Between Method/Laboratory MSMS Analyte Harmonization Using CDC Quality Control Materials

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4. Centers for Disease Control and Prevention, Atlanta, GA.
2009 Directive

- Validate PerkinElmer NeoBase™ Non-derivatized MSMS Kit on Waters TQD
  - Previously PerkinElmer NeoGram® Derivatized MSMS Kit on SCIEX 2000
- Evaluate cutoffs with respect to R4 target cutoff ranges
Validation Assessments

- Precision
- Linearity
- Accuracy
  - NeoBase™ Kit Controls
  - CDC Quality Control Samples
  - Cutoffs: NeoGram-NeoBase Method Comparison
Method Comparison Analysis

NeoBase (μmol/L) vs. NeoGram (μmol/L)

- Platelet (PT) Samples
- CDC QC Samples
- 332 Normal Patient samples
- High and Low Kit Controls
- True Positive samples

Slope: 0.775  
Intercept: -1.033  
R: 0.9862

Methionine (Met)
Methionine (Met)

NeoBase ≈ 0.775 * NeoGram

Slope: 0.775
Intercept: -1.033
R: 0.9862
Methionine (Met)

Method Comparison Analysis

![Graph showing method comparison analysis for Methionine (Met). The graph plots NeoBase (µmol/L) against NeoGram (µmol/L). The graph includes data points and a trend line. The inset box provides the slope, intercept, and R value.]

- Slope: 0.731
- Intercept: 1.743
- R: 0.9992

Averaged CDC QC Values
NeoGram Met Cutoff (74)
NeoBase Met Cutoff (56)

Method Comparison Analysis

Methionine (Met)

Slope: 0.731
Intercept: 1.743
R: 0.9992
Alternate (Quantitative) Method Comparison

X Method: NeoGram
Y Method: NeoBase

Scatter Plot

Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>Deming</th>
<th>Regular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope</td>
<td>0.731</td>
<td>0.731</td>
</tr>
<tr>
<td>Intercept</td>
<td>1.743 (-0.832 to 4.318)</td>
<td>1.830 (-0.744 to 4.405)</td>
</tr>
<tr>
<td>Std Err Est:</td>
<td>4.996</td>
<td>4.996</td>
</tr>
</tbody>
</table>

95% Confidence Intervals are shown in parentheses

Medical Decision Point Analysis

<table>
<thead>
<tr>
<th>X Method MDP</th>
<th>Y Method Pred. MDP</th>
<th>95% Conf. Limits</th>
</tr>
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<tbody>
<tr>
<td>74</td>
<td>55.9</td>
<td>53.8 to 57.9</td>
</tr>
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</table>
Validation Goals

Evaluate Cutoffs

- **NeoGram/NeoBase** Method Comparison
  - All MSMS analytes cutoffs evaluated

- **Region 4** Cutoff Range Comparison:
  - Could this Method Comparison technique work for Between Laboratory Cutoff Comparison?
Cutoffs

Cutoff evaluation with respect to Region 4 target cutoff ranges...

- **Why** do some of our cutoffs *not* coincide with the R4 target cutoff range?

  - Differences in the Methods
    - Extraction technique
    - Instrumentation
    - Internal Standard
    - Calibration Technique
    - Standard Calibration Material Use
      - (Traceable to National Standards)

- Cutoffs in question are not clinically valid
Target Range

MI NeoGram Cutoff = 74
MI NeoBase Cutoff = 56
Better?

Target Range
Target Range

Equivalent!

Better?
Target Range:
Succinylacetone (SA)

NeoBase \approx 0.144 \times CDC
NeoBase \approx 0.247 \times \text{Mayo}
Alternate (Quantitative) Method Comparison

X Method: Mayo Medical Lab
Y Method: MI NeoBase

Regression Analysis

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<tr>
<td>Slope</td>
<td>0.247 (0.242 to 0.251)</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.07339 (0.05085 to 0.09593)</td>
</tr>
<tr>
<td>Std Err Est</td>
<td>0.03732</td>
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95% Confidence Intervals are shown in parentheses

Medical Decision Point Analysis
Calculated by Deming Regression (R>=0.9)

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<tr>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>5.0</td>
<td>1.31</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.32</td>
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EP Evaluator®
Michigan Department of Community Health – Newborn Screening

