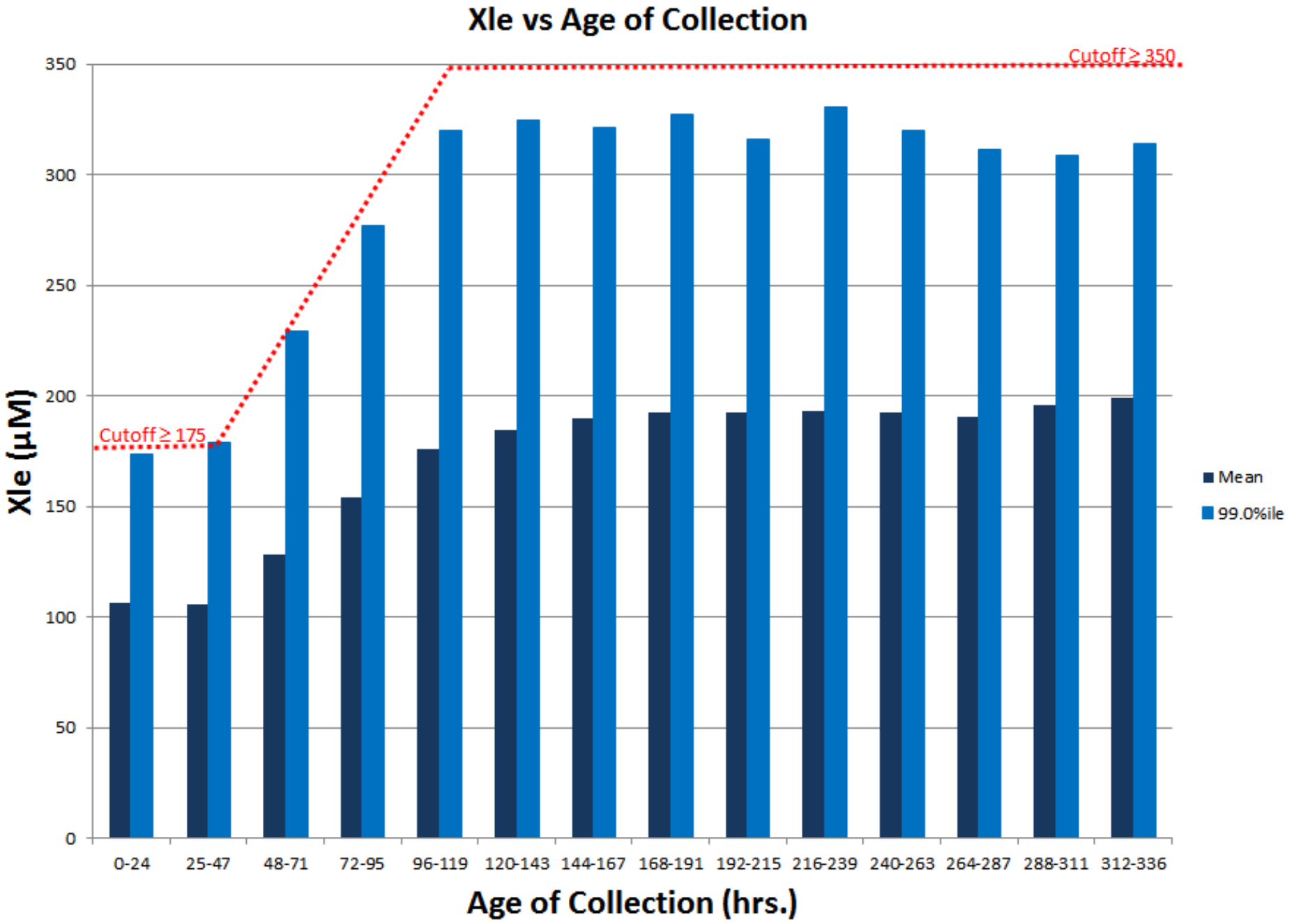

Xle vs Age of Collection
350
300
250
200
150
100
50
0
Xle (µM)
0-24
25-47
48-71
72-95
96-119
120-143
144-167
168-191
192-215
216-239
240-263
264-287
288-311
312-336
Age of Collection (hrs.)
Mean
99.0%ile

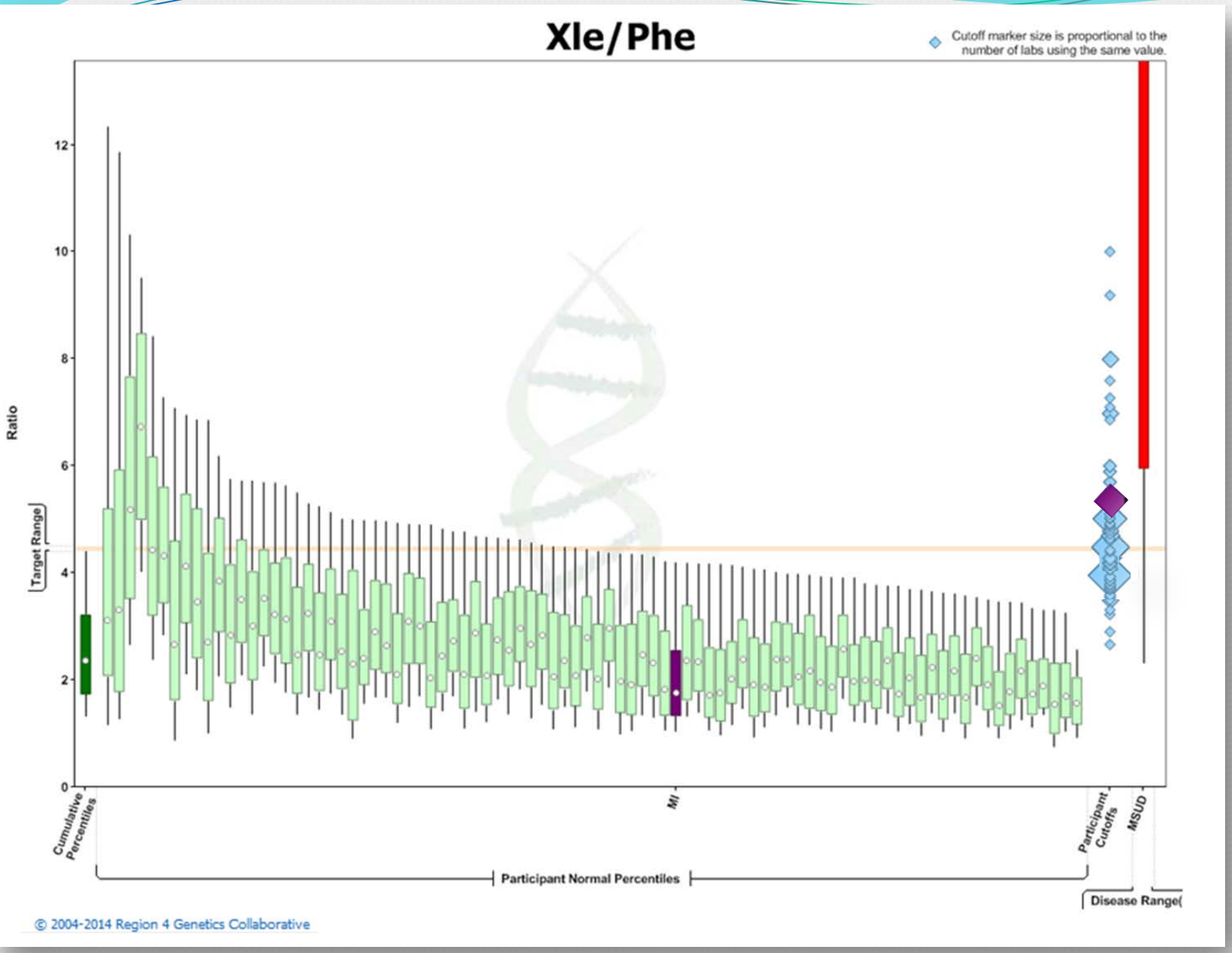

Number of Specimens vs Age of Collection
250000
200000
150000
100000
50000
0
Number of Specimen
0-24
25-47
48-71
72-95
96-119
120-143
144-167
168-191
192-215
216-239
240-263
264-287
288-311
312-336
Age of Collection (hrs.)

