Toward Reliable Lipoprotein Particle Predictions from NMR Spectra of Human Blood

An Interlaboratory Ring Test

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Supporting Information

Towards reliable lipoprotein particle predictions from NMR spectra of human blood: an interlaboratory ring test

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Abstract: Lipoprotein profiling of human blood by ^{1}H Nuclear Magnetic Resonance (NMR) spectroscopy is a rapid and promising approach to monitor health and disease states in medicine and nutrition. However, lack of standardization of measurement protocols has prevented the use of NMR-based lipoprotein profiling in meta-studies.

In this study, a standardized NMR measurement protocol was applied in a ring test performed across three different laboratories in Europe on plasma and serum samples from 28 individuals. Data was evaluated in terms of (i) spectral differences, (ii) differences in LPD predictions obtained using an existing prediction model and (iii) agreement of predictions with cholesterol concentrations in high and low density lipoproteins (HDL and LDL) particles measured by standardized clinical assays.

ANOVA-simultaneous component analysis (ASCA) of the ring test spectral ensemble that contains methylene and methyl peaks (1.4-0.6 ppm) showed that 97.99% of the variance in the data is related to subject, 1.62% to sample type (serum or plasma) and 0.39% to laboratory. This interlaboratory variation is in fact smaller than the maximum acceptable intralaboratory variation on quality control samples. It is also shown that the reproducibility between laboratories is good enough for the LPD predictions to be exchangeable when the standardized NMR measurement protocol is followed.

With the successful implementation of this protocol, which results in reproducible prediction of lipoprotein distributions across laboratories, a step is taken towards bringing NMR more into scope of prognostic and diagnostic biomarkers, reducing the need for less efficient methods

Supplementary Materials and Methods

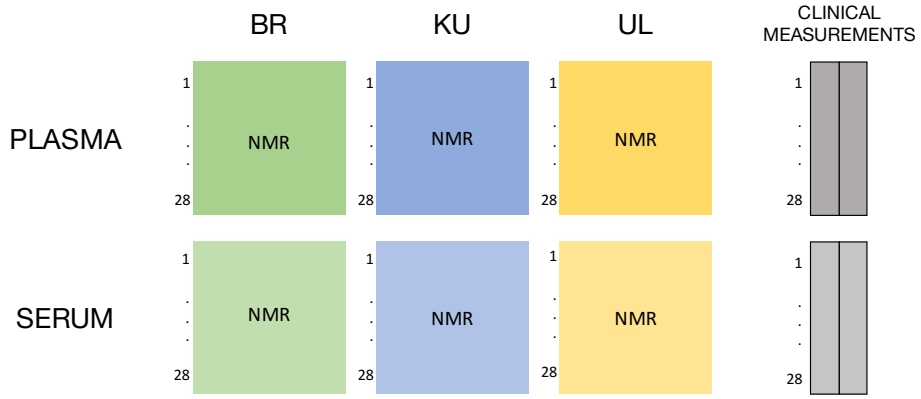


Figure S1. Experimental design of the ring test study. NMR spectra from plasma and serum samples of 28 individuals were obtained at the same time in three different locations (Bruker, University of Copenhagen and Unilever). Clinical measurements (HDL-C and LDL-C) for plasma and serum samples separately were obtained for model performance assessment.

Table S1. Spectrometer and probe used in the ring test at each of the three laboratories.

	BR	**KU**	**UL**
Magnet	ASCEND	UltraShield Plus	UltraShield Plus
Shim System	BOSS III	BOSS II	BOSS II
Console	AVANCE III HD	AVANCE III HD	AVANCE III
Probe	inverse RT (BBI)	inverse RT (BBI)	Inverse Cryo (TCI)

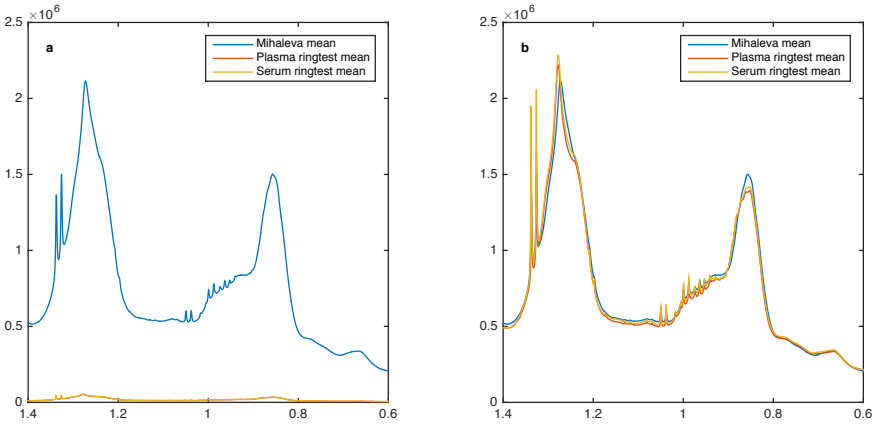


Figure S2. Mihaleva mean spectra, plasma ring test mean spectra and serum ring test mean spectra (a) before and (b) after scaling of the ring test data with the scaling factor *c*.

(Equation S1) $$r = \sqrt{\frac{SS(\mathbf{A}-\mathbf{B})}{SS(\mathbf{A})+SS(\mathbf{B})}} \qquad 0 \le r \le 1,$$

$$0 \le r = \frac{tr(\mathbf{A}\text{-}\mathbf{B})'(\mathbf{A}\text{-}\mathbf{B})}{tr(\mathbf{A}'\mathbf{A}) + tr(\mathbf{B}'\mathbf{B})} = \frac{\|\mathbf{A}-\mathbf{B}\|^2}{\|\mathbf{A}\|^2 + \|\mathbf{B}\|^2} = \frac{SS(\mathbf{A}-\mathbf{B})}{SS(\mathbf{A}) + SS(\mathbf{B})}$$

for $\mathbf{A} = \mathbf{B} \rightarrow r = 0$

for $\|\mathbf{A}\|^2 \approx \|\mathbf{B}\|^2$ (spectral matrices of similar size)

then max r = 1 (for **A'B** = 0; **B⊥A**)

So, in practice $0 \leq r \leq 1$

0 = maximum agreement/similarity

1 = maximum disagreement/dissimilarity

Supplementary Results. Characterization of the ring test population

Table S2. Distribution of the 28 ring test plasma and serum samples and of 189 Mihaleva training samples according to the serum lipid classification of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (2002). Clinical data for one of the original 190 Mihaleva training samples was not available.

LIPID	ATPIII group	Ring test (plasma)	Ring test (serum)	Mihaleva training
Total cholesterol	Desirable (<5.18 mM)	24	21	19
	Borderline high (5.18-6.18 mM)	3	6	61
	High (≥ 6.20 mM)	1	1	109
HDL-C	Low (<1 mM)	2	2	4
	Average (1-1.55 mM)	16	15	75
	High (>1.55 mM)	10	11	110
LDL-C	Optimal (<2.59 mM)	12	10	12
	Near/above optimal (2.59-3.34 mM)	14	14	46
	Borderline high (3.35-4.12 mM)	2	4	69
	High (4.15-4.90 mM)	0	0	46
	Very high (>4.90 mM)	0	0	16
Total triglycerides	Desirable (<1.70 mM)	25	25	173
	Borderline high (1.70-2.20 mM)	1	1	16
	High (2.30-5.60 mM)	2	2	0
	Very high (>5.60 mM)	0	0	0

Supplementary Results. Level 1

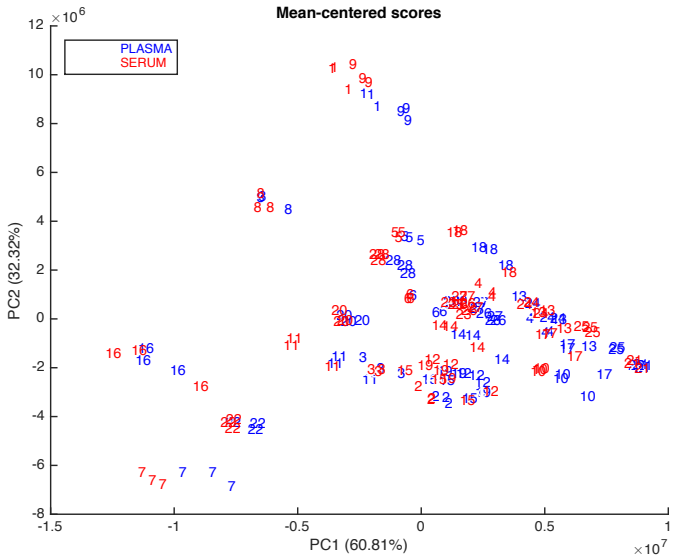


Figure S3. Scores plot of a 2-component PCA model of all spectra (plasma and serum).

