

Supplementary Materials for

A cost-consequence analysis of preemptive *SLCO1B1* testing for statin myopathy risk compared to usual care

Charles A. Brunette, Olivia M. Dong, Jason L. Vassy, Morgan E. Danowski, Nicholas Alexander,
Ashley A. Antwi, Kurt D. Christensen

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Other Supplementary Materials for this manuscript include:

File S1. Consolidated Health Economic Reporting Standards (CHEERS) Checklist.

1. Methods and Materials

1.1. Statistical Analysis

Generalized estimating equations (GEE) have been consistently used within health economic settings to account for dependence among outcome data [1-5] and are amenable to the analysis of non-normally distributed data such as medical costs [6-11]. Moreover, GEEs have demonstrated appropriate performance in the estimation of treatment effects in cluster randomized trials with varying cluster size, when the number of clusters is sufficiently large ($n > 30$), and within the context of pseudo-cluster randomization [12-15]. Per recommendations from Harden [16], parameters to calculate mean differences across arms were estimated using GEE and 95% cluster bootstrapped confidence intervals were calculated using resampling with replacement at the provider level [17,18]. *P*-values were calculated using the initial GEE parameter as reference to the bootstrapped distribution at the alpha 0.05 level (corresponding to a 95% confidence interval) [17]. In situations where sparse outcome data or small subsamples made it infeasible to perform cluster bootstrapping (e.g. SAMS), we used model-based standard error estimates to construct corresponding confidence intervals and *p*-values as recommended by Kahan et al. [15]. GEE bootstrapped estimates were comparable to those obtained using cluster bootstrapping with generalized linear models [19].

For the purposes of our primary analysis we included patient randomization status as the only covariate in our base GEE models given initial randomization at the provider level as well as unremarkable differences in observed patient characteristics across treatment arms [20] (**Table 1**) and clusters (e.g.

average cluster size) [21]. To further investigate the robustness of our findings for lipid medication, directly attributable, and total costs and to better parse potential cost drivers over and above randomization status alone, we conducted additional analyses including 12-month health care utilization (inpatient stays and outpatient encounter days) and prior 12-month health care utilization and costs as model covariates (**Supplementary Table S5**).

Table S1. Managerial Cost Accounting System (MCA) National Data Extracts inpatient Medicare-Severity Diagnosis Related Group (MS-DRG) codes excluded from inpatient health care costs and stop codes used to derive total outpatient health care costs.

Inpatient care category	Excluded MS-DRG codes [22,23]
Mental health, alcohol, and drug abuse and dependence care	876, 880, 881, 882, 883, 884, 885, 886, 887, 894, 895, 896, 897
Outpatient care category	Included outpatient stop codes [24,25]
Primary care	322, 323, 338
Cardiology	106, 107, 303, 311, 333, 334, 369, 391, 392
Medications (Lipid therapy prescriptions)	PHA, 160
Laboratory	108
Imaging	105, 109, 115, 150, 151, 153, 703
Home-based care	118, 171, 172, 173, 174, 175, 176, 178
Other general and specialty medical care (Other general and specialty medical care does not include mental health care, social and welfare services, dental, optometry or visual services, speech pathology, or prosthetics costs)	103, 104, 116, 120, 123, 124, 130, 131, 139, 147, 148, 149, 182, 191, 197, 202, 205, 206, 210, 212, 214, 224, 225, 230, 241, 290, 291, 293, 301, 302, 304, 305, 307, 308, 309, 310, 312, 313, 314, 315, 316, 318, 321, 324, 325, 326, 328, 330, 336, 337, 340, 349, 350, 352, 353, 372, 373, 401, 402, 403, 404, 405, 406, 409, 410, 411, 413, 414, 415, 416, 419, 420, 421, 422, 424, 427, 429, 430, 432, 433, 434, 435, 529, 566, 571, 575, 593, 674, 683, 685, 999

Table S2. List of statin and non-statin pharmacologic agents included in study data extraction from the VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction (Versions 3* and 4) [26,27].