False Positive MSUD cases




Xle vs Age of Collection
Cutoff ≥ 350
Cutoff ≥ 300
Cutoff ≥ 175
350
300
250
200
150
100
50
0
Xle (µM)
0-24
25-47
48-71
72-95
96-119
120-143
144-167
168-191
192-215
216-239
240-263
264-287
288-311
312-336
Age of Collection (hrs.)
Mean
99.0%ile


Xle vs Age of Collection
Cutoff ≥ 350
Cutoff ≥ 175
350
300
250
200
150
100
50
0
Xle (µM)
0-24
25-47
48-71
72-95
96-119
120-143
144-167
168-191
192-215
216-239
240-263
264-287
288-311
312-336
Age of Collection (hrs.)
Mean
99.0%ile



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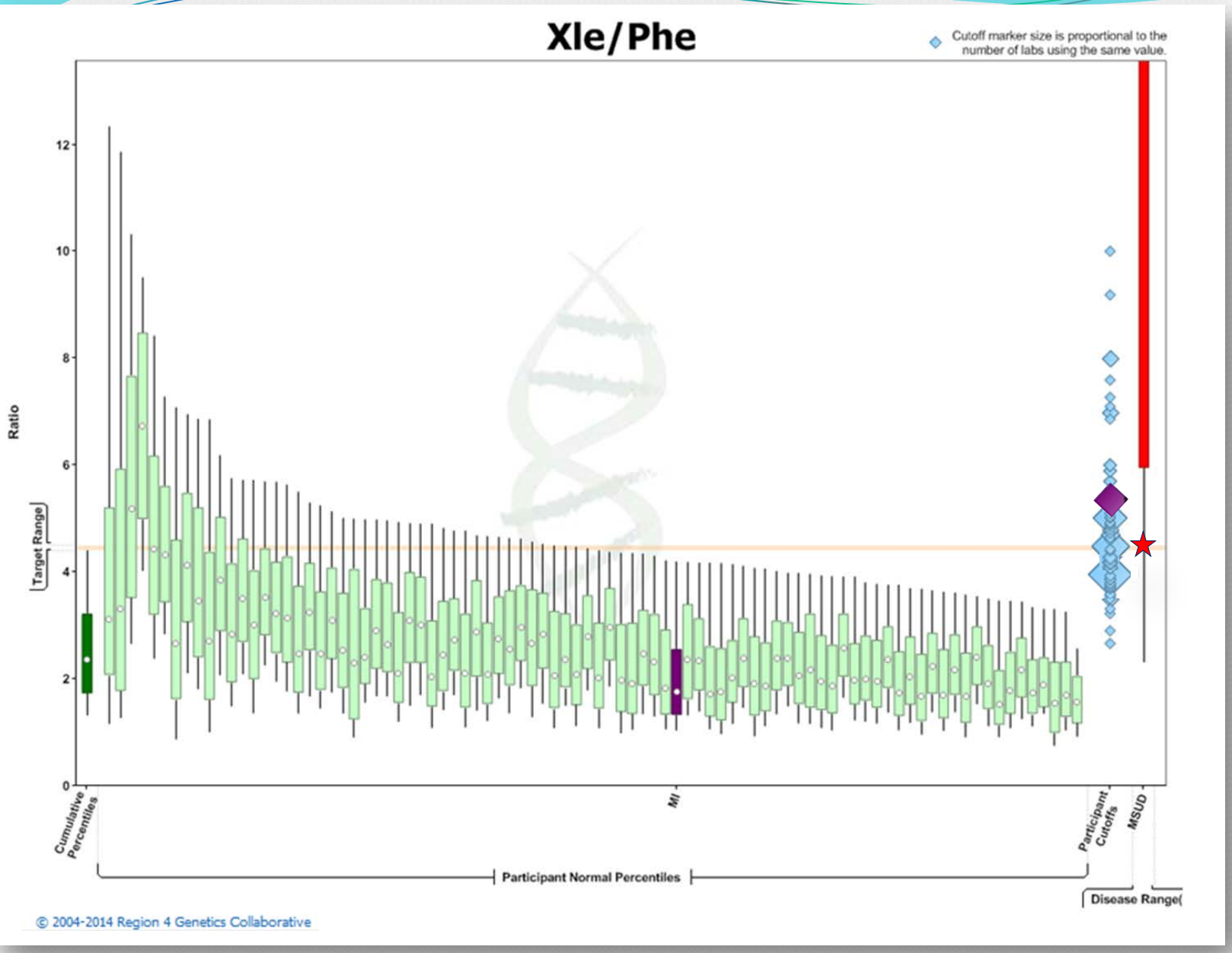

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Xle/Phe vs. Age of Collection - Data

Age Range (hrs.)	Number of samples	% of samples	Xle/Phe Average (µM)	SD	99.0%ile
0-24	77811	24.1	1.7	0.33	2.7
25-47	232522	72.1	1.8	0.35	2.8
48-71	1766	0.5	2.3	0.52	3.6
72-95	520	0.16	2.8	0.67	4.6
96-119	656	0.20	3.1	0.73	4.9
120-143	775	0.24	3.4	0.77	5.3
144-167	833	0.26	3.6	0.77	5.5
168-191	762	0.24	3.7	0.78	5.8
192-215	558	0.17	3.8	0.73	5.5
216-239	415	0.13	3.7	0.76	5.8
240-263	371	0.12	3.8	0.80	5.8
264-287	317	0.10	3.8	0.79	5.4
288-311	304	0.09	3.9	0.76	5.9
312-336	299	0.09	3.8	0.72	5.3