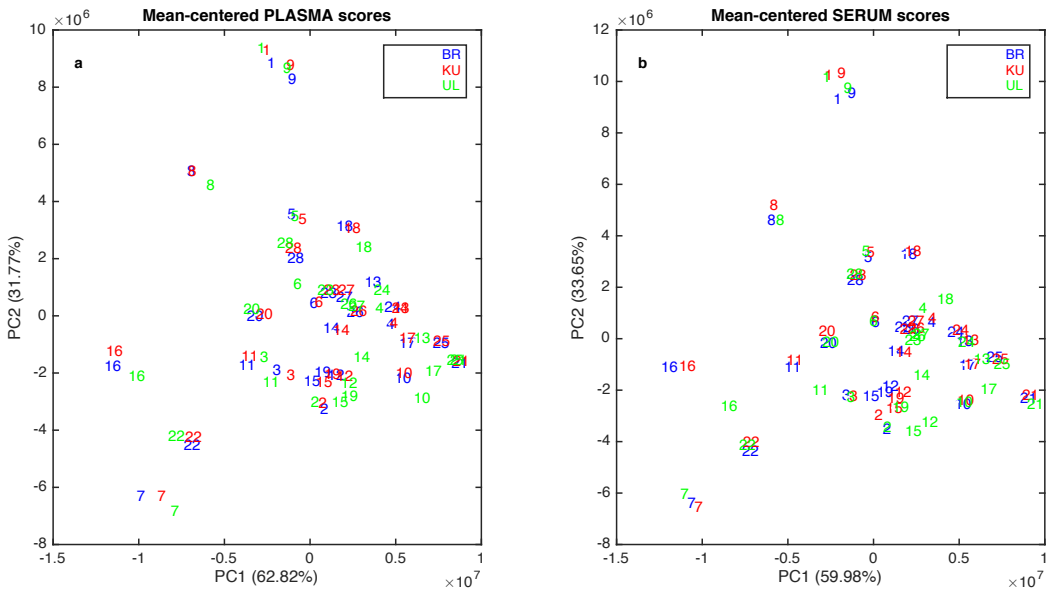


Figure S4. Scores plot of a 2-component PCA model of the (a) plasma and (b) serum spectra.

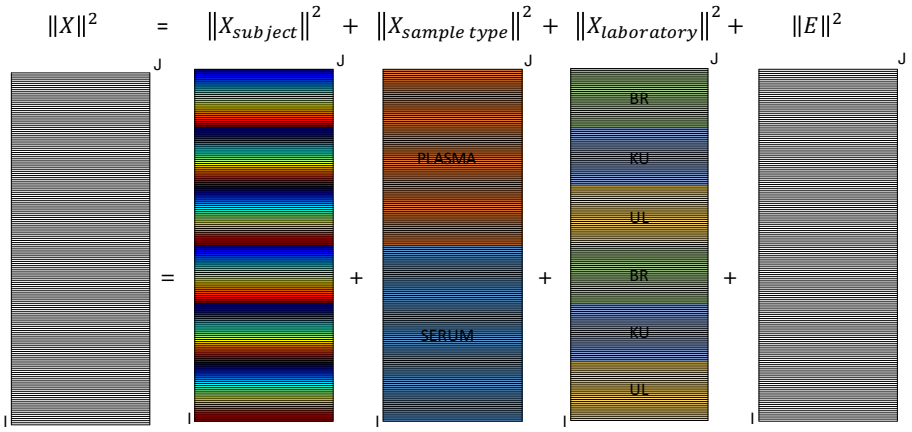
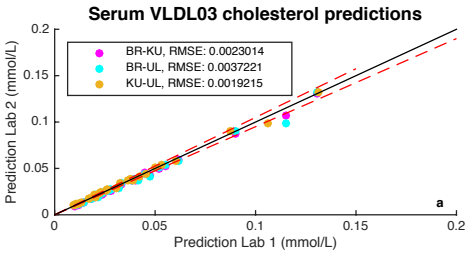
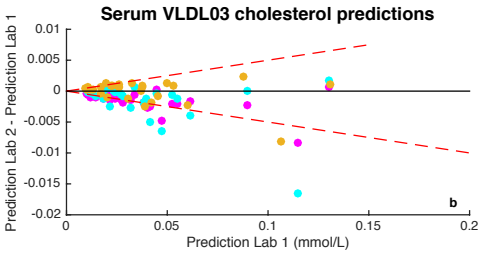
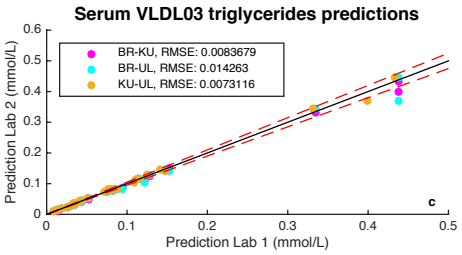


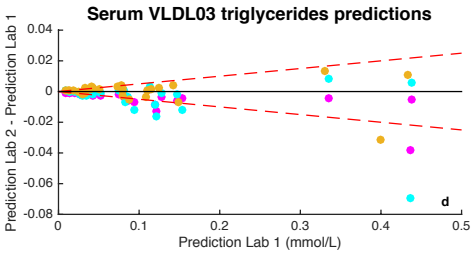
Figure S5. Partitioning of the NMR spectral data (mean centered) in the ASCA analysis. The contribution of each of the factors to the explained variance can be determined as the sum of squares of each of the matrices IxJ (I=168, J=1746).

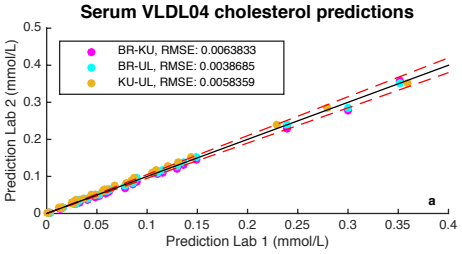
Supplementary Results. Level 2. Serum

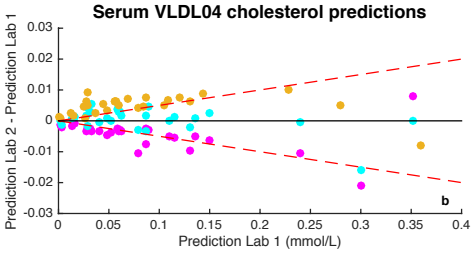


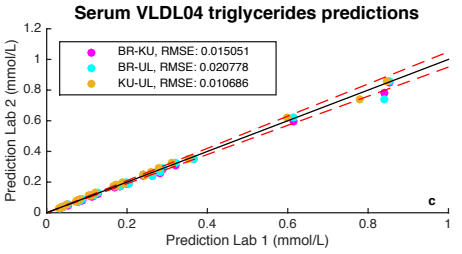


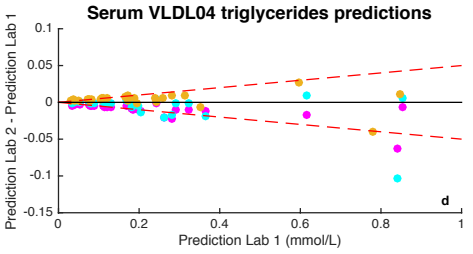


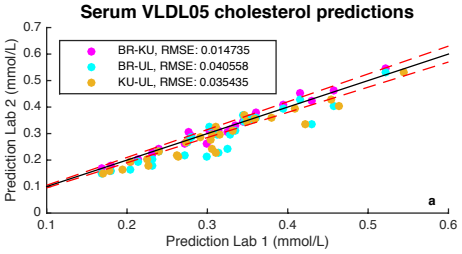


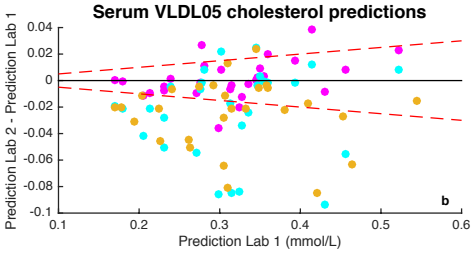


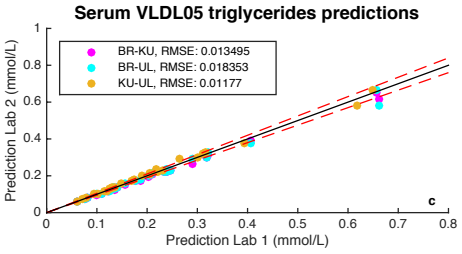


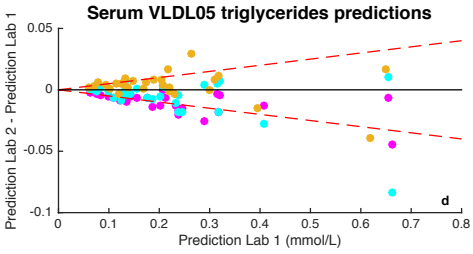


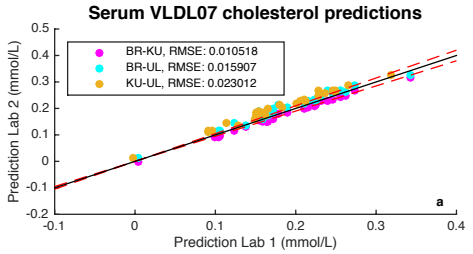


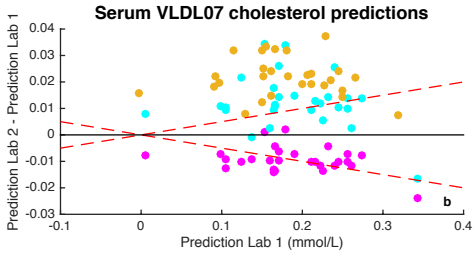


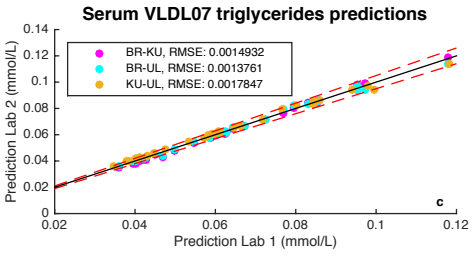


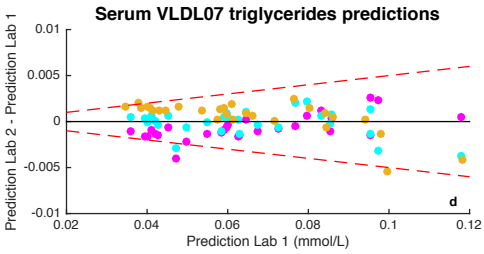


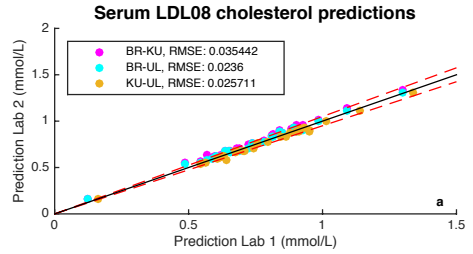


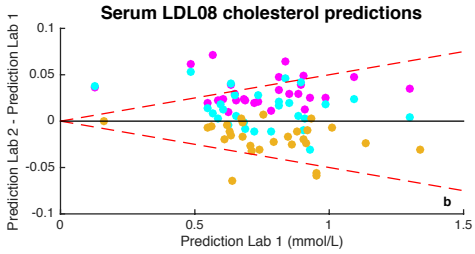

Serum VLDL07 cholesterol predictions
BR-KU, RMSE: 0.010518
BR-UL, RMSE: 0.015907
KU-UL, RMSE: 0.023012
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

