

SUPPLEMENTAL MATERIAL

**Supplemental Table 1: Equivalent population percentiles of LDL-C, non-HDL-C and TC/HDL-C ratio from the Very Large Database of**

**Lipids.** The **bold** and *italic* numbers correspond to LDL-C guideline cut-points.

VLDL database percentile	LDL-C (mg/dl)	Non-HDL-C (mg/dl)	TC/HDL-C ratio
1 <sup>st</sup>	37	60	1.9
5 <sup>th</sup>	54	76	2.2
10 <sup>th</sup>	63	86	2.4
<b>15<sup>th</sup></b>	<b>70</b>	<b>93</b>	<b>2.6</b>
20 <sup>th</sup>	77	100	2.7
25 <sup>th</sup>	82	106	2.9
<b>44<sup>th</sup></b>	<b>100</b>	<b>125</b>	<b>3.3</b>
50 <sup>th</sup>	106	132	3.5
<b>72<sup>nd</sup></b>	<b>130</b>	<b>157</b>	<b>4.2</b>
75 <sup>th</sup>	134	161	4.3
<b>90<sup>th</sup></b>	<b>160</b>	<b>190</b>	<b>5.2</b>
95 <sup>th</sup>	177	209	5.9
99 <sup>th</sup>	215	251	7.2

**Supplemental Table 2: Patient-level percentile discordance between TC/HDL-C compared to direct LDL-C and LDL-C estimated by the novel method<sup>2</sup> across triglyceride categories.**

	Triglyceride categories (mg/dl)				
	<100 N = 520,879	100-149 N = 398,170	150-199 N = 204,144	200-399 N = 187,239	Total N = 1,310,432
<b>A) TC/HDL-C and direct LDL-C percentile discordance</b>					
<b>TC/HDL-C percentile minus LDL-C percentile median (Q1-Q3)</b>	-9.74 (-26.4, 2.9)	0.64 (-13.8, 15.6)	8.38 (-4.3, 24.7)	17.26 (2.5, 35.9)	-0.11 (-15.8, 15.6)
<b>≥10 percentile units discordance</b>					
TC/HDL-C < LDL-C, n (%)	258,049 (49.5)	121,405 (30.5)	34,341 (16.8)	13,322 (7.1)	427,117 (32.6)
Concordant, n (%)	183,141 (35.2)	144,116 (36.2)	73,488 (36.0)	58,602 (31.3)	459,347 (35.1)
TC/HDL-C > LDL-C, n (%)	79,689 (15.3)	132,649 (33.3)	96,315 (47.2)	115,315 (61.6)	423,968 (32.3)
<b>≥25 percentile units discordance</b>					
TC/HDL-C < LDL-C, n (%)	139,502 (26.8)	50,924 (12.8)	11,195 (5.5)	3,484 (1.8)	205,105 (15.7)
Concordant, n (%)	357,582 (68.6)	290,501 (73.0)	142,580 (69.8)	111,186 (59.4)	901,849 (68.8)
TC/HDL-C > LDL-C, n (%)	23,795 (4.6)	56,745 (14.2)	50,369 (24.7)	72,569 (38.8)	203,478 (15.5)
<b>B) TC/HDL-C and LDL-C by novel method percentile discordance</b>					
<b>TC/HDL-C percentile minus LDL-C percentile median (Q1-Q3)</b>	-9.59 (-26.1, 2.9)	0.65 (-13.5, 15.3)	8.26 (-4.0, 24.1)	16.95 (2.8, 34.9)	-0.03 (-15.5, 15.3)
<b>≥10 percentile units discordance</b>					
TC/HDL-C < LDL-C, n (%)	256,661 (49.3)	120,048 (30.1)	33,215 (16.3)	12,002 (6.4)	421,926 (32.2)
Concordant, n (%)	185,394 (35.6)	146,797 (36.9)	75,264 (36.9)	59,831 (32.0)	467,286 (35.7)
TC/HDL-C > LDL-C, n (%)	78,824 (15.1)	131,325 (33.0)	95,665 (46.8)	115,406 (61.6)	421,220 (32.1)
<b>≥25 percentile units discordance</b>					
TC/HDL-C < LDL-C, n (%)	137,210 (26.3)	49,028 (12.3)	10,236 (5.0)	2,886 (1.5)	199,360 (15.2)
Concordant, n (%)	360,443 (69.2)	294,159 (73.9)	145,324 (71.2)	113,185 (60.5)	913,111 (69.7)
TC/HDL-C > LDL-C, n (%)	23,226 (4.5)	54,983 (13.8)	48,584 (23.8)	71,168 (38.0)	197,961 (15.1)