Data analyzed: N>320,000 specimens, No NICU, No TPN, Feb. 2011 - April. 2014

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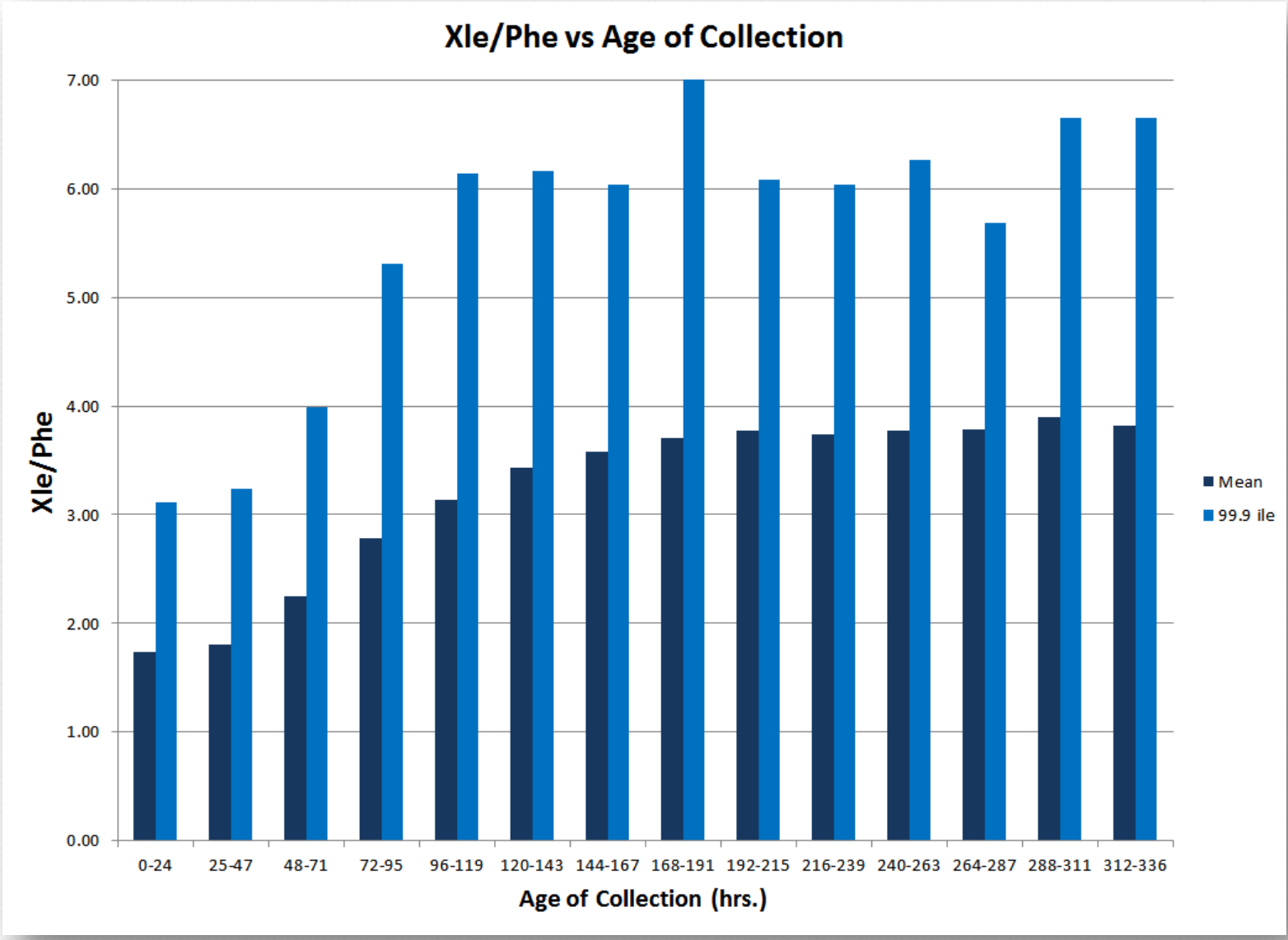
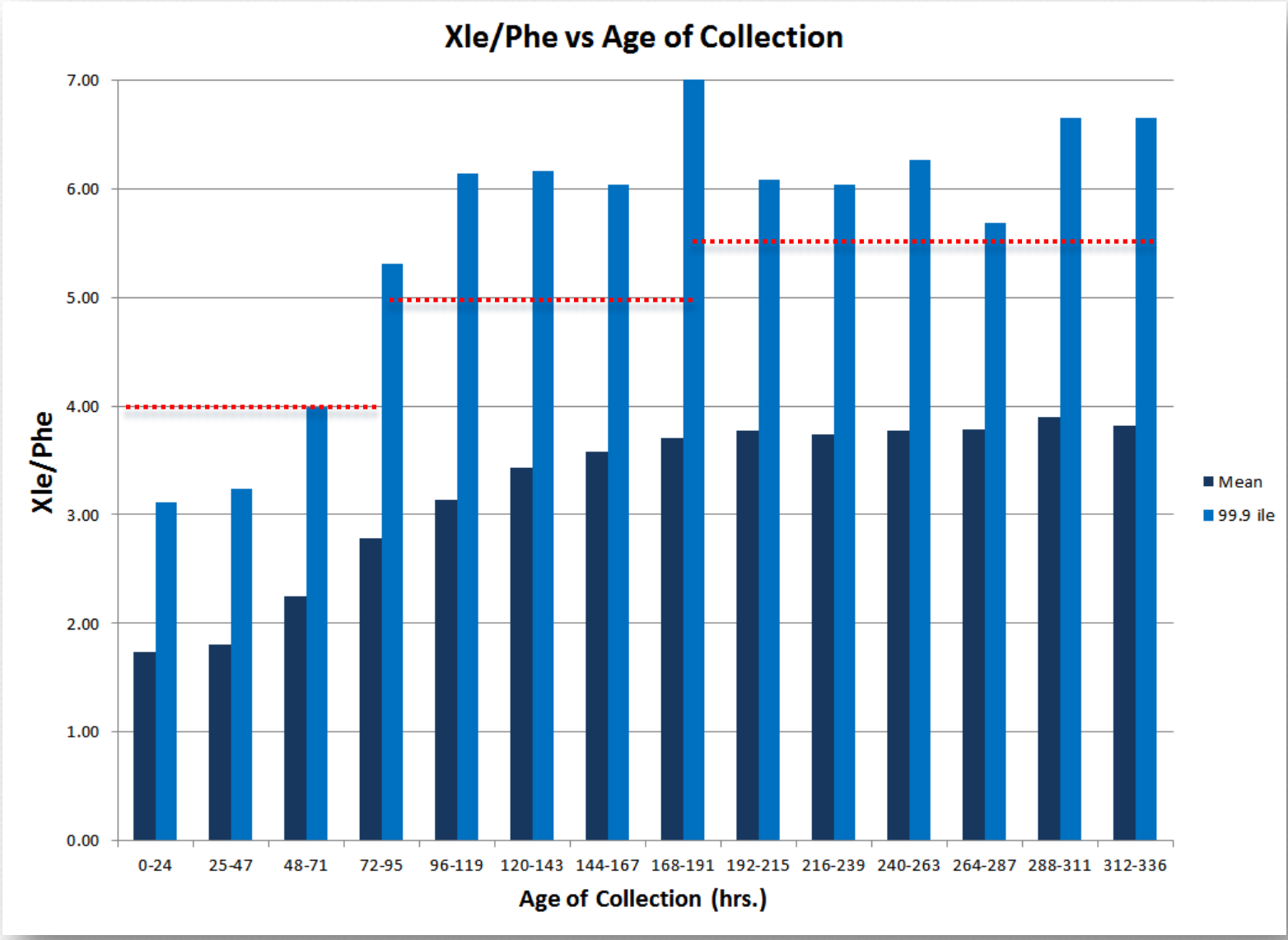
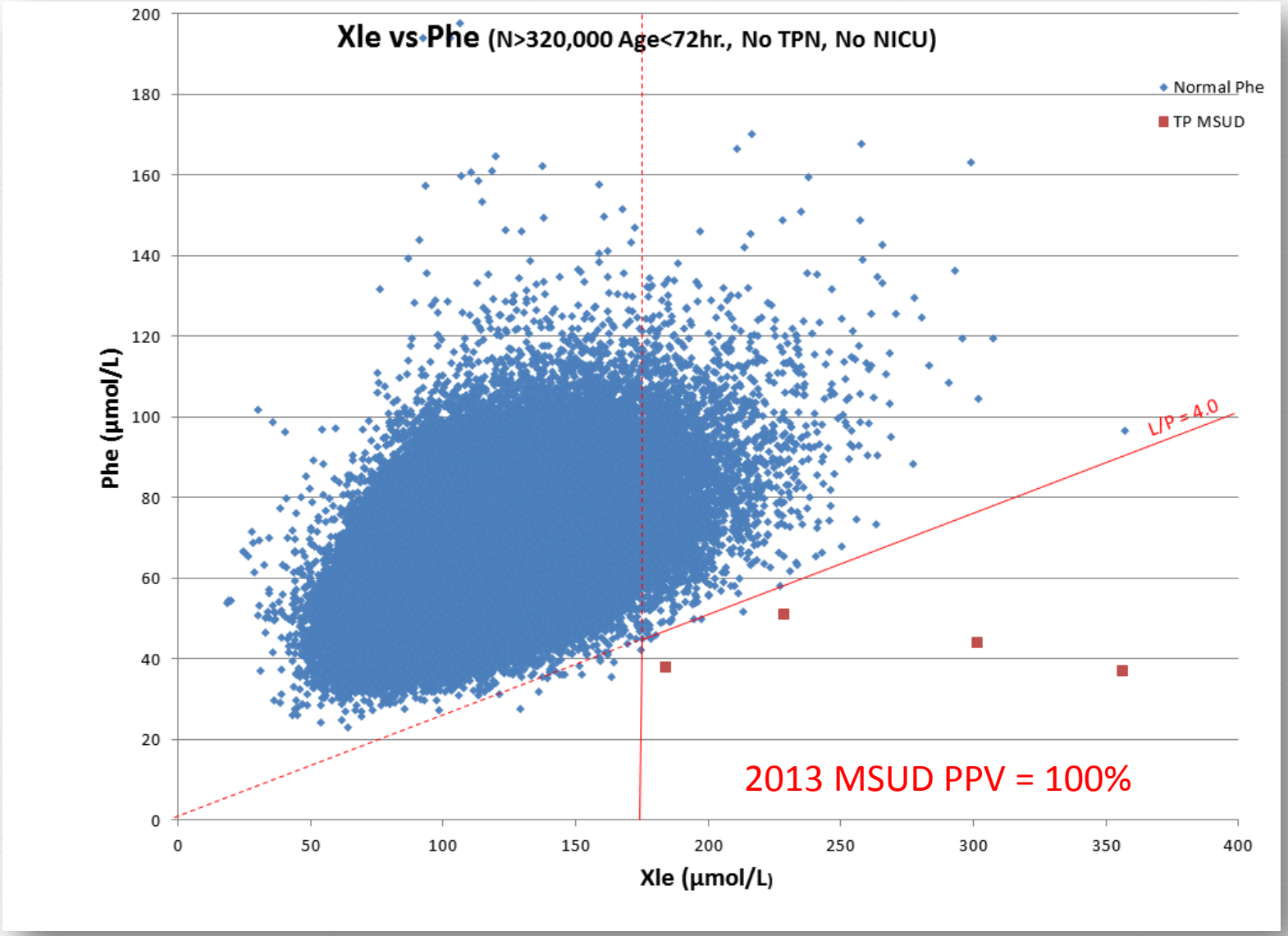
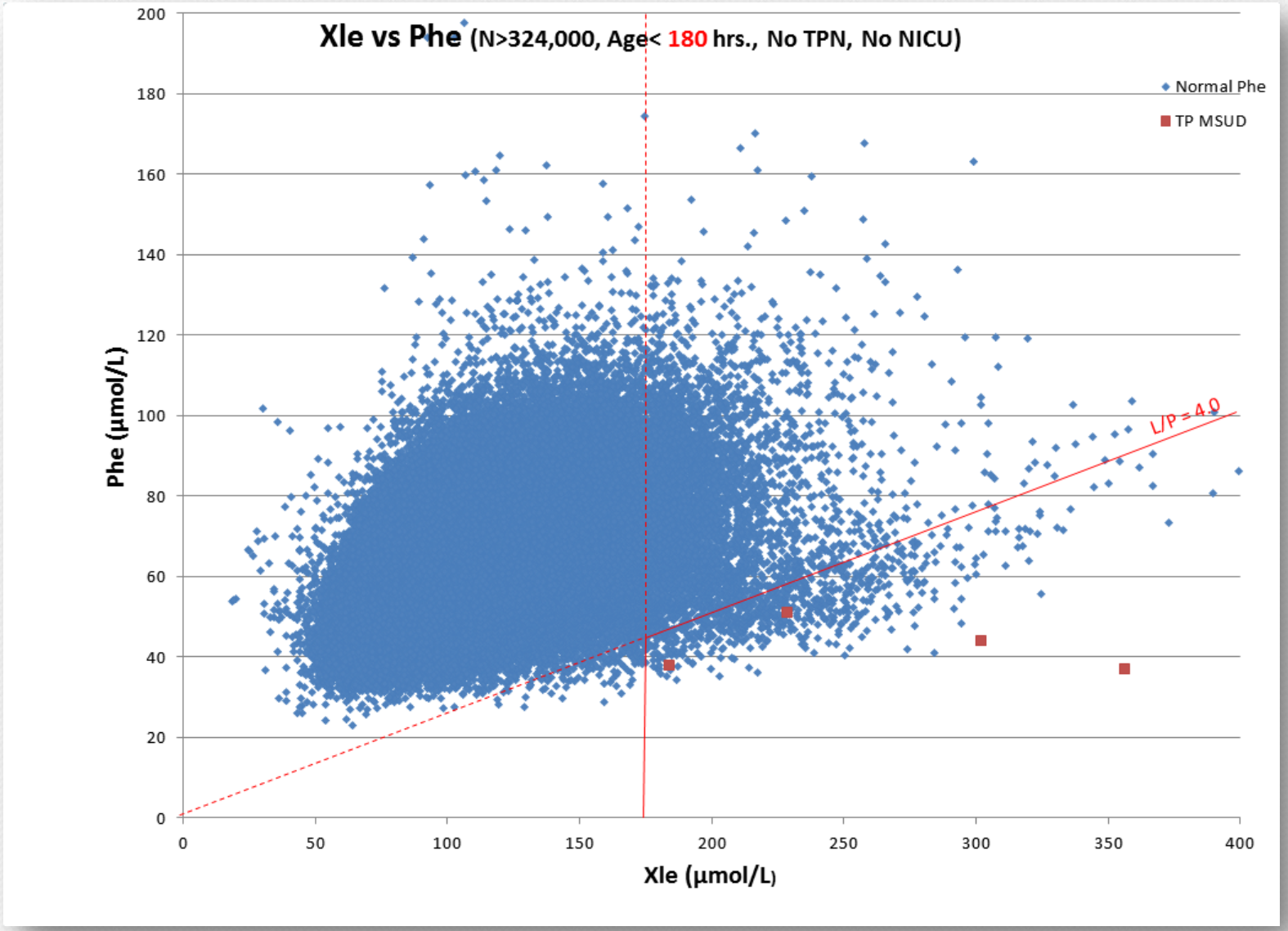