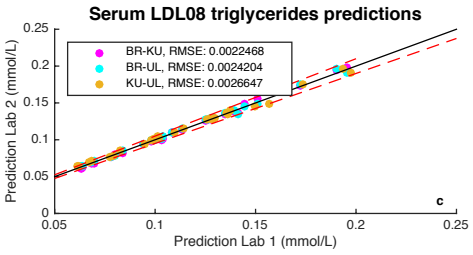

Serum VLDL07 cholesterol predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
b

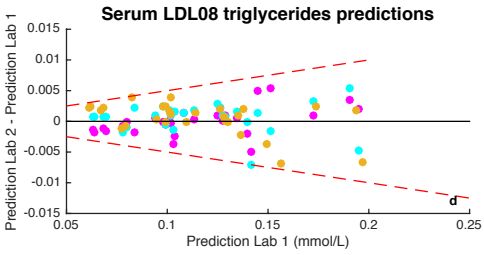

Serum VLDL07 triglycerides predictions
BR-KU, RMSE: 0.0014932
BR-UL, RMSE: 0.0013761
KU-UL, RMSE: 0.0017847
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
c

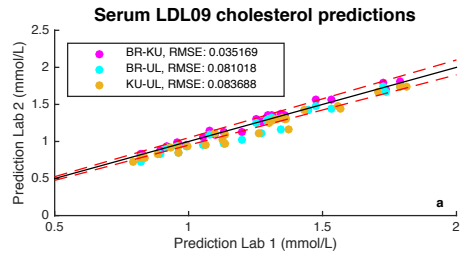

Serum VLDL07 triglycerides predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
d

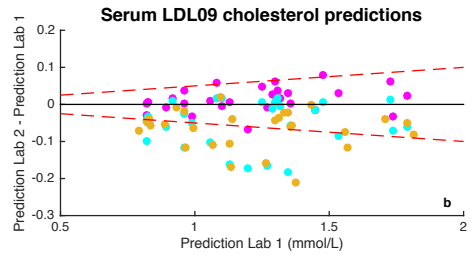

Serum LDL08 cholesterol predictions
BR-KU, RMSE: 0.035442
BR-UL, RMSE: 0.0236
KU-UL, RMSE: 0.025711
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

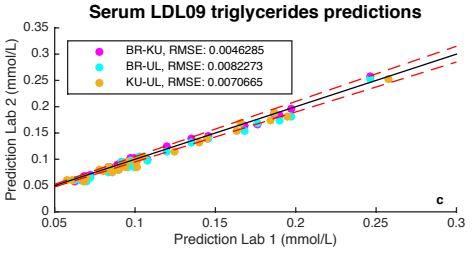

Serum LDL08 cholesterol predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
b

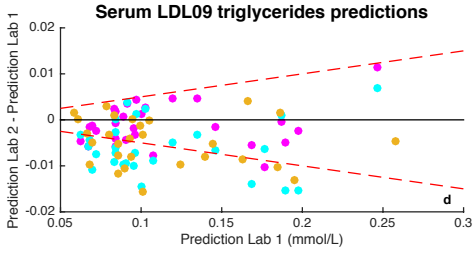

Serum LDL08 triglycerides predictions
BR-KU, RMSE: 0.0022468
BR-UL, RMSE: 0.0024204
KU-UL, RMSE: 0.0026647
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
c

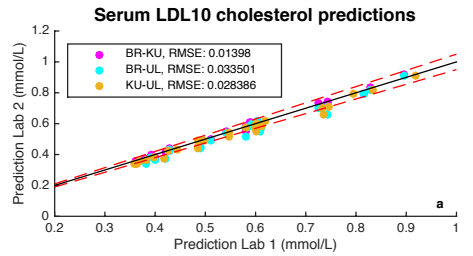

Serum LDL08 triglycerides predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
d

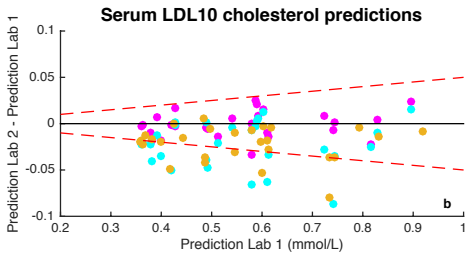

Serum LDL09 cholesterol predictions
BR-KU, RMSE: 0.035169
BR-UL, RMSE: 0.081018
KU-UL, RMSE: 0.083688
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

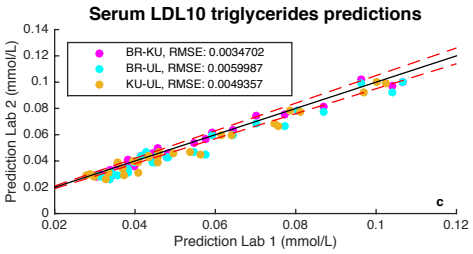

Serum LDL09 cholesterol predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
b

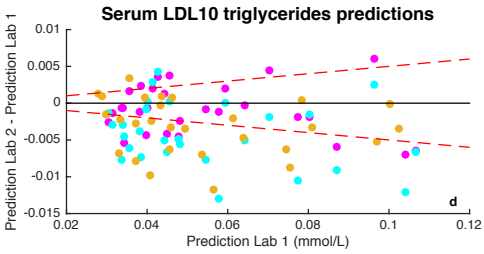

Serum LDL09 triglycerides predictions
BR-KU, RMSE: 0.0046285
BR-UL, RMSE: 0.0082273
KU-UL, RMSE: 0.0070665
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
c

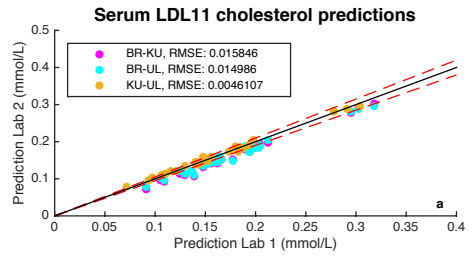

Serum LDL09 triglycerides predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
d

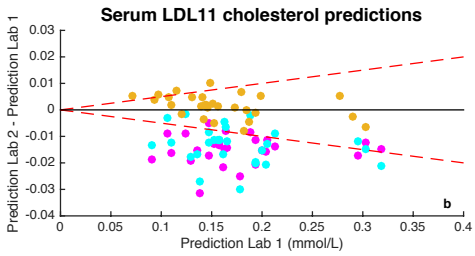

Serum LDL10 cholesterol predictions
BR-KU, RMSE: 0.01398
BR-UL, RMSE: 0.033501
KU-UL, RMSE: 0.028386
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

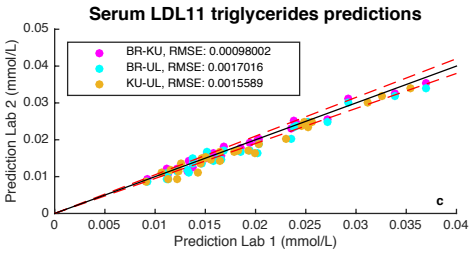

Serum LDL10 cholesterol predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
b

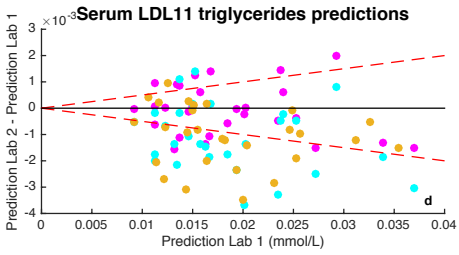

Serum LDL10 triglycerides predictions
BR-KU, RMSE: 0.0034702
BR-UL, RMSE: 0.0059987
KU-UL, RMSE: 0.0049357
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
c

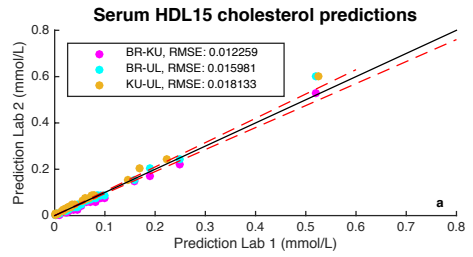

Serum LDL10 triglycerides predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
d

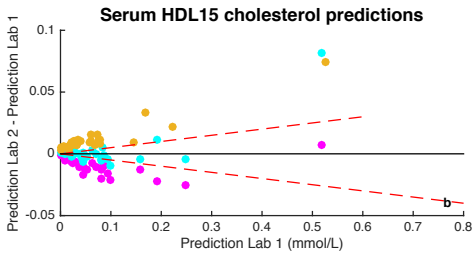

Serum LDL11 cholesterol predictions
BR-KU, RMSE: 0.015846
BR-UL, RMSE: 0.014986
KU-UL, RMSE: 0.0046107
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