**Supplemental Table 3A: Multivariable linear regression analysis to predict percentile discordance between TC/HDL-C versus LDL-C.**

	TC/HDL-C vs. LDL-C percentile discordance					
	A	B	C	D	E	F
<b>Constant</b>	-7.66 (0.03); -301.07	-3.83 (0.02); -234.36	-0.91 (0.01); -76.48	-0.70 (0.01); -59.54	-1.75 (0.01); -128.33	-1.58 (0.01); -135.08
<b>ln(TG)</b>	16.07 (0.02); 787.95	20.03 (0.01); 1513.74	12.46 (0.01); 1086.47	12.31 (0.01); 1077.42	15.30 (0.01); 1235.91	12.26 (0.01); 1059.61
<b>Age</b>	0.17 (0.02); 9.01	-1.76 (0.01); -150.99	-0.32 (0.01); -38.23	-0.30 (0.01); -36.06	-0.43 (0.01); -44.37	-0.67 (0.01); -80.60
<b>Gender (male)</b>	16.41 (0.04); 446.19	8.38 (0.02); 349.42	2.03 (0.02); 113.89	1.62 (0.02); 89.89	3.44 (0.02); 166.86	2.75 (0.02); 155.50
<b>HDL-C</b>			-13.24 (0.01); -1140.88	-12.99 (0.01); -1114.59		
<b>HDL<sub>2</sub>-C</b>					-9.68 (0.01); -794.73	
<b>HDL<sub>3</sub>-C</b>						-13.17 (0.01); -1140.68
<b>TC</b>		-17.27 (0.01); -1393.68	-11.52 (0.01); -1142.03	-11.32 (0.01); -1116.92	-13.78 (0.01); -1244.73	-11.29 (0.01); -1104.96
<b>LLDR</b>				1.22 (0.01); 134.93		
<b>R<sup>2</sup></b>	0.4025	0.7601	0.8801	0.8821	0.8384	0.8800

\* Natural log of triglycerides due to log normal distribution of triglycerides

Results shown are: coefficient (Standard Error); T statistic

All covariates, except gender, were standardized.

All values are statistically significant (p<0.0001)

TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; LLDR = logarithmic LDL density ratio

**Supplemental Table 3B: Multivariable linear regression analysis to predict percentile discordance between TC/HDL-C versus non-HDL-**

**C.**

	TC/HDL-C vs. non-HDL-C percentile discordance					
	A	B	C	D	E	F
<b>Constant</b>	-7.32 (0.02); -312.3	-3.96 (0.02); -246.56	-0.78 (0.01); -76.11	-0.62 (0.01); -60.81	-1.67 (0.01); -132.83	-1.54 (0.01); -149.57
<b>ln(TG)</b>	6.39 (0.02); 339.97	9.87 (0.01); 759.52	1.64 (0.01); 165.56	1.52 (0.01); 153.70	4.65 (0.01); 409.53	1.51 (0.01); 148.78
<b>Age</b>	-0.04 (0.02); -2.09	-1.73 (0.01); -150.83	-0.16 (0.01); -22.27	-0.14 (0.01); -20.12	-0.26 (0.01); -29.08	-0.55 (0.01); -75.80
<b>Gender (male)</b>	15.65 (0.03); 461.78	8.60 (0.02); 364.92	1.70 (0.02); 110.00	1.38 (0.02); 88.66	3.15 (0.02); 166.15	2.54 (0.02); 163.28
<b>HDL-C</b>			-14.39 (0.01); -1434.58	-14.21 (0.01); -1406.97		
<b>HDL<sub>2</sub>-C</b>					-10.70 (0.01); -956.86	
<b>HDL<sub>3</sub>-C</b>						-14.18 (0.01); -1398.02
<b>TC</b>		-15.18 (0.01); -1247.17	-8.94 (0.01); -1022.61	-8.79 (0.01); -1000.83	-11.33 (0.01); -1115.53	-8.74 (0.01); -974.26
<b>LLDR</b>				0.94 (0.01); 119.08		
<b>R<sup>2</sup></b>	0.2138	0.6417	0.8611	0.8631	0.7896	0.8567