Xle/Phe vs Age of Collection
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Xle/Phe
0-24
25-47
48-71
72-95
96-119
120-143
144-167
168-191
192-215
216-239
240-263
264-287
288-311
312-336
Age of Collection (hrs.)
Mean
99.9 ile

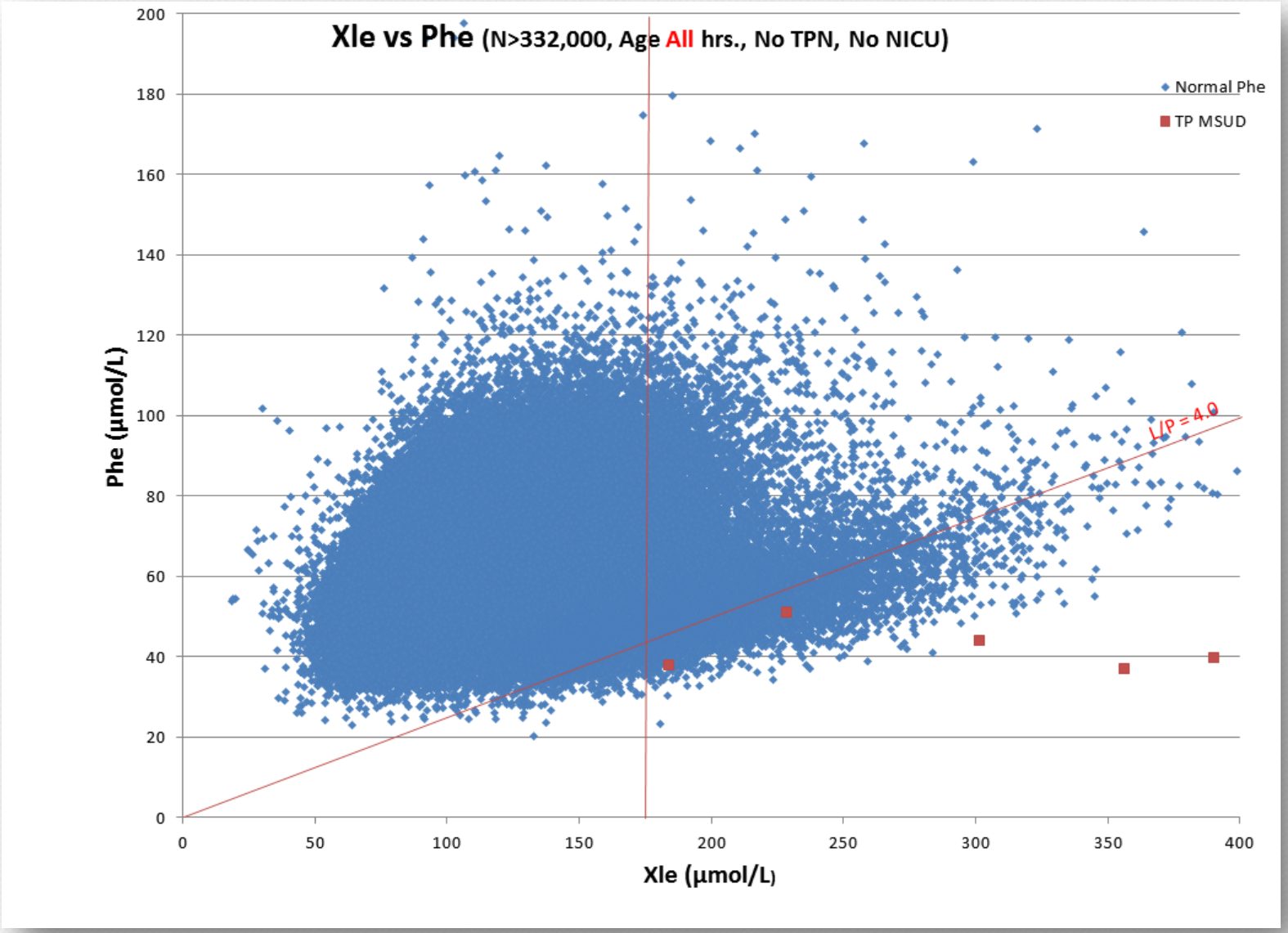

Xle/Phe vs Age of Collection
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Xle/Phe
0-24
25-47
48-71
72-95
96-119
120-143
144-167
168-191
192-215
216-239
240-263
264-287
288-311
312-336
Age of Collection (hrs.)
Mean
99.9 ile

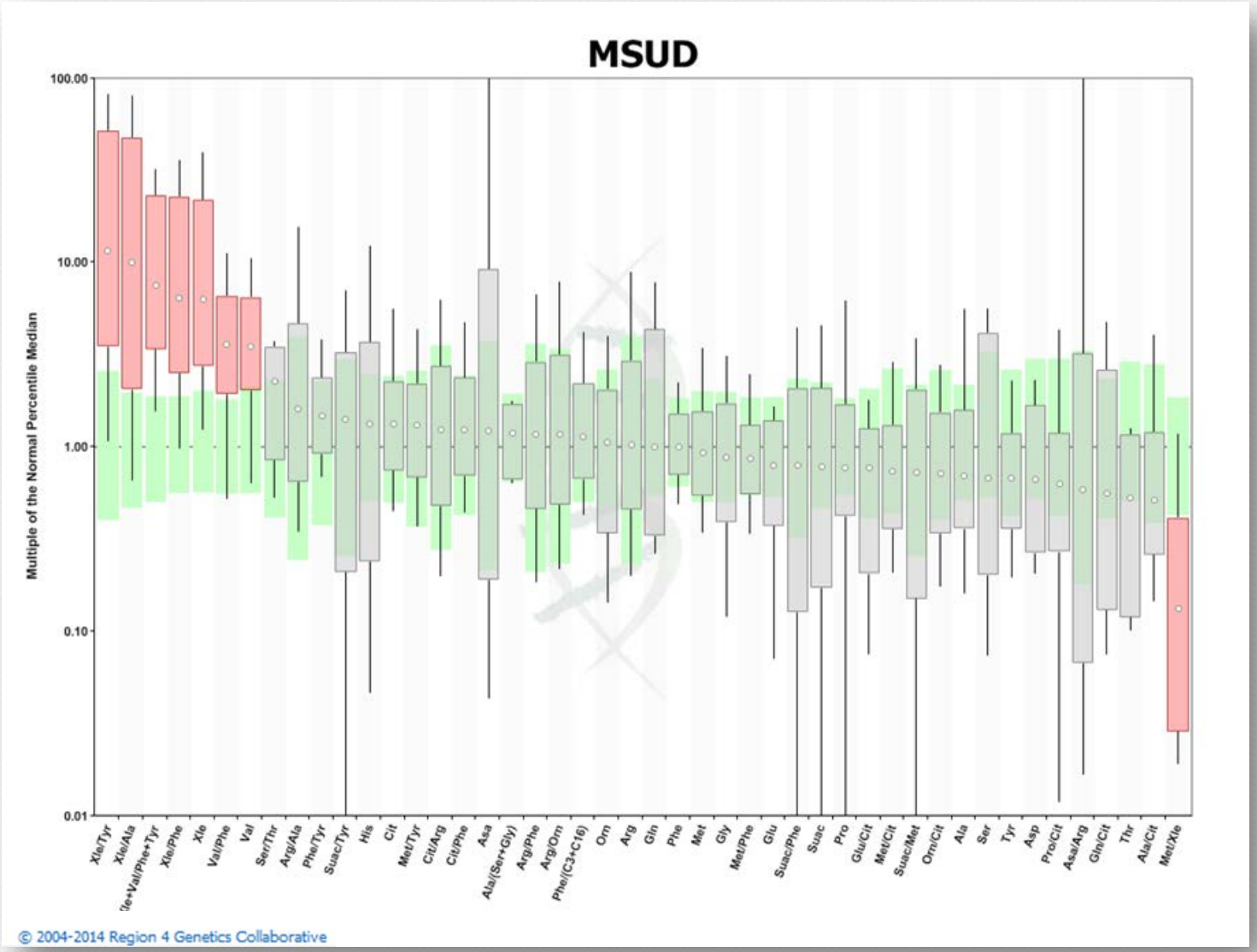
MSUD Cutoffs/Logic

Analyte(s)	0-71 hrs. old	72-179 hrs.	≥180 hrs-1 yr.	Action
Leu	≥175	≥300	na	Repeat Specimen
Leu/Phe	≥4.0	≥5.0	na	
Leu	≥225	≥350	≥350	S+
Leu/Phe	≥4.5	≥5.5	≥5.5	