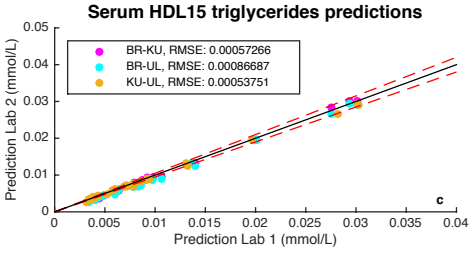

Serum LDL11 cholesterol predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
b

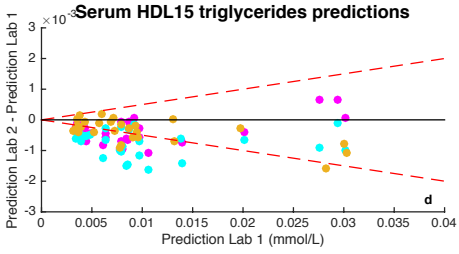

Serum LDL11 triglycerides predictions
BR-KU, RMSE: 0.00098002
BR-UL, RMSE: 0.0017016
KU-UL, RMSE: 0.0015589
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
c

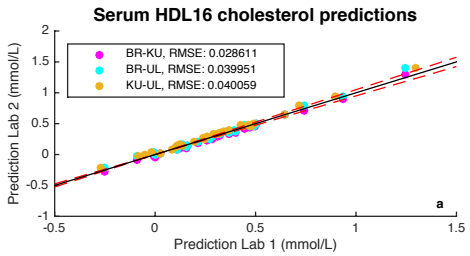

Serum LDL11 triglycerides predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
d

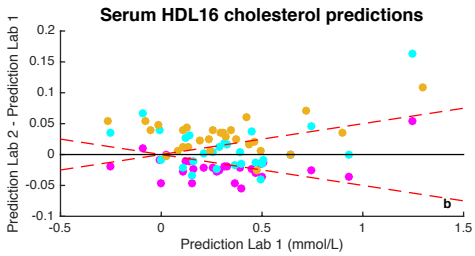

Serum HDL15 cholesterol predictions
BR-KU, RMSE: 0.012259
BR-UL, RMSE: 0.015981
KU-UL, RMSE: 0.018133
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

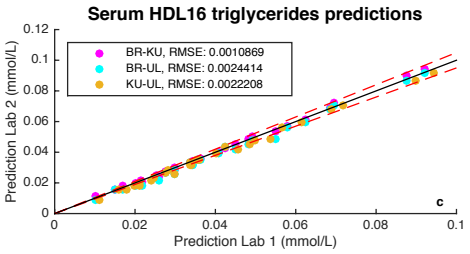

Serum HDL15 cholesterol predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
b

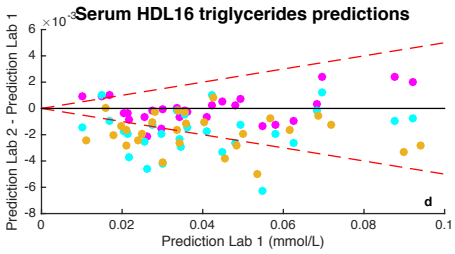

Serum HDL15 triglycerides predictions
BR-KU, RMSE: 0.00057266
BR-UL, RMSE: 0.00086687
KU-UL, RMSE: 0.00053751
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
c

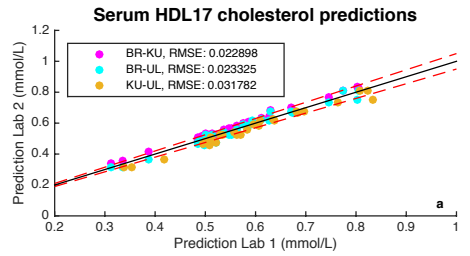

Serum HDL15 triglycerides predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
d

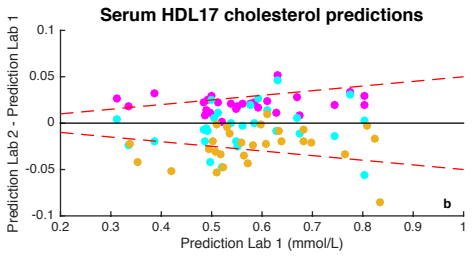

Serum HDL16 cholesterol predictions
BR-KU, RMSE: 0.028611
BR-UL, RMSE: 0.039951
KU-UL, RMSE: 0.040059
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

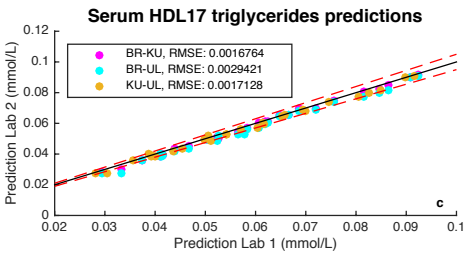

Serum HDL16 cholesterol predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
b

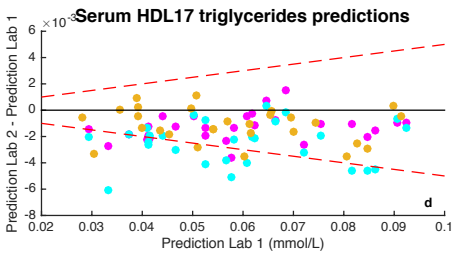

Serum HDL16 triglycerides predictions
BR-KU, RMSE: 0.0010869
BR-UL, RMSE: 0.0024414
KU-UL, RMSE: 0.0022208
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
c

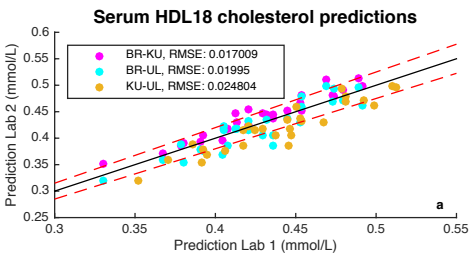

Serum HDL16 triglycerides predictions
×10⁻³
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
d

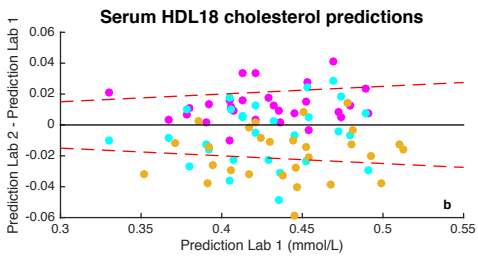

Serum HDL17 cholesterol predictions
BR-KU, RMSE: 0.022898
BR-UL, RMSE: 0.023325
KU-UL, RMSE: 0.031782
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

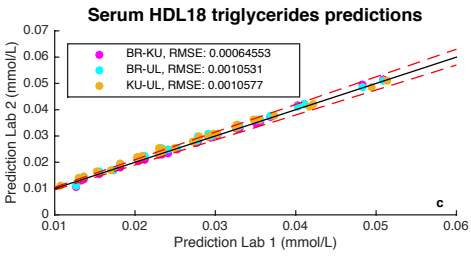

Serum HDL17 cholesterol predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
b

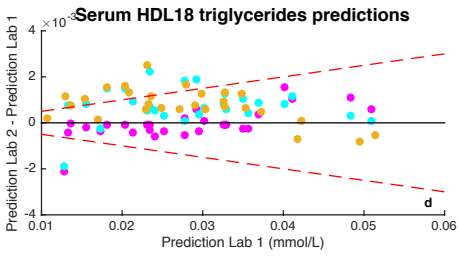

Serum HDL17 triglycerides predictions
BR-KU, RMSE: 0.0016764
BR-UL, RMSE: 0.0029421
KU-UL, RMSE: 0.0017128
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
c


Serum HDL17 triglycerides predictions
×10⁻³
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
d


Serum HDL18 cholesterol predictions
BR-KU, RMSE: 0.017009
BR-UL, RMSE: 0.01995
KU-UL, RMSE: 0.024804
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a


Serum HDL18 cholesterol predictions
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
b


Serum HDL18 triglycerides predictions
BR-KU, RMSE: 0.00064553
BR-UL, RMSE: 0.0010531
KU-UL, RMSE: 0.0010577
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
c


Serum HDL18 triglycerides predictions
×10⁻³
Prediction Lab 2 - Prediction Lab 1
Prediction Lab 1 (mmol/L)
d