Drug category	Drug name
Statin	Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin
Cholesterol absorption inhibitors	Ezetimibe
PCSK9 inhibitors^	Alirocumab, Evolocumab
Fibrate	Fenofibrate, Fenofibric acid, Gemfibrozil
Bile acid sequestrant	Cholestyramine, Colestipol, Colesevelam
Niacin	Niaspan, Niacor
Fish oil	Fish oil

* Version 3.0 applicable during study period. ^Included from version 4.0.

Table S3. International Classification of Disease (ICD) and Current Procedural Terminology (CPT) codes used for the identification of costs potentially associated with provider-documented SAMS [28,29].

Disease state	ICD-9 code [30]	ICD-10 code [31]
Aminotransferase, elevated	790.4	R74.0
Creatinine clearance	794.4	R94.4
Electrolyte imbalance	276.9	E87.8
Hyperkalemia	276.7	E87.5
Hyperphosphatemia	275.3	E83.39
Hyperuricemia (asymptomatic)	790.6	E79.0
Hypocalcemia	275.41	E83.51
Hypovolemia	276.52	E86.1
Metabolic acidosis	276.2	E87.2
Myalgia (unspecified)	729.1	M79.10
Myoglobinuria	791.3	R82.1
Myopathy (drug induced)	359.4	G72.0
Myopathy (toxic)	359.4	G72.2
Myopathy (unspecified)	359.9	G72.9
Myositis (unspecified)	729.1	M60.9
Rhabdomyolysis (idiopathic)	728.88	M62.82
Elevated erythrocyte sedimentation rate	790.1	R70.0
Elevated C-Reactive Protein	790.95	R79.82
Aminotransferase, elevated	790.4	R74.0

Procedure	CPT code [32]
Creatinine Kinase	82550, 82552, 82553, 82554, 82565, 82570, 82575
Myoglobin	83874, 83885
Complete Blood Count	82025, 85027
Erythrocyte Sedimentation Rate (ESR)	85651, 85652
C-Reactive Protein	86141
Peripheral White Blood Cell (WBC) Count	85048
Potassium	84132, 84133
Phosphorous	84100, 84105
Calcium	82310, 82330, 82340
SGOT (aspartate aminotransferase)	84450
SGPT (alanine aminotransferase)	84460
LDH (lactic acid dehydrogenase)	83625

*Costs only considered if occurred in conjunction with provider-documented SAMS after date of documentation.

Table S4. Model inputs. Input parameters assume 100% initiation of simvastatin to provide insight about the maximum expected benefits from preemptive *SLCO1B1* genotyping (best-case scenario).

Input	Best-case value	Distribution (Range)	Reference
Cohort size	10,000		
Receiving genetic testing	10,000		
SLCO1B1 variant carriers	0.256	Triangle (0.233-0.349)	[33], IPICC study (low and high bounds)
Statin therapy assignment			
Proportion offered statin	1.0		Assumption
Proportion initiated statin	1.0		Assumption
Atorvastatin	0		Assumption
Rosuvastatin	0		Assumption
Simvastatin	1.0		Assumption
1-month statin-related event probabilities			
SLCO1B1-induced myalgia	0.0426	Beta (alpha: 182; beta: 4222)	[34]
Non-SLCO1B1 induced myalgia	0.0284	Beta (alpha: 122, beta: 4282)	[34]
Discontinue statin after myalgia	0.266	NA	[34]
SLCO1B1-induced myopathy	0.00111	Beta (alpha=11.1, beta=9989)	[34]

Non-SLCO1B1 induced myopathy	0.00074	Beta (alpha=7.4, beta=9992.6)	[34]
Discontinue statin after myopathy	0.403	NA	[34]

Cost (2020 USD)

SLCO1B1 test	\$99		IPICC study
Atorvastatin, 10-80 mg (per day)	\$0.62	Triangle (\$0.41,\$0.62,\$0.83)	[35]
Rosuvastatin, 5-40 mg (per day)	\$0.69	Triangle (\$0.52, \$0.69, \$0.87)	[35]
Simvastatin, 20-40 mg (per day)	\$0.33	Triangle (\$0.27, \$0.33, \$0.38)	[35]
Myopathy/myalgia management	\$440	Triangle (\$261, \$440, \$670)	[34]

Table S5. Results from analyses accounting for 12-month health care utilization and prior 12-month health care utilization and costs on 12-month lipid prescription costs, attributable costs, and total costs.