Xle vs Phe (N>320,000 Age<72hr., No TPN, No NICU)
Normal Phe
TP MSUD
L/P = 4.0
2013 MSUD PPV = 100%
Phe (µmol/L)
Xle (µmol/L)
0
20
40
60
80
100
120
140
160
180
200
0
50
100
150
200
250
300
350
400


Xle vs Phe (N>324,000, Age< 180 hrs., No TPN, No NICU)
Normal Phe
TP MSUD
L/P = 4.0
Phe (µmol/L)
Xle (µmol/L)
0
20
40
60
80
100
120
140
160
180
200
0
50
100
150
200
250
300
350
400


Xle vs Phe (N>332,000, Age All hrs., No TPN, No NICU)
Normal Phe
TP MSUD
L/P = 4.0
Phe (µmol/L)
Xle (µmol/L)
0
20
40
60
80
100
120
140
160
180
200
0
50
100
150
200
250
300
350
400



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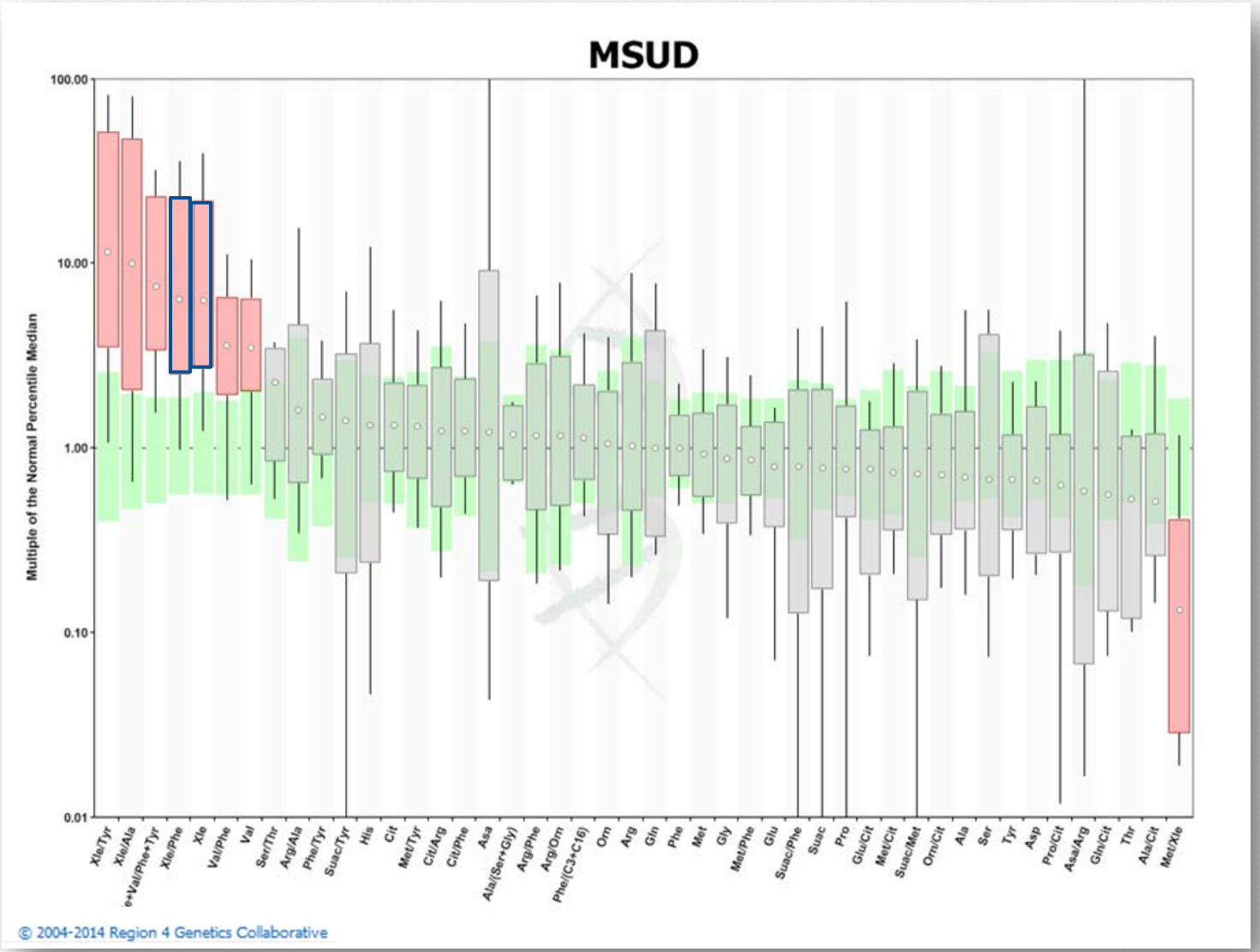