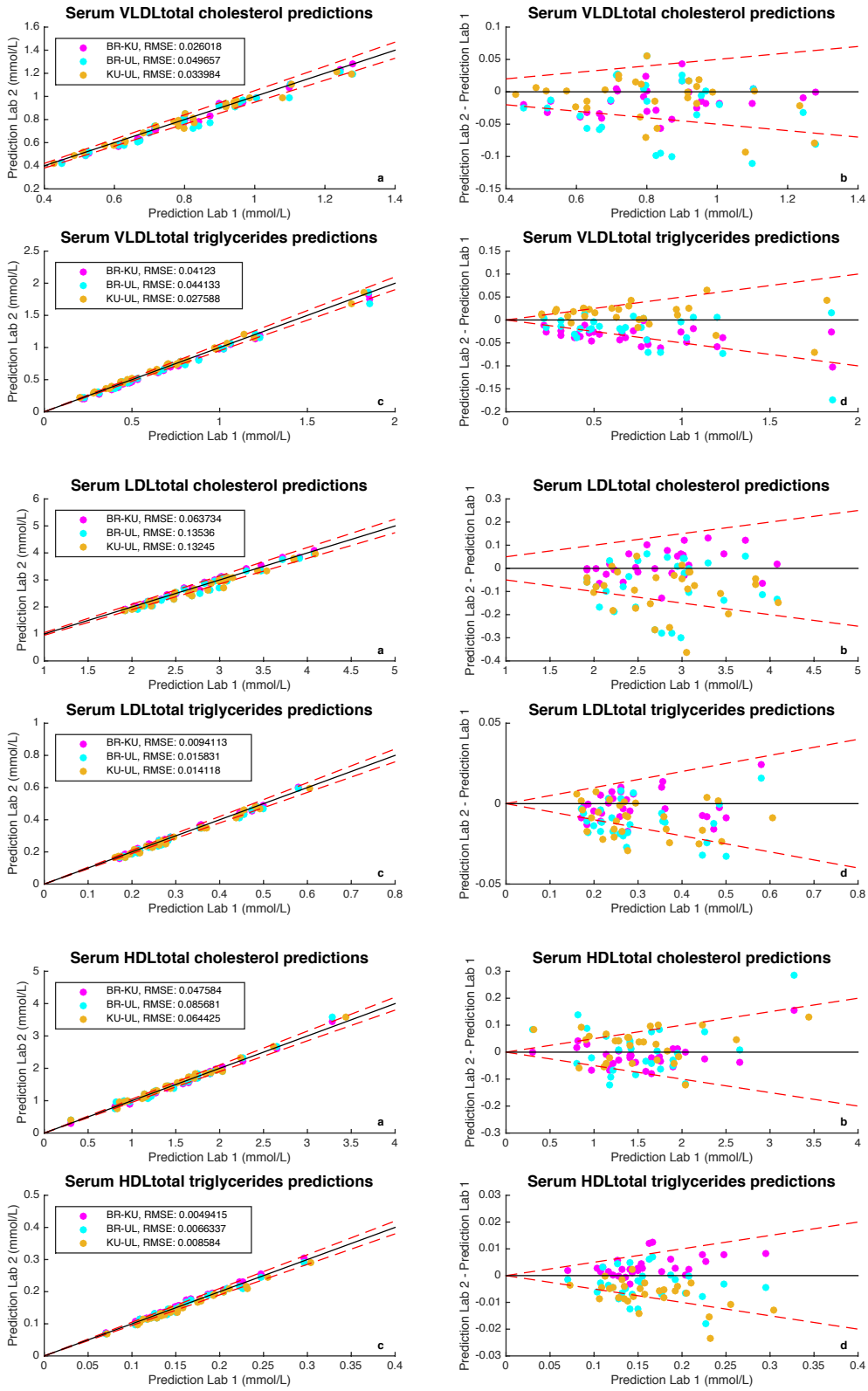
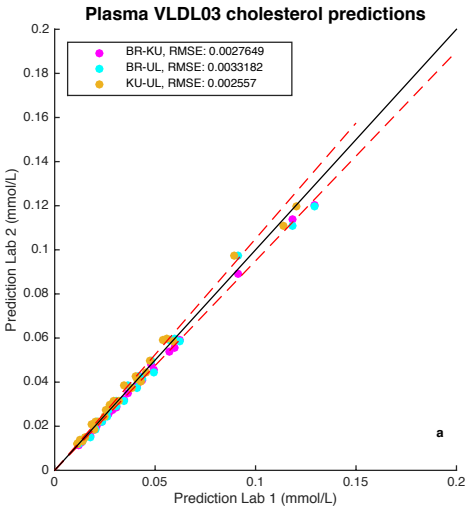
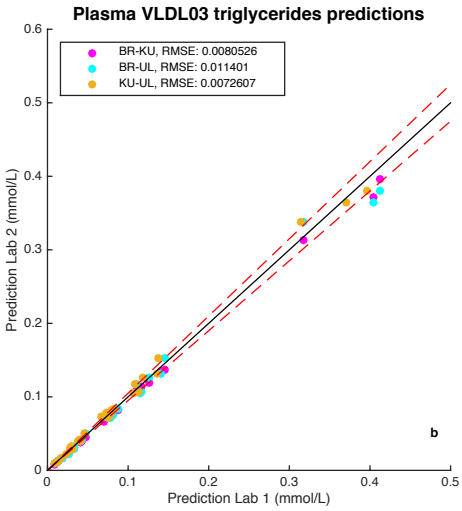
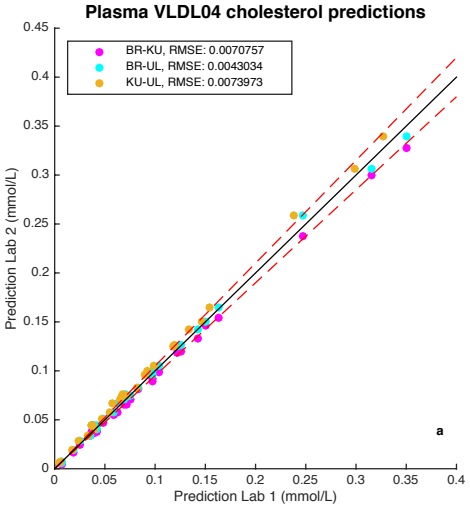


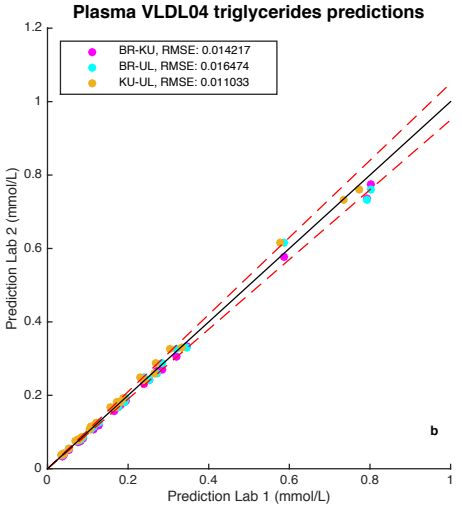
Figure S6. Between-lab differences in serum cholesterol and triglycerides predictions for all subclasses (except VLDL06, see main text) and main fractions obtained using the Mihaleva-derived PLS model. BR versus KU, BR versus UL and UL versus KU (a and b) cholesterol and (c and d) triglycerides serum predictions. (a and c) On the x axis, the value of the prediction of the first laboratory; on the y axis, the value of the prediction of the second laboratory. (b and d) Zoom-in of the differences between labs: On the x axis, the value of the prediction of the first laboratory; on the y axis, the difference between the prediction of the second laboratory and the prediction of the first one. The black line is drawn where predictions are equal, the red dashed lines indicate a deviation of 5%.