\* Natural log of triglycerides due to log normal distribution of triglycerides

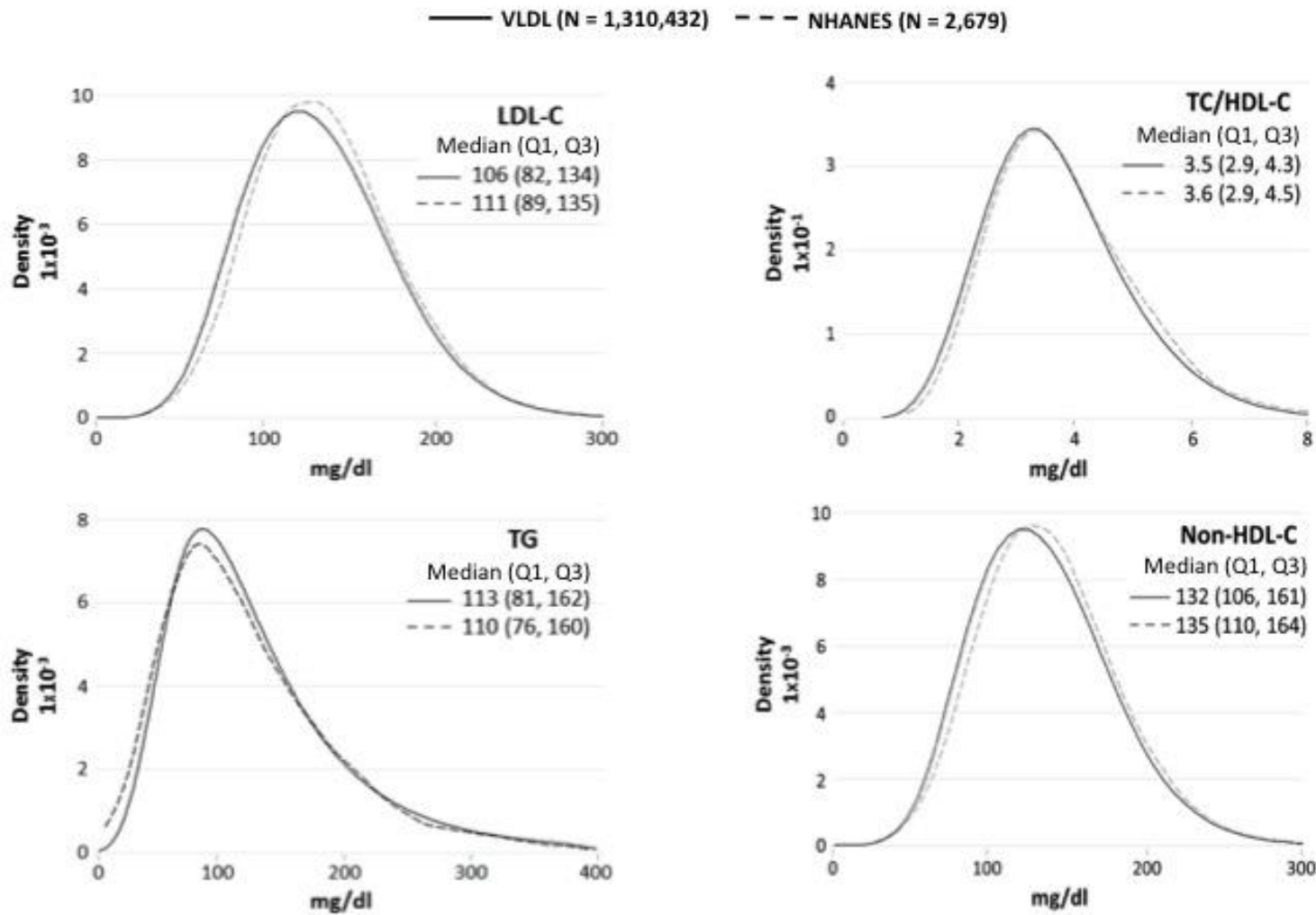
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TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; LLDR = logarithmic LDL density ratio