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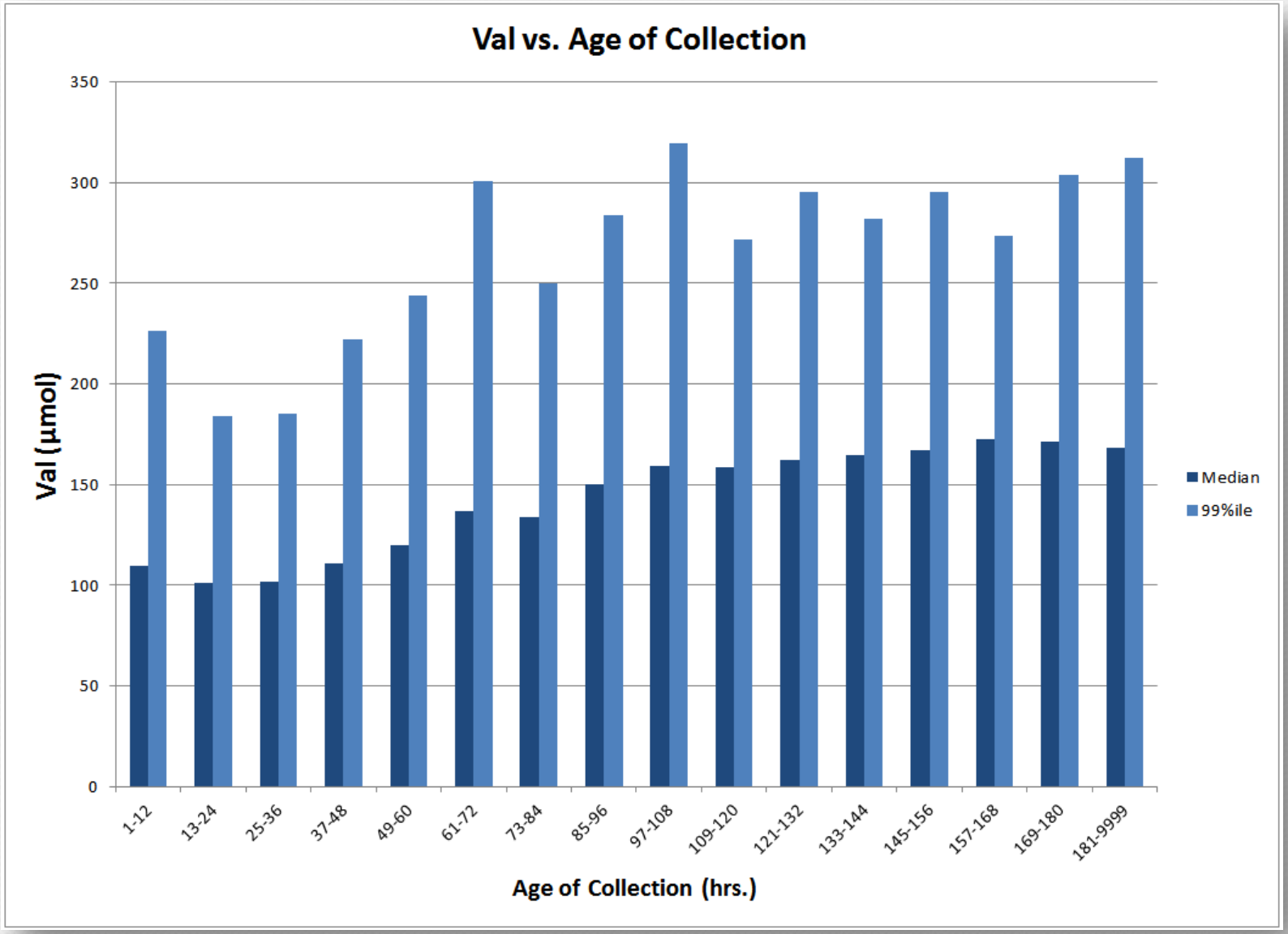
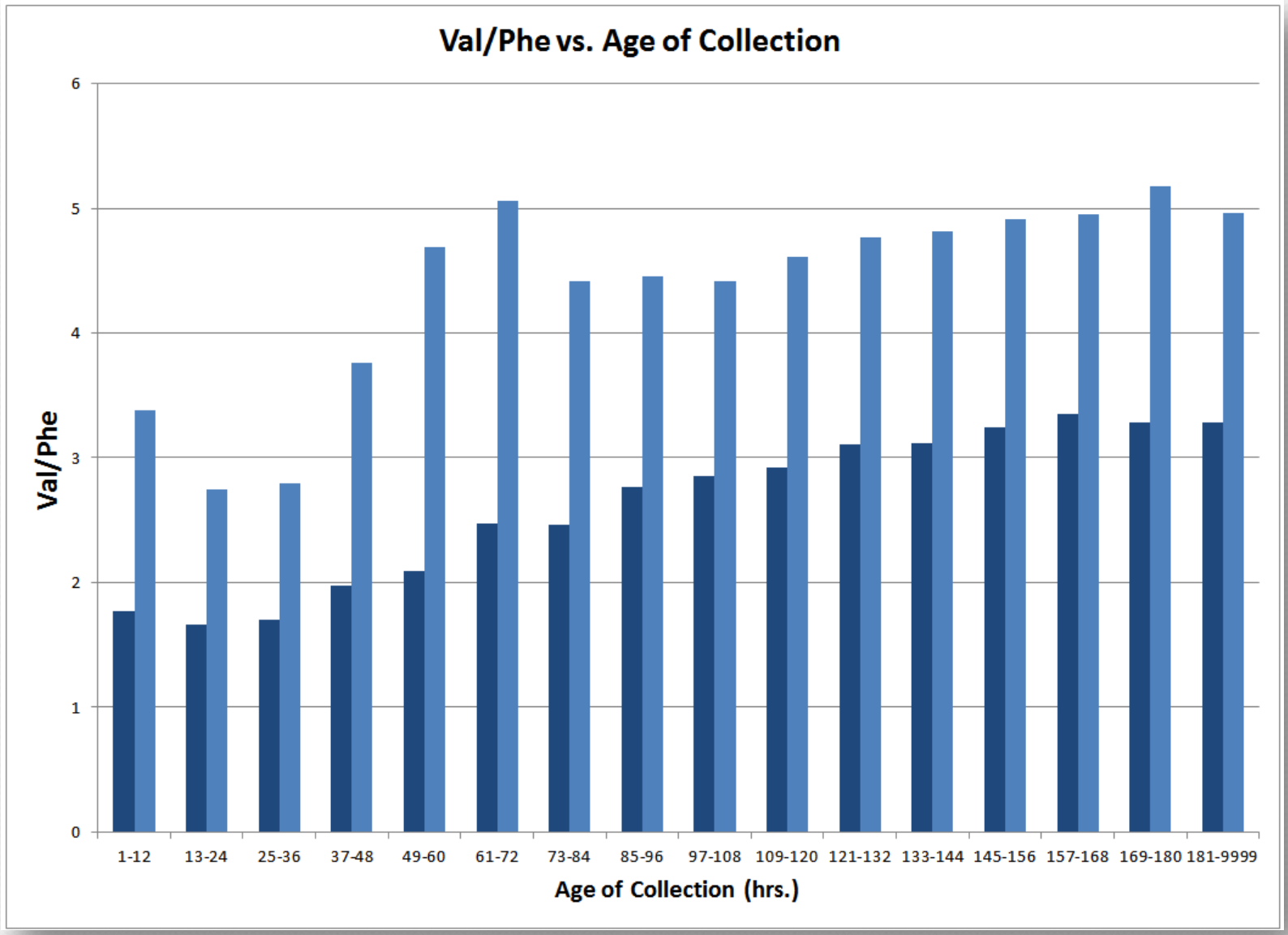