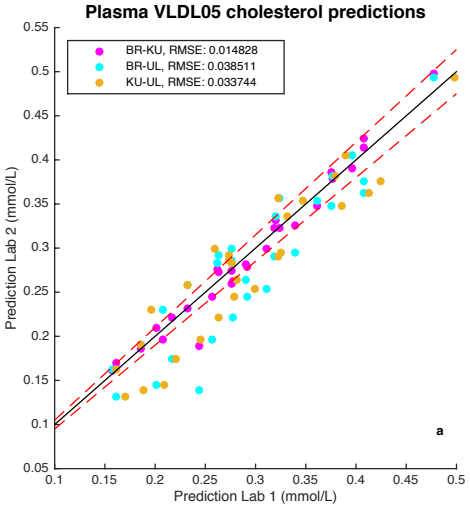
Supplementary Results. Level 2. Plasma

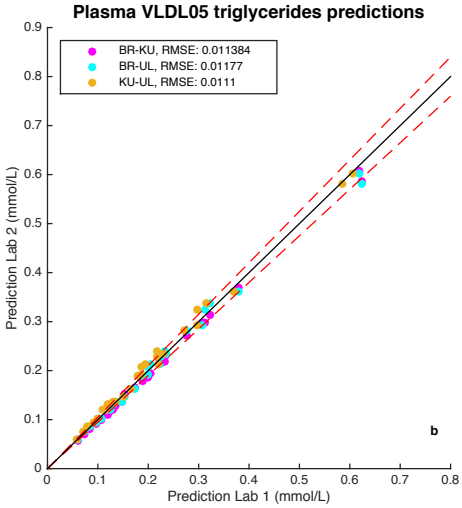


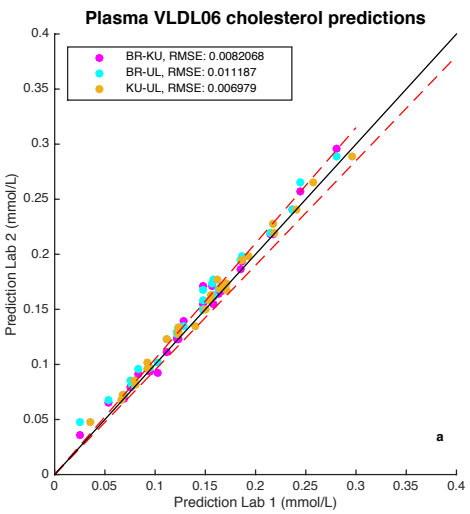


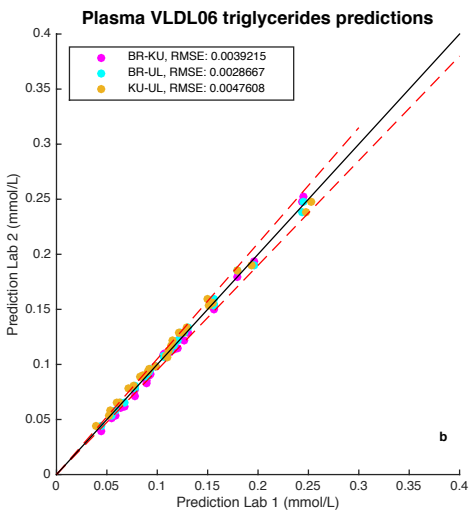


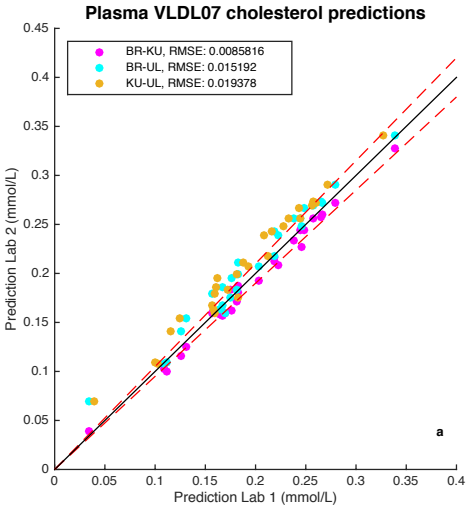


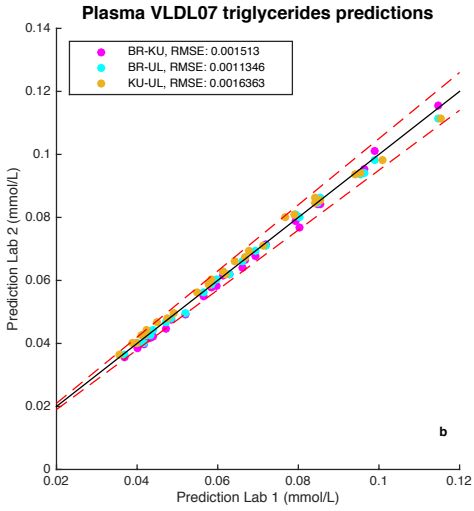


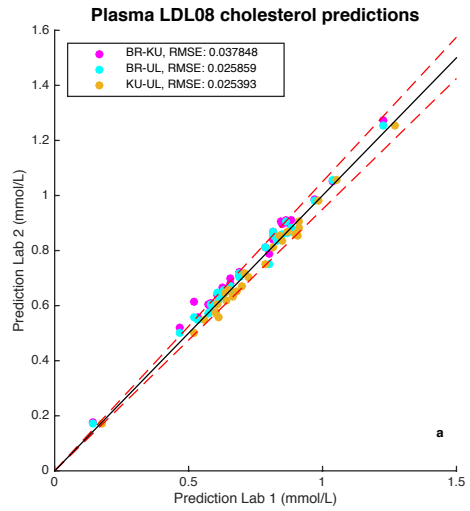


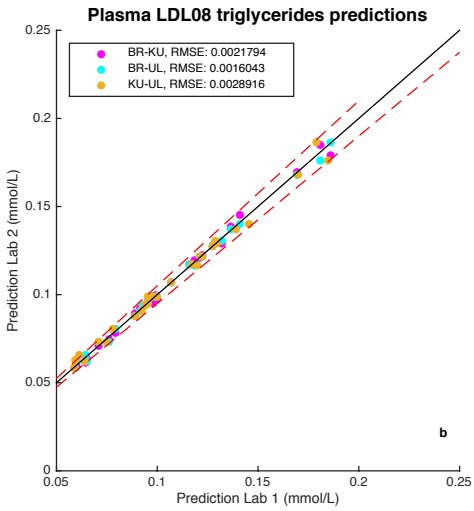

Plasma VLDL06 cholesterol predictions
BR-KU, RMSE: 0.0082068
BR-UL, RMSE: 0.011187
KU-UL, RMSE: 0.006979
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

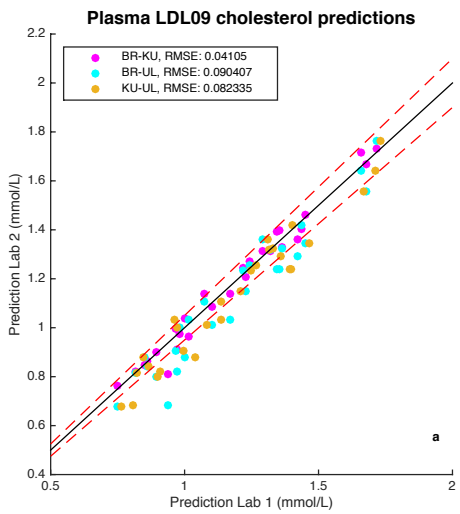

Plasma VLDL06 triglycerides predictions
BR-KU, RMSE: 0.0039215
BR-UL, RMSE: 0.0028667
KU-UL, RMSE: 0.0047608
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b

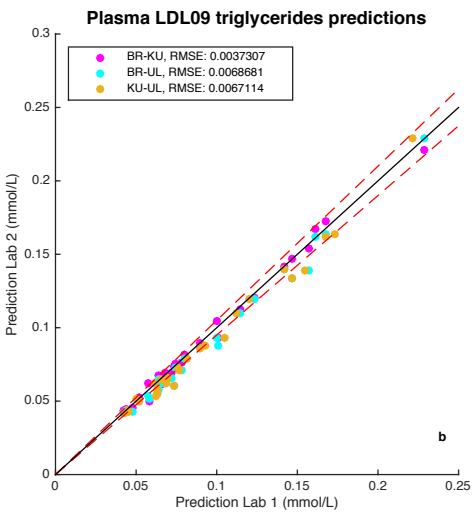

Plasma VLDL07 cholesterol predictions
BR-KU, RMSE: 0.0085816
BR-UL, RMSE: 0.015192
KU-UL, RMSE: 0.019378
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

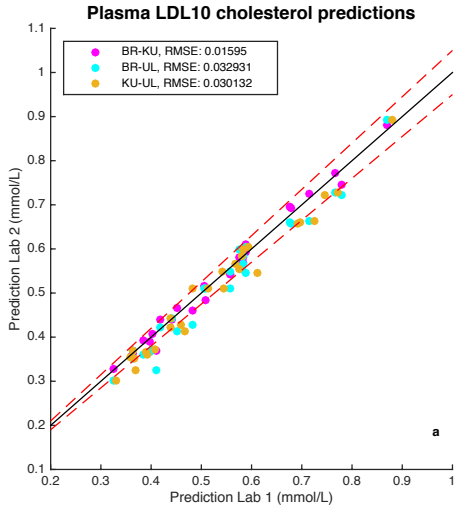

Plasma VLDL07 triglycerides predictions
BR-KU, RMSE: 0.001513
BR-UL, RMSE: 0.0011346
KU-UL, RMSE: 0.0016363
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b

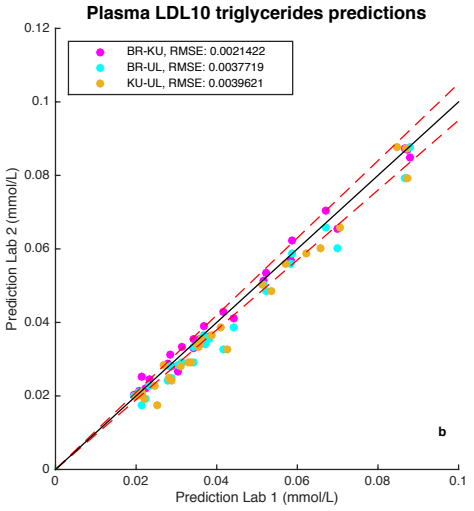

Plasma LDL08 cholesterol predictions
BR-KU, RMSE: 0.037848
BR-UL, RMSE: 0.025859
KU-UL, RMSE: 0.025393
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

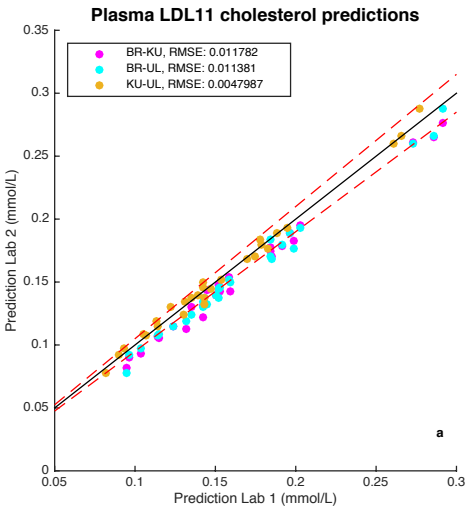

Plasma LDL08 triglycerides predictions
BR-KU, RMSE: 0.0021794
BR-UL, RMSE: 0.0016043
KU-UL, RMSE: 0.0028916
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b

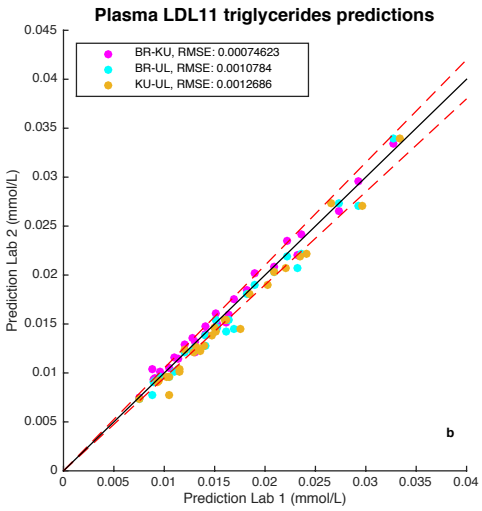

Plasma LDL09 cholesterol predictions
BR-KU, RMSE: 0.04105
BR-UL, RMSE: 0.090407
KU-UL, RMSE: 0.082335
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