Alternate (Quantitative) Method Comparison

X Method: Mayo Medical Lab
Y Method: MI NeoBase

Scatter Plot

Regression Analysis

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</tr>
<tr>
<td>Intercept</td>
<td>0.07339 (0.05085 to 0.09593)</td>
<td>0.07358 (0.05104 to 0.09612)</td>
</tr>
<tr>
<td>Std Err Est</td>
<td>0.03732</td>
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Medical Decision Point Analysis
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Mayo SUAC Cutoff: Cutoff set to 1.0 (99.99%ile = 0.82)
Succinylacetone (SA)

NeoBase ≈ 4.051 * Mayo

Slope: 4.051
Intercept: -0.29731
R: 0.9984
Succinylacetone (SA)

TP TYR1: SUAC

Mayo = 35.2 µmol/L

MI Neobase = 8.76 µmol/L

Mayo = 4.051 * Neobase – 0.29731

Calculated Mayo = 35.2 µmol/L
NeoGram Cutoff = 0.41

Target Range
Glutaryl carnitine (C5DC)

NeoGram \approx 5.168 \times \text{Mayo}
Target Range

- MI Equivalent Cutoff = 0.765
- NeoBase C5DC 99.99\%tile = 0.732
- NeoGram Cutoff = 0.41
- MI TP GAI: C5DC = 0.46
- Mayo Cutoff = 0.15

C5DC + C10-OH
Target Range

MI Cutoff = 68
Arginine (Arg)

NeoGram \approx 3.550 \times \text{Mayo}

MI = 107 \mu\text{mol/L}

NeoGram = 150

TP ARG

Mayo = 29.5 \mu\text{mol/L}
**Alternate (Quantitative) Method Comparison**

**X Method:** Mayo Medical Lab  
**Y Method:** MI NeoGram

**Regression Analysis**

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<tr>
<td>Slope</td>
<td>3.551 (3.246 to 3.857)</td>
<td>3.319 (3.023 to 3.615)</td>
</tr>
<tr>
<td>Intercept</td>
<td>-4.0952 (-12.2819 to 4.0915)</td>
<td>1.1319 (-6.8029 to 9.0668)</td>
</tr>
<tr>
<td>Std Err Est</td>
<td>14.0499</td>
<td>13.6177</td>
</tr>
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**Medical Decision Point Analysis**

Calculated by Deming Regression (R >= 0.9)

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<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>84.7</td>
<td>80.2</td>
</tr>
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</table>

**Mayo Arg Cutoff**  
**Equivalent NeoGram Arg Cutoff**
MI Cutoff = 68
Mayo Cutoff = 25
MI Equivalent Cutoff = 85

Target Range

Cutoff marker size is proportional to the number of labs using the same value.
Free carnitine (C0)

NeoGram ≈ 1.781 * Mayo
Sample Exchange - 6 months.

Free carnitine (C0)

NeoBase ≈ 1.781 * Mayo
Malonylcarnitine (C3DC)

NeoBase \approx 0.096 \times \text{Missouri}
MI NeoBase \( \approx 0.096 \times \text{Missouri} \)

\[
\text{MO C3DC} = 5.75 \mu\text{mol/L} \\
\text{MI C3DC} = 0.60 \mu\text{mol/L} \\
\text{Calculated MI} = 0.60 \mu\text{mol/L}
\]
Conclusions

Harmonization Using CDC Quality Control Materials:

- Allows Harmonization of Cutoffs
- Allows Harmonization of TP Analyte Concentrations
Conclusions

- Allowed for an accurate comparison of Cutoff Values between Michigan and Mayo.

- Identified that C16OH, C0, Cit, Cit/Arg, and Met cutoffs required correction.
Acknowledgements:

MI NBS Team – Eleanor Stanley
Dr. Robert Grier – CHMMC, BGL
Patrick V. Hopkins – Missouri
Marie-Thérèse Berthier, Quebec – NeoBase
Sheila Weiss/Bill Hoffman – Washington
Dr. Victor DeJesus/CDC Quality Assurance Program
Dr. Piero Rinaldo/David McHugh - Region 4 Collaborative
NeoBase (μmol/L)

CDC (μmol/L)

Slope 0.986
Intercept -0.005
R 0.9999
CDC equivalent uMol/L