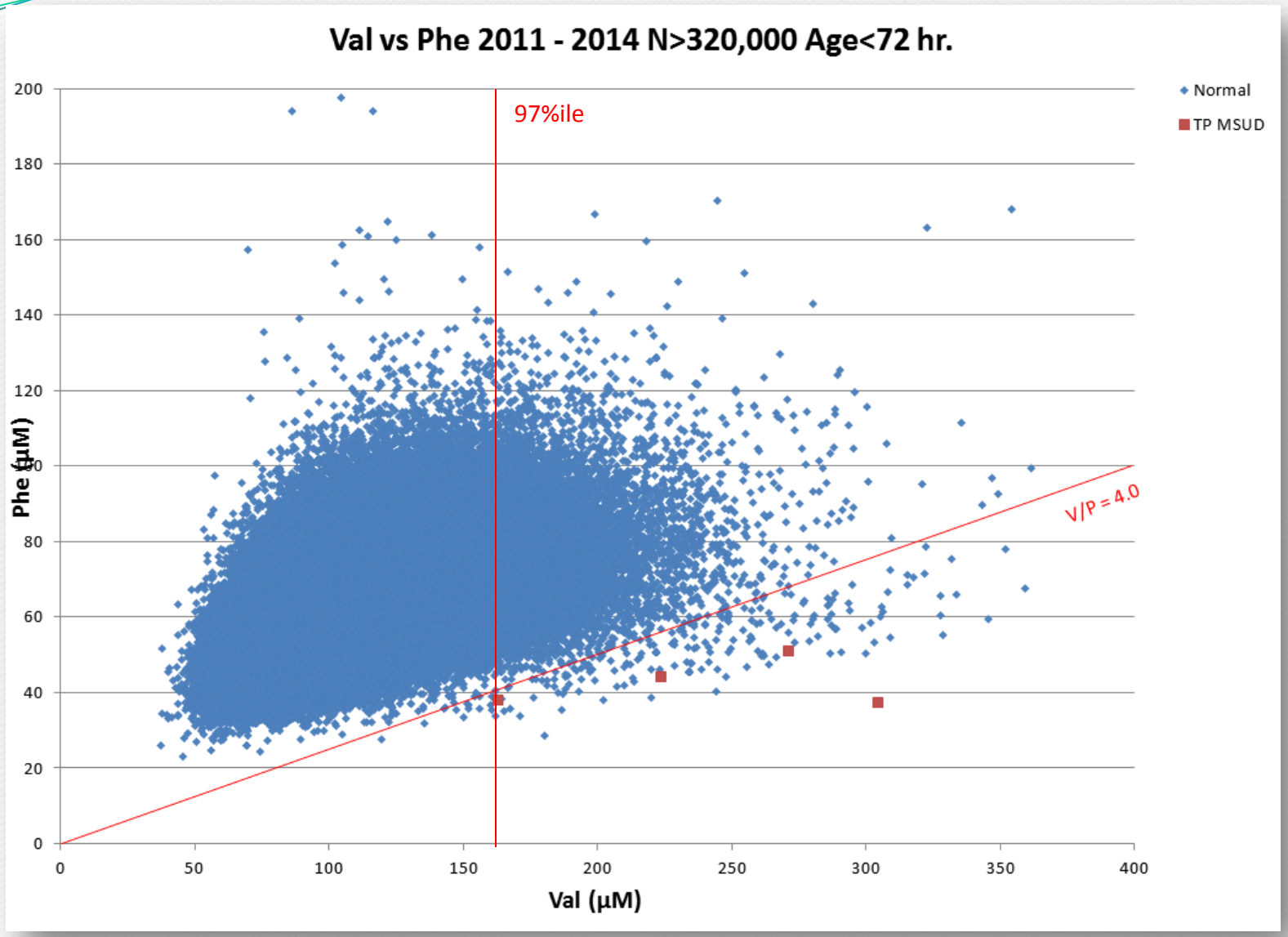
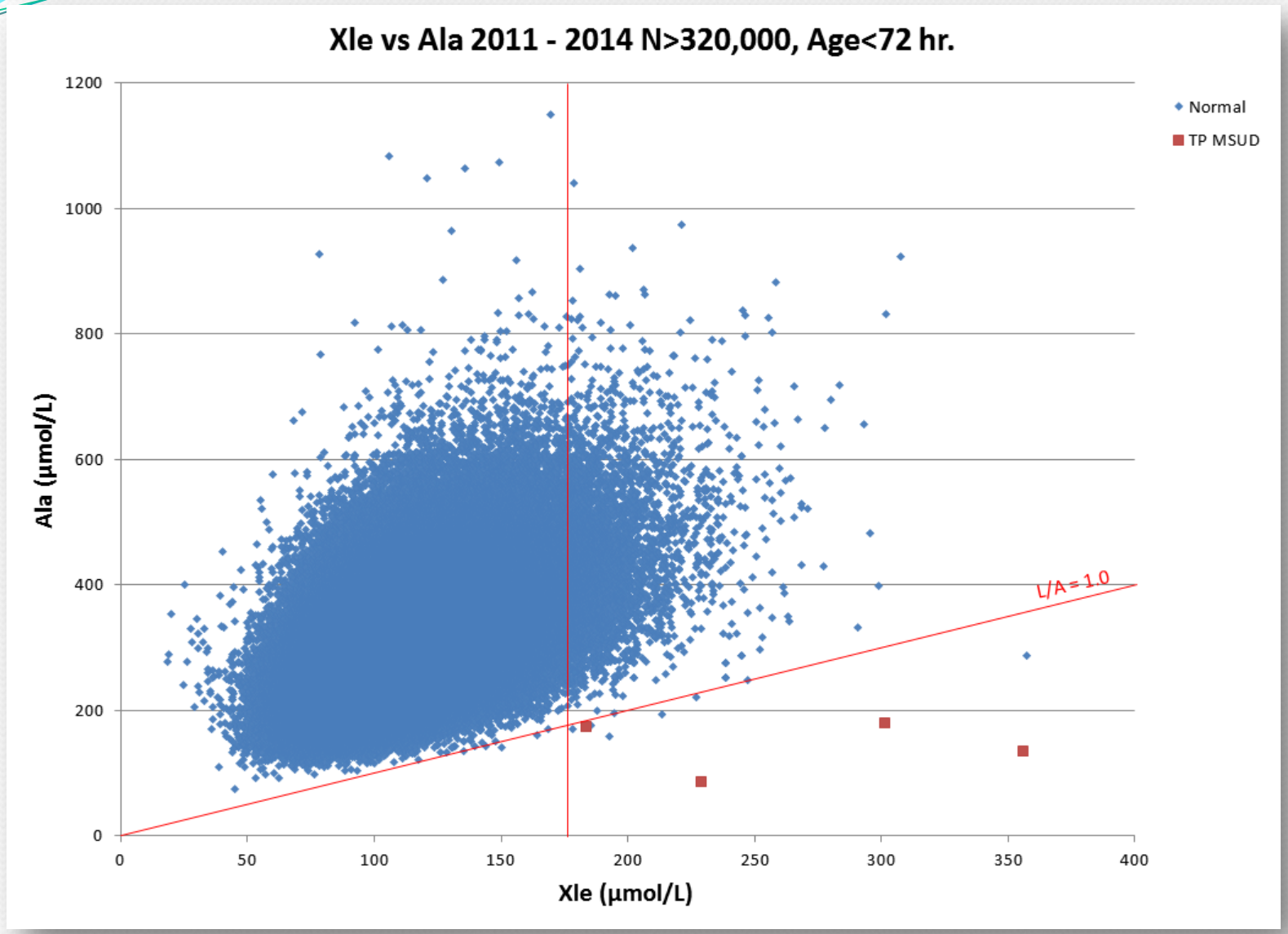
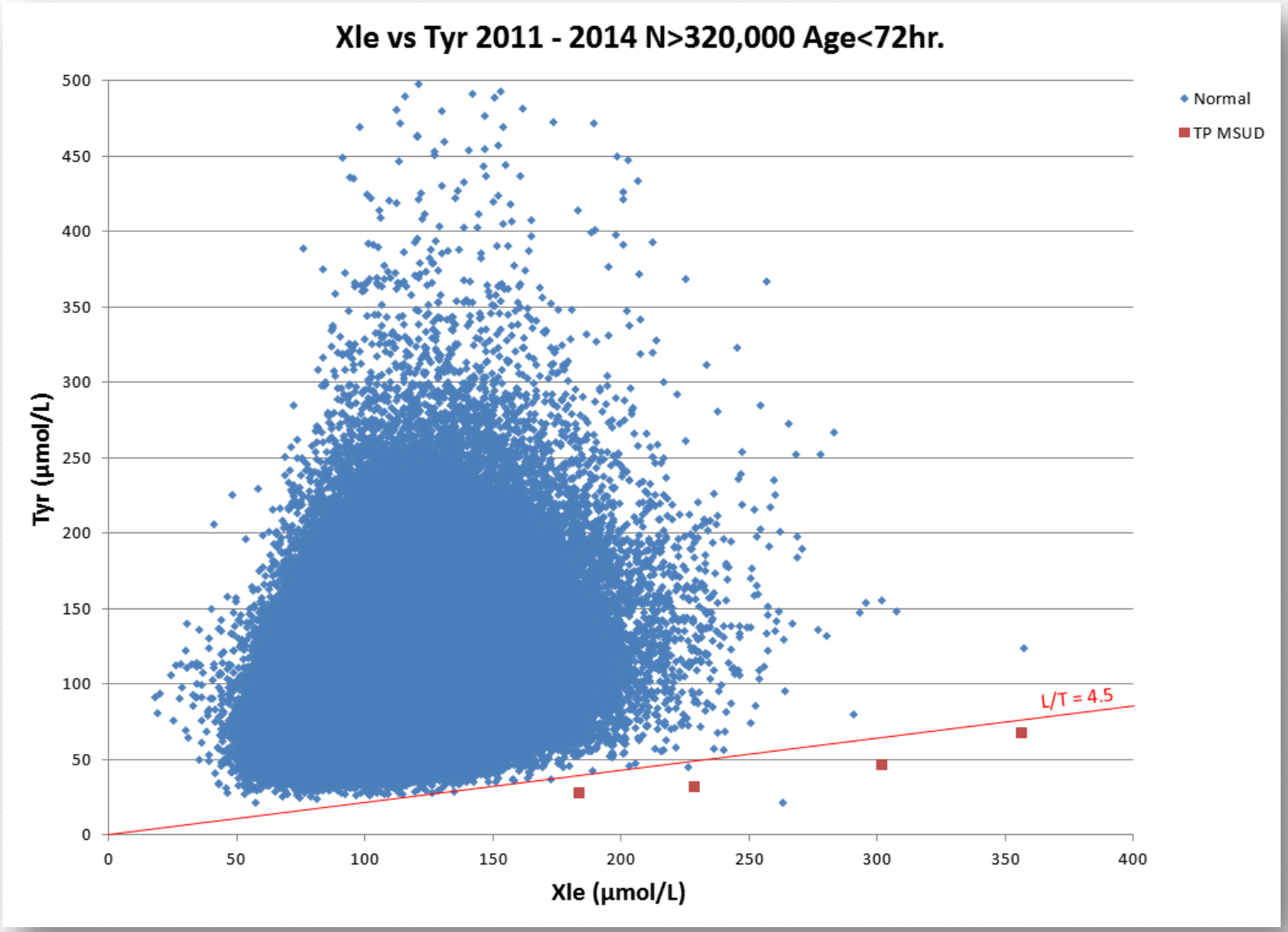
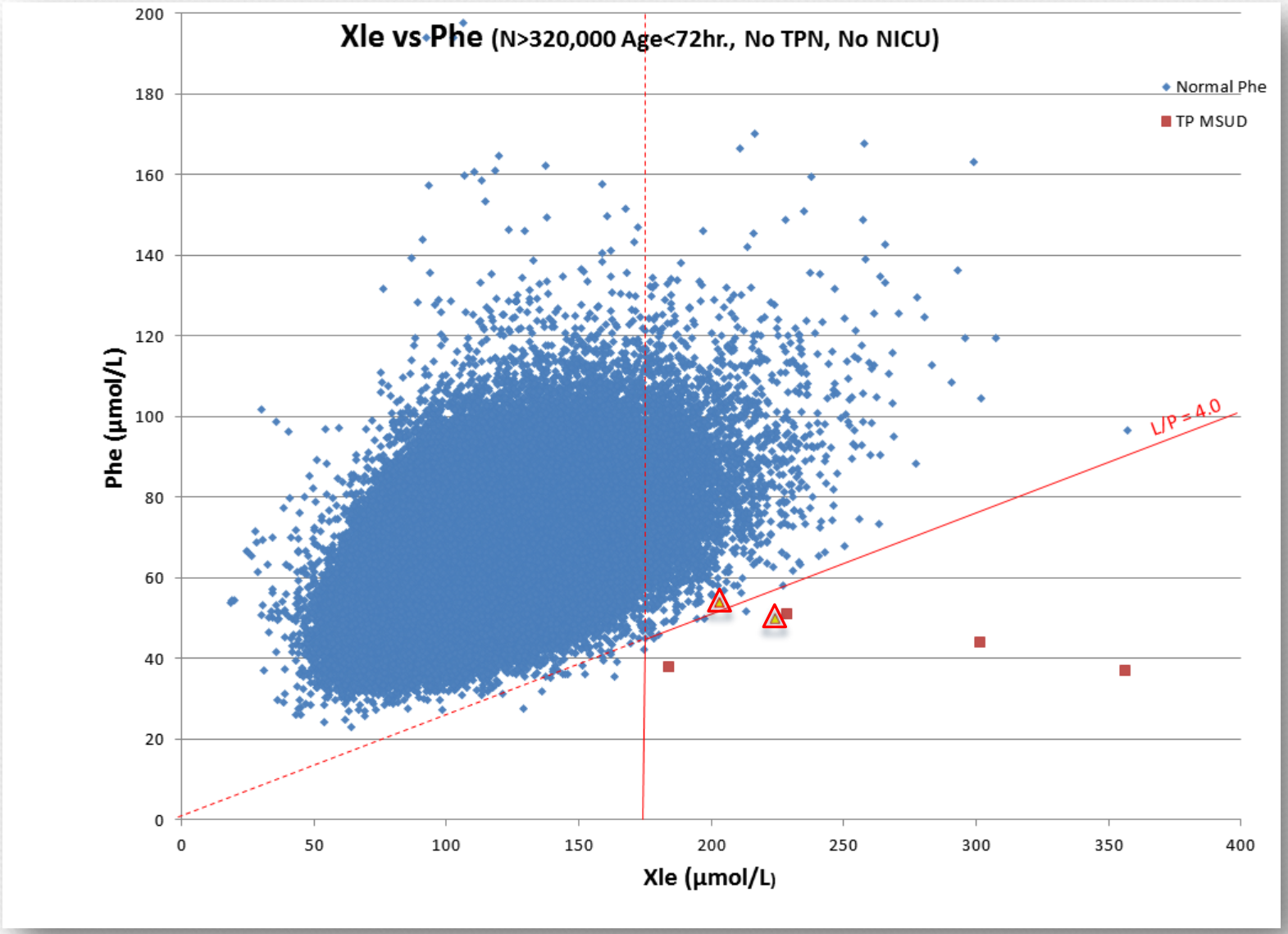