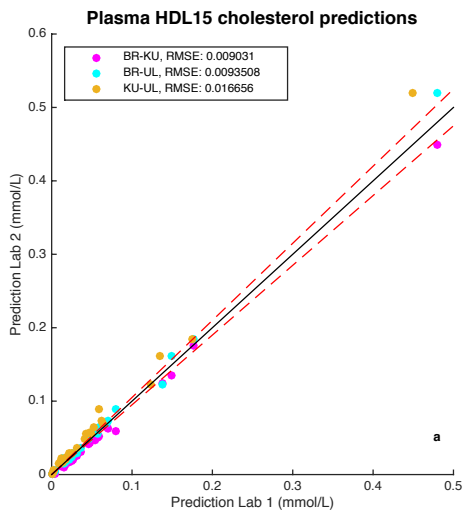

Plasma LDL09 triglycerides predictions
BR-KU, RMSE: 0.0037307
BR-UL, RMSE: 0.0068681
KU-UL, RMSE: 0.0067114
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b

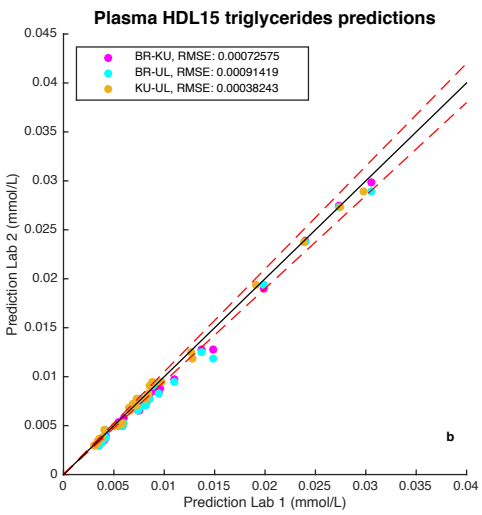

Plasma LDL10 cholesterol predictions
BR-KU, RMSE: 0.01595
BR-UL, RMSE: 0.032931
KU-UL, RMSE: 0.030132
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

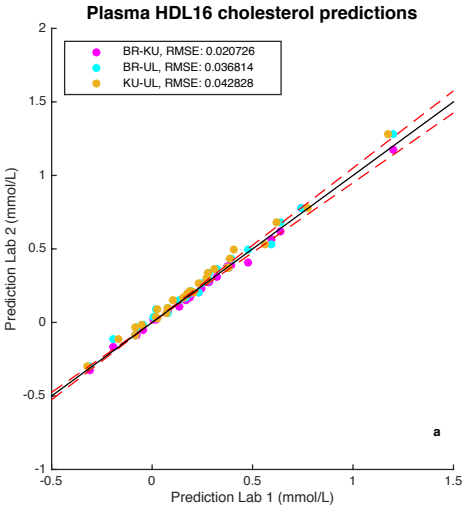

Plasma LDL10 triglycerides predictions
BR-KU, RMSE: 0.0021422
BR-UL, RMSE: 0.0037719
KU-UL, RMSE: 0.0039621
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b

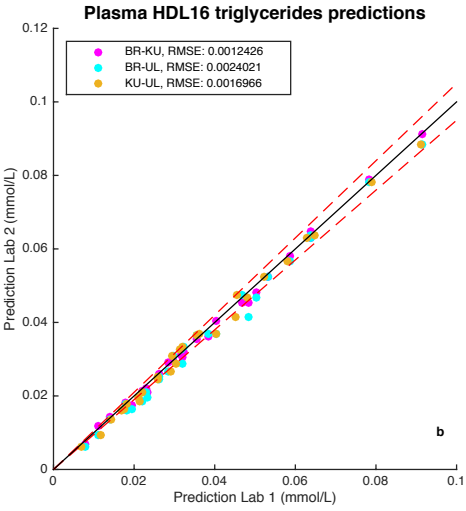

Plasma LDL11 cholesterol predictions
BR-KU, RMSE: 0.011782
BR-UL, RMSE: 0.011381
KU-UL, RMSE: 0.0047987
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

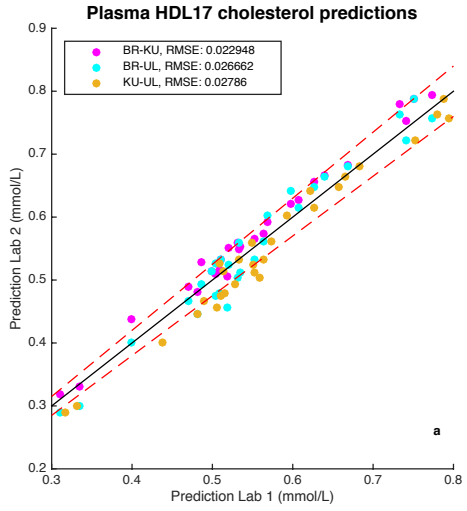

Plasma LDL11 triglycerides predictions
BR-KU, RMSE: 0.00074623
BR-UL, RMSE: 0.0010784
KU-UL, RMSE: 0.0012686
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b

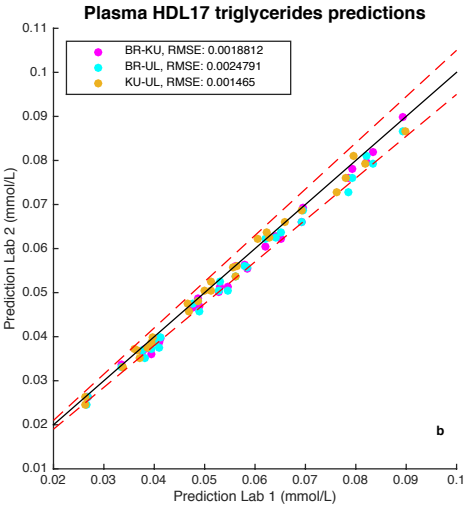

Plasma HDL15 cholesterol predictions
BR-KU, RMSE: 0.009031
BR-UL, RMSE: 0.0093508
KU-UL, RMSE: 0.016656
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

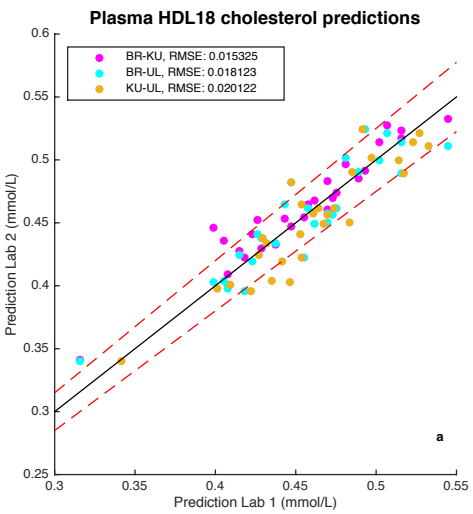

Plasma HDL15 triglycerides predictions
BR-KU, RMSE: 0.00072575
BR-UL, RMSE: 0.00091419
KU-UL, RMSE: 0.00038243
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b

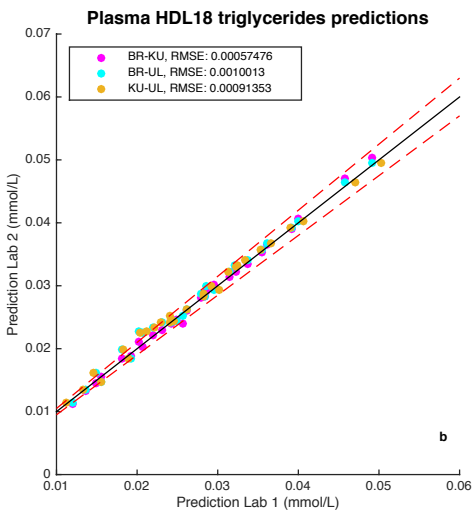

Plasma HDL16 cholesterol predictions
BR-KU, RMSE: 0.020726
BR-UL, RMSE: 0.036814
KU-UL, RMSE: 0.042828
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

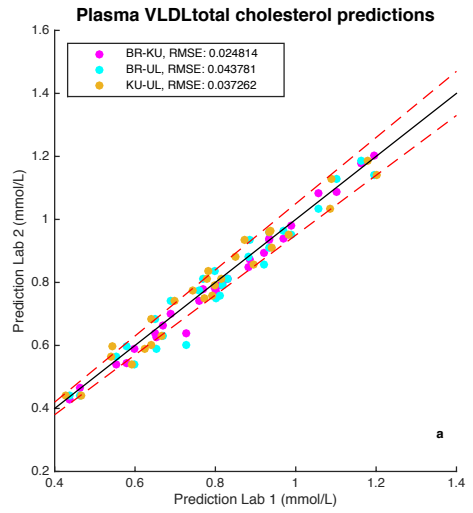

Plasma HDL16 triglycerides predictions
BR-KU, RMSE: 0.0012426
BR-UL, RMSE: 0.0024021
KU-UL, RMSE: 0.0016966
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b

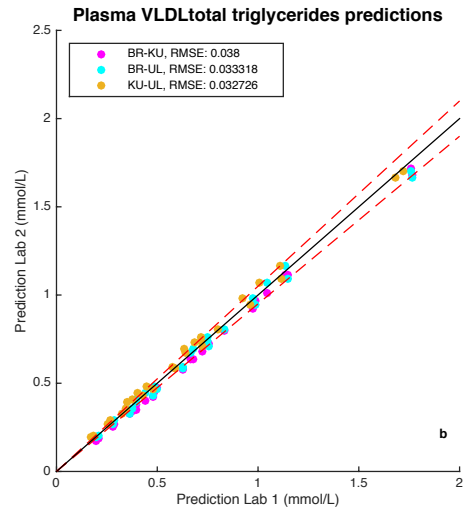

Plasma HDL17 cholesterol predictions
BR-KU, RMSE: 0.022948
BR-UL, RMSE: 0.026662
KU-UL, RMSE: 0.02786
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a