	Prior and post 12-month adjusted costs and mean difference				
	PGx+ (n=193)	PGx- (n=215)	Mean difference	95% CI	p*
Costs, mean (SD), US dollars					
Prior 12-Month Lipid Prescription Costs	8.79 (37)	5.81 (31)	2.98	-4.01, 9.95	0.404
Post 12-Month Lipid Prescription Costs	17.90 (65)	8.40 (28)	9.53	-1.38, 22.38	0.140
Prior 12-Month Attributable Costs	5818 (7835)	5621 (5293)	197	-938, 1476	0.745
Post 12-Month Attributable Costs+	5684 (5724)	6688 (10,440)	-1004	-2684, 1009	0.284
Prior 12-Month Total Costs	22,790 (58,862)	18,327 (28,622)	4,536	-3097, 15,761	0.289
Post 12-Month Total Costs	21,502 (53,500)	21,554 (32,757)	-52	-6660, 8475	0.990
	12-month adjusted costs and mean difference				
	PGx+ (n=193)	PGx- (n=215)	Mean difference	95% CI	p*
Lipid Medication Costs					
12-Month Covariates					
Outpatient encounters^	13.79 (51)	7.11 (19)	6.68	0.43, 18.20	0.032
Prior 12-Month Covariates					
Prior 12-Month Lipid Prescription Costs^	14.63 (31)	12.79 (27)	1.84	-2.29, 5.96	0.382
Prior 12-Month Outpatient encounters^	14.71 (28)	13.37 (25)	1.34	-0.46, 3.15	0.145
Prior 12-Month Lipid Prescription Costs^					
Attributable Costs					
12-Month Covariates					
Inpatient stays^	4821 (3973)	4937 (3065)	-116	-775, 642	0.751
Outpatient encounters^					
Prior 12-Month Covariates					
Prior 12-Month Attributable Costs^	5094 (3612)	5738 (6217)	-644	-1555, 459	0.236

<i>Prior 12-Month Outpatient encounters</i> [^]					
<i>Prior 12-Month Attributable Costs</i> [^]	5006 (3584)	5731 (6672)	-725	-1645, 401	0.190
Total Costs					
12-Month Covariates					
<i>Inpatient stays</i> [^]					
<i>Outpatient encounters</i> [^]	13,515 (14,823)	14,560 (10,924)	-1045	-3087, 1310	0.374
Prior 12-Month Covariates					
<i>Prior 12-Month Total Costs</i> [^]	16,625 (27,952)	18,994 (18,959)	-2369	-5774, 1899	0.256
<i>Prior 12-Month Outpatient encounters</i> [^]	15,376 (21,533)	18,526 (18,417)	-3150	-5891, 185	0.064
<i>Prior 12-Month Total Costs</i> [^]					

Prior 12-month attributable costs include primary care, cardiology, imaging, laboratory, and lipid medication costs. Post 12-month attributable costs include primary care, cardiology, imaging, laboratory, lipid medication, SAMS, and PGx testing costs. Models included randomization status and additional covariates as described. Covariates were included or transformed if they provided better model fit via the QIC statistic [36]. Generalized Estimating Equations (GEEs) were used to correct within-group means, standard deviations, and mean differences for clustering. 95% confidence interval estimates and *p*-values were estimated using robust standard error estimates for models including covariates that did not converge when using cluster bootstrapped samples. **P*-value estimate for randomization status model coefficient. +Estimated using exchangeable correlation structure with log-transformed dependent variable. [^]Model coefficients significant at *p* < 0.05. Abbreviations: CI, confidence interval; SD, standard deviation.

Table S6. Best-case estimates and 95% CIs of 1-month muscle-related outcomes from modeling the best-case scenario.