Val vs. Age of Collection
Val (µmol)
350
300
250
200
150
100
50
0
1-12
13-24
25-36
37-48
49-60
61-72
73-84
85-96
97-108
109-120
121-132
133-144
145-156
157-168
169-180
181-9999
Age of Collection (hrs.)
Median
99%ile


Val/Phe vs. Age of Collection
Val/Phe
0
1
2
3
4
5
6
1-12
13-24
25-36
37-48
49-60
61-72
73-84
85-96
97-108
109-120
121-132
133-144
145-156
157-168
169-180
181-9999
Age of Collection (hrs.)


Val vs Phe 2011 - 2014 N>320,000 Age<72 hr.
97%ile
V/P = 4.0
Normal
TP MSUD
Phe (µM)
Val (µM)
0
20
40
60
80
100
120
140
160
180
200
0
50
100
150
200
250
300
350
400


Xle vs Ala 2011 - 2014 N>320,000, Age<72 hr.
Normal
TP MSUD
L/A = 1.0
Ala (µmol/L)
Xle (µmol/L)
0
200
400
600
800
1000
1200
0
50
100
150
200
250
300
350
400


Xle vs Tyr 2011 - 2014 N>320,000 Age<72hr.
Tyr (µmol/L)
Xle (µmol/L)
Normal
TP MSUD
L/T = 4.5
0
50
100
150
200
250
300
350
400
450
500



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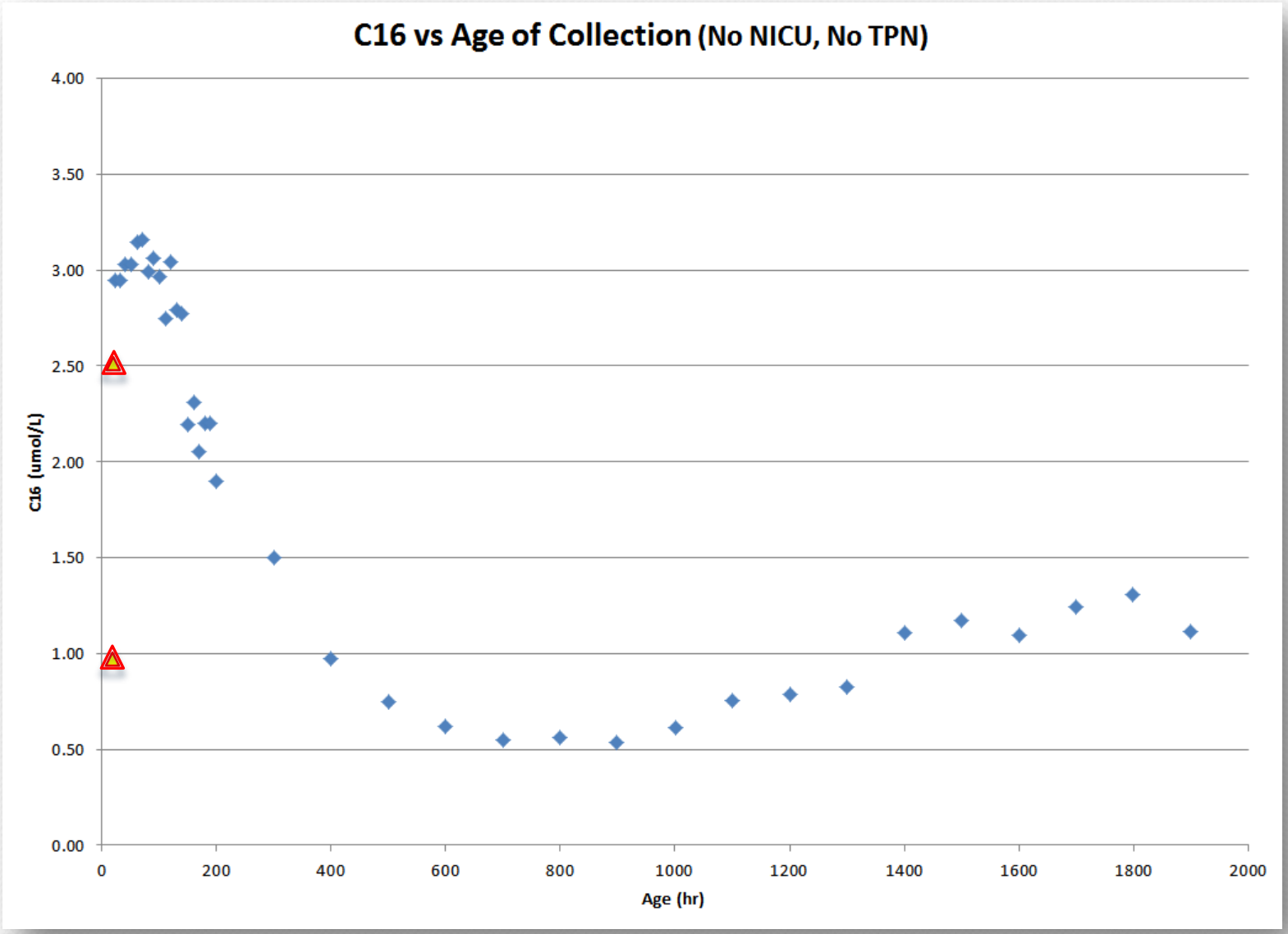
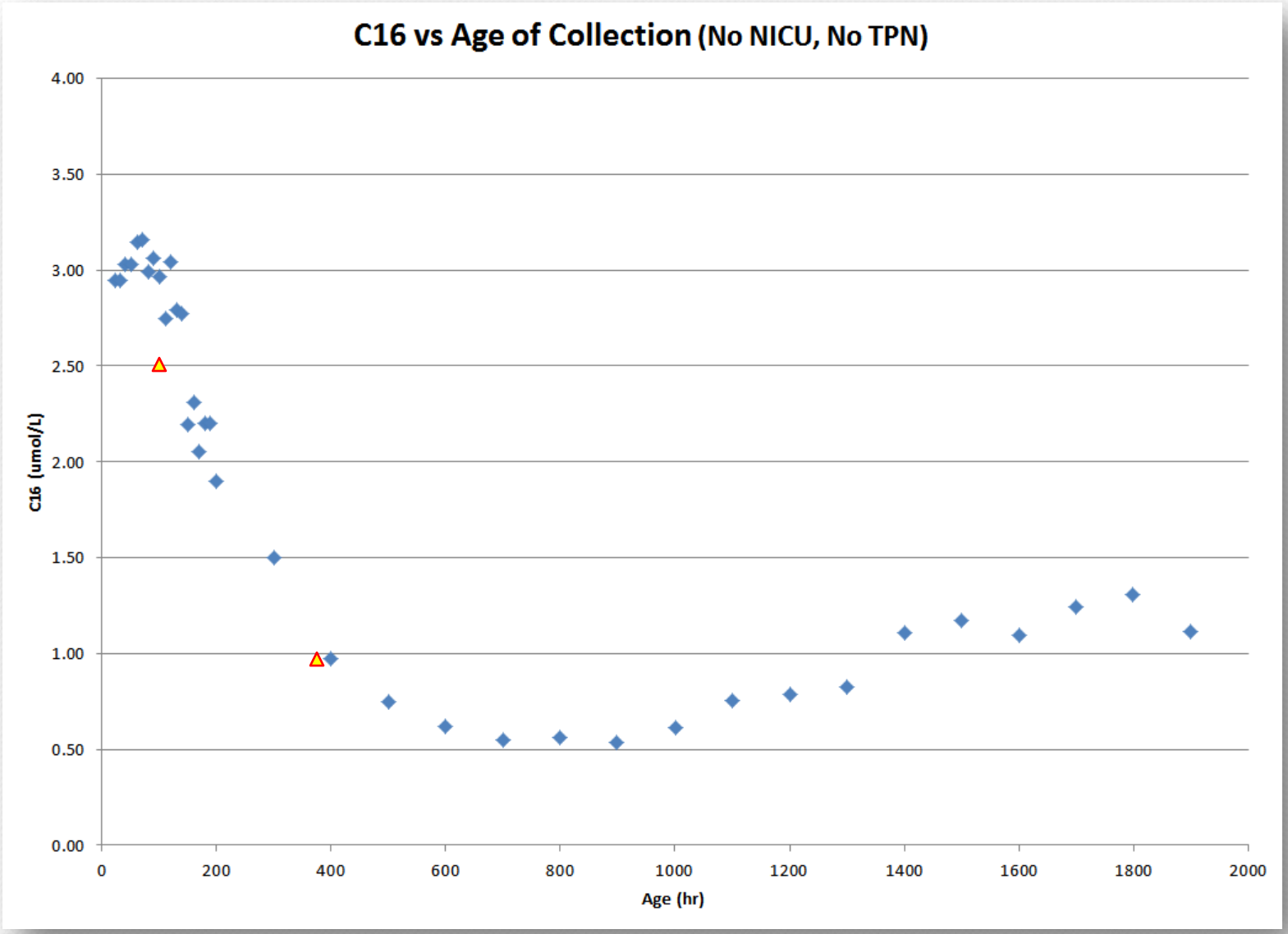

C16 vs Age of Collection (No NICU, No TPN)
C16 (umol/L)
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0
200
400
600
800
1000
1200
1400
1600
1800
2000
Age (hr)


C16 vs Age of Collection (No NICU, No TPN)
C16 (umol/L)
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0
200
400
600
800
1000
1200
1400
1600
1800
2000
Age (hr)

Conclusions

- MSUD Analyte concentrations
  - Leu, L/P, Val & V/P
  - Increase with Age of Collection
- Age specific cutoffs will reduce both
  - False Negatives
  - False Positives

Acknowledgements

Michigan Department of Community Health

Newborn Screening Team

- Hospitals
- Laboratory
- Follow-up
- Clinic