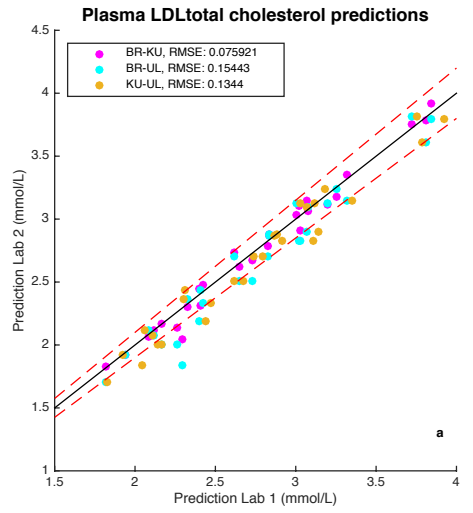

Plasma HDL17 triglycerides predictions
BR-KU, RMSE: 0.0018812
BR-UL, RMSE: 0.0024791
KU-UL, RMSE: 0.001465
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b

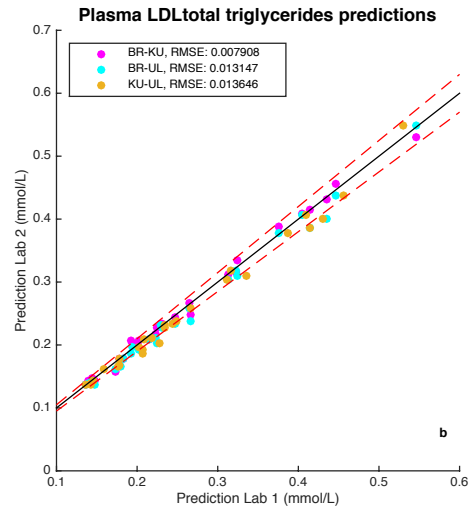

Plasma HDL18 cholesterol predictions
BR-KU, RMSE: 0.015325
BR-UL, RMSE: 0.018123
KU-UL, RMSE: 0.020122
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a


Plasma HDL18 triglycerides predictions
BR-KU, RMSE: 0.00057476
BR-UL, RMSE: 0.0010013
KU-UL, RMSE: 0.00091353
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b


Plasma VLDLtotal cholesterol predictions
BR-KU, RMSE: 0.024814
BR-UL, RMSE: 0.043781
KU-UL, RMSE: 0.037262
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a


Plasma VLDLtotal triglycerides predictions
BR-KU, RMSE: 0.038
BR-UL, RMSE: 0.033318
KU-UL, RMSE: 0.032726
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b


Plasma LDLtotal cholesterol predictions
BR-KU, RMSE: 0.075921
BR-UL, RMSE: 0.15443
KU-UL, RMSE: 0.1344
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
a


Plasma LDLtotal triglycerides predictions
BR-KU, RMSE: 0.007908
BR-UL, RMSE: 0.013147
KU-UL, RMSE: 0.013646
Prediction Lab 2 (mmol/L)
Prediction Lab 1 (mmol/L)
b

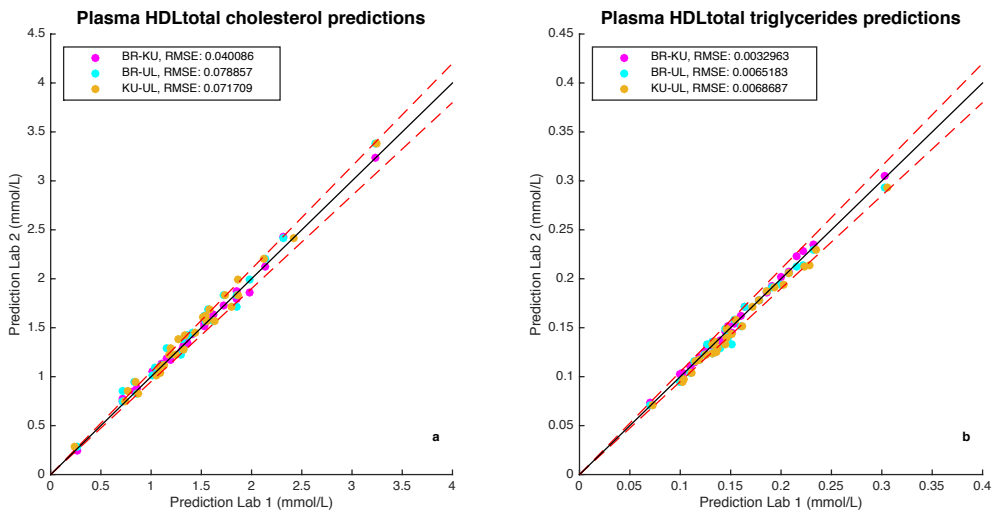


Figure S7. Between-lab differences in plasma cholesterol and triglycerides predictions for all subclasses and main classes obtained using the Mihaleva-derived PLS model. BR versus KU, BR versus UL and UL versus KU (a) cholesterol and (b) triglycerides serum predictions. On the x axis, the value of the prediction of the first laboratory; on the y axis, the value of the prediction of the second laboratory. The black line is drawn where predictions are equal, the red dashed lines indicate a deviation of 5%.

Supplementary Results. Level 3

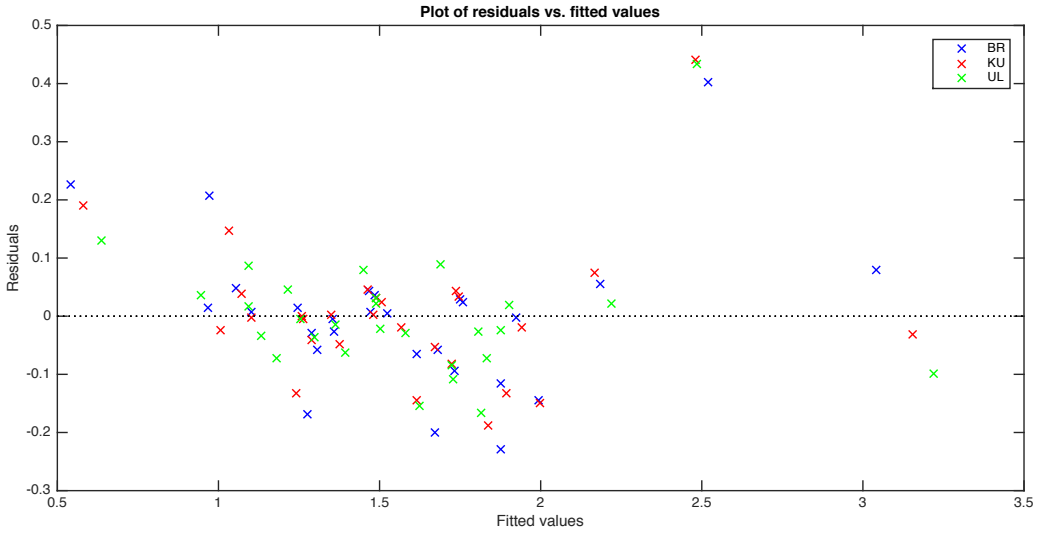


Figure S8. Ring test HDL cholesterol residual plot (PLS predictions vs. HDL-C clinical values).

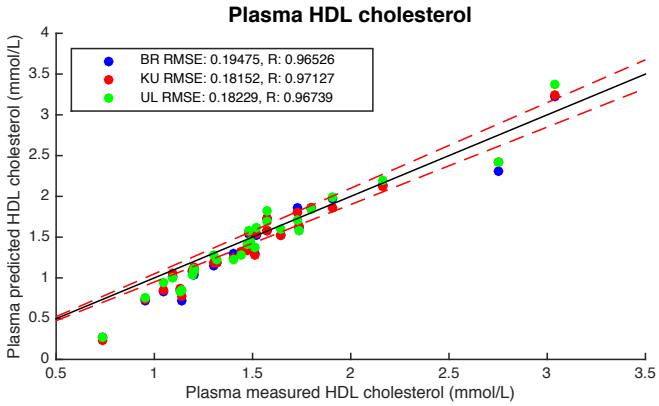


Figure S9. HDL-C predictions of the PLS model on plasma spectra from the three laboratories. The black line is drawn where prediction and measurement are equal, the red dashed lines indicate plus or minus 5%.

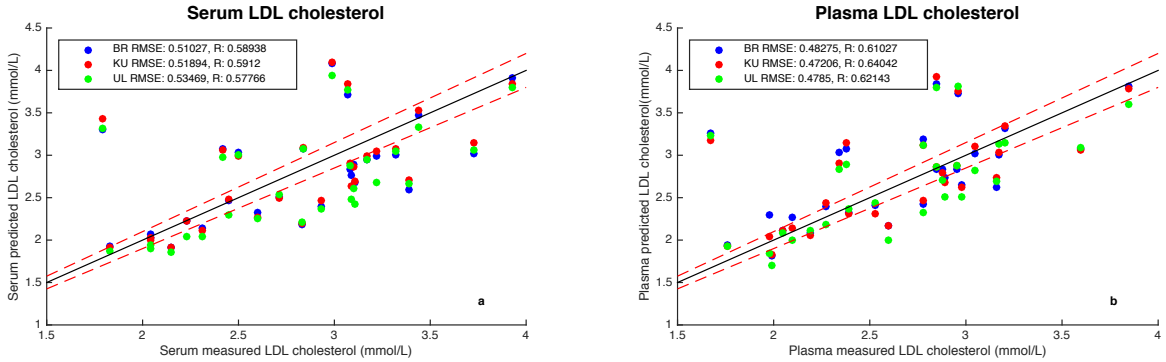


Figure S10. LDL-C predictions of the PLS model on (a) serum and (b) plasma spectra from the three laboratories. The black line is drawn where prediction and measurement are equal, the red dashed lines indicate plus or minus 5%.