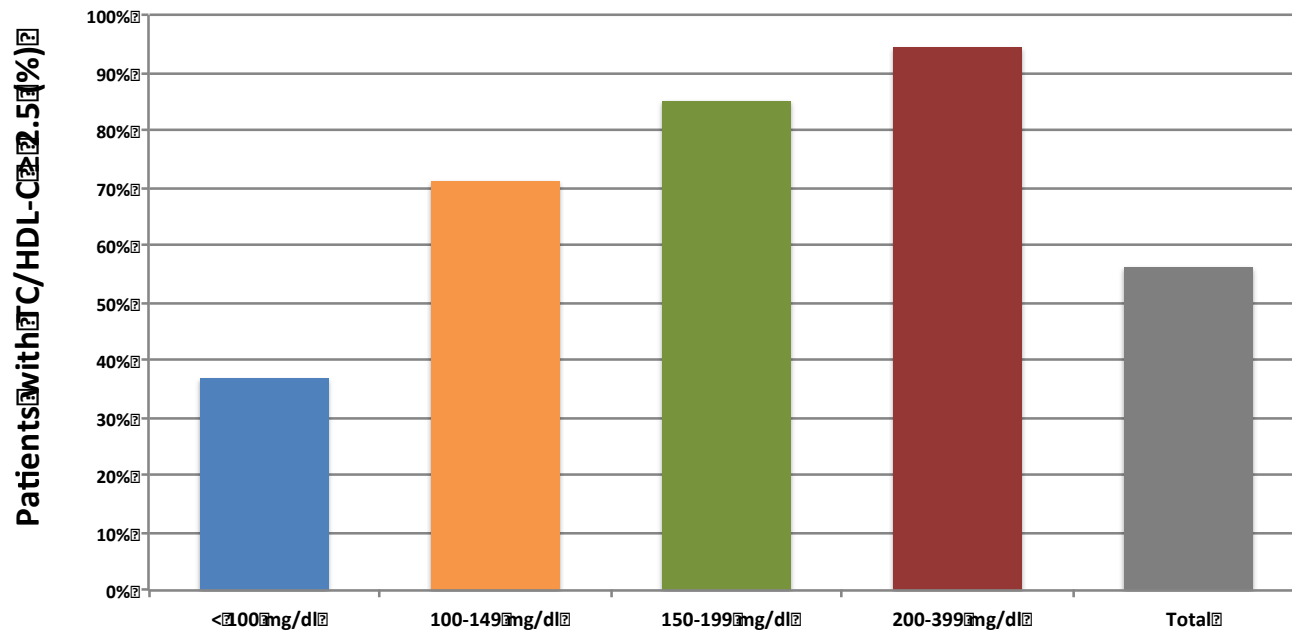
Supplemental Figure 1: Lipid distributions in *VLDL* and NHANES. Kernel density plots of multiple lipid parameters in the Very Large Database of Lipids (*VLDL*) 2009-2011 and the National Health and Nutrition Examination Survey (NHANES) 2007 to 2008.<sup>1</sup>



**Supplemental Figure 2: Proportions with direct or novel LDL-C <12<sup>th</sup> population percentile but discordantly high TC/HDL-C.**

**A)** Proportion of patients with direct LDL-C <70 mg/dL and TC/HDL-C  $\geq 2.5$  (12<sup>th</sup> percentile equivalent cutpoints) across various triglyceride categories; **B)** proportion of patients with novel method LDL-C <70 mg/dL and TC/HDL-C  $\geq 2.5$  (12<sup>th</sup> percentile equivalent cutpoints) across various triglyceride categories. TC/HDL-C (Total Cholesterol to HDL-C ratio); LDL-C (Low-density Lipoprotein Cholesterol); non-HDL-C (Non-High-density Lipoprotein Cholesterol)

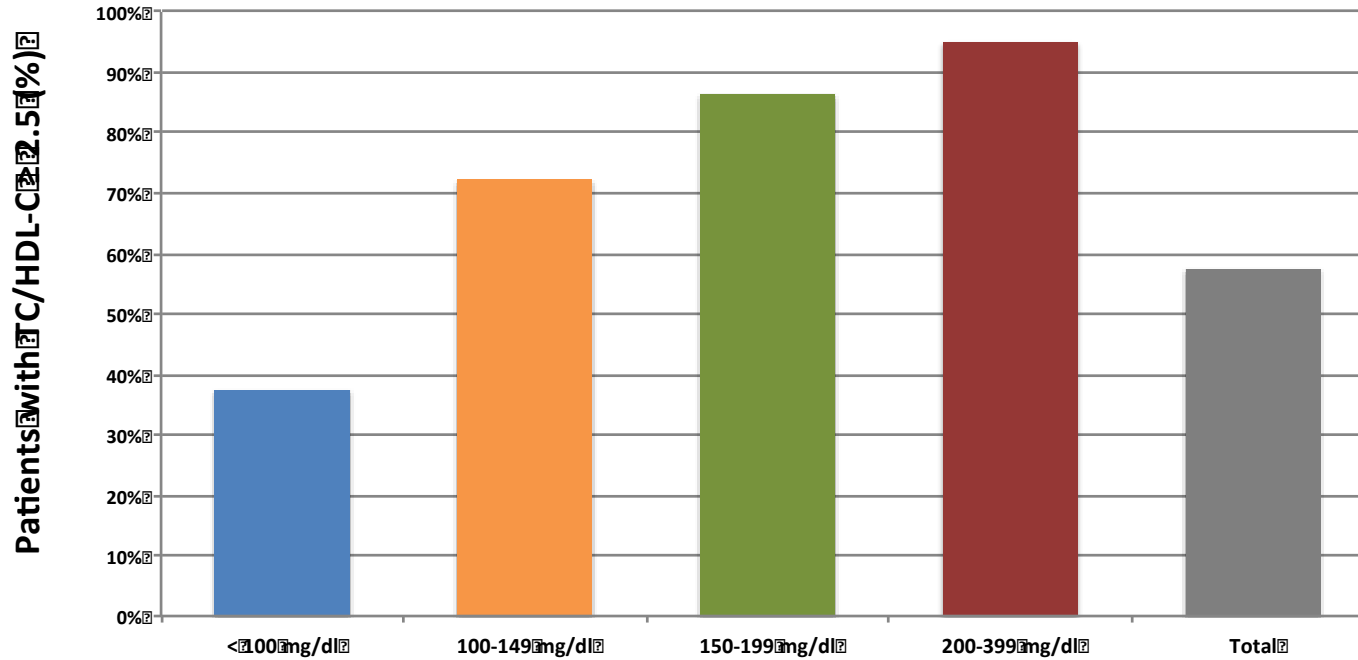
**A) TC/HDL-C percentile discordance in patients with novel method LDL-C < 70 mg/dL (12<sup>th</sup> percentile)**



Triglyceride Category	<100 mg/dL N=2,631	100-149 mg/dL N=4,740	150-199 mg/dL N=16,170	200-399 mg/dL N=13,376	Total N=153,917
TC/HDL-C $\geq 2.5$ , N	30,458	29,667	13,763	12,637	86,525
%	36.9%	71.1%	85.1%	94.5%	56.2%

B)

**TC/HDL-C percentile discordance in patients with direct LDL-C < 70 mg/dL (12<sup>th</sup> percentile)**



Triglyceride category	< 100 mg/dL N = 1,727	100-149 mg/dL N = 2,058	150-199 mg/dL N = 1,215	200-399 mg/dL N = 1,325	Total N = 15,725
TC/HDL-C ≥ 2.5, N	30582	30355	14870	13039	88846
%	37.4%	72.2%	86.4%	95.0%	57.4%



## **References:**

1. Kuklina EV. Trends in High Levels of Low-Density Lipoprotein Cholesterol in the United States, 1999-2006. *JAMA*. 2009;302:2104.
2. Martin SS, Blaha MJ, Elshazly MB, Toth PP, Kwiterovich PO, Blumenthal RS, Jones SR. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA*. 2013;310:2061–2068.