	PGx testing	No PGx testing
Myalgia (SLCO1B1-induced)	0 (NA)*	109 (94-141)
Myalgia (non-SLCO1B1-induced)	284 (231-325)	284 (231-325)
Myopathy (SLCO1B1-induced)	0 (NA)*	3 (2-5)
Myopathy (non-SLCO1B1-induced)	7 (5-10)	7 (5-10)

*Model assumes all patients with informative SLCO1B1 genotypes would not receive simvastatin therapy.

Table S7. Directly attributable and total costs among statin users and non-users over 12-month trial period.

	Unadjusted mean (SD) costs, US dollars		Adjusted mean difference and 95% CI [^]	<i>p</i>
Statin Users (n=50)	PGx+ (n=26)	PGx- (n=24)		
Statins	44 (49)	37 (45)	8 (-18, 34)	0.560
Lipid Rx	45 (49)	44 (50)	0 (-27, 27)	0.979
PGx, Statins, SAMS	164 (90)	37 (45)	127 (93, 171)	0.001
PGx, Lipid Rx, SAMS	164 (90)	44 (50)	121 (80, 165)	0.001
PGx, Lipid Rx, SAMS, Cardiology	679 (1182)	1139 (2113)	-498 (-1386, 563)	0.312
PGx, Lipid Rx, SAMS, Primary Care	3683 (2503)	4549 (3748)	-973 (-2693, 987)	0.265
PGx, Lipid Rx, SAMS, Cardiology, Primary Care	4198 (3061)	5644 (4823)	-1893 (-3659, 917)	0.101
PGx, Lipid Rx, SAMS, Cardiology, Primary Care, Laboratory, Imaging	7621 (9207)	7975 (7009)	-474 (-4303, 4484)	0.834
Total costs	20,842 (31,176)	28,914 (36,149)	-9225 (-27,150, 11,876)	0.346
Non-users (n=358)	PGx+ (n=167)	PGx- (n=191)		
Lipid Rx	13 (77)	4 (19)	9 (-1, 24)	0.156
PGx, Lipid Rx	112 (77)	4 (19)	108 (96, 120)	0.002
PGx, Lipid Rx, Cardiology+	396 (859)	587 (2623)	-191 (-754, 144)	0.400
PGx, Lipid Rx, Primary Care+	2979 (2850)	3265 (9400)	-286 (-1229, 660)	0.611
PGx, Lipid Rx, Cardiology, Primary Care+	3263 (3122)	3848 (9793)	-585 (-1627, 428)	0.307
PGx, Lipid Rx, SAMS, Cardiology, Primary Care, Laboratory, Imaging	5341 (4885)	6210 (11,125)	-1124 (-3028, 664)	0.201
Total costs	20,443 (39,278)	19,675 (29,976)	585 (-7519, 9014)	0.868

[^]Generalized Estimating Equations (GEEs) used to correct mean difference and 95% confidence interval estimates for clustering by provider. +Estimated using log-transformed dependent variable and heteroscedastic backtransformation. Abbreviations: CI, confidence interval; PGx, pharmacogenetic testing; SAMS, statin-associated muscle symptoms; SD, standard deviation.

Table S8. Total costs among I-PICC study participants over the 12-month trial period by high-risk subpopulation.

	Unadjusted mean (SD) costs, US dollars		Adjusted mean difference, 95% CI	95% CI	<i>p</i>
High-risk subpopulation	PGx+	PGx-			
ASCVD (<i>n</i> =98)	20,823 (34,011)	21,046 (20,739)	-168	-9697, 13,684	0.972
LDL-C \geq 190 (<i>n</i> =10)*	16,532 (22,575)	12,622 (12,744)	-202	-33,073, 25,670	0.805
Diabetes (<i>n</i> =77)	21,829 (44,989)	23,934 (40,384)	-2950	-22,354, 19,983	0.769
Risk \geq 7.5% (<i>n</i> =223)	20,098 (38,912)	19,729 (30,619)	131	-9397, 13,346	0.981

Utilization and cost data are summarized as mean per-patient estimates. Data presented here address total observed costs for I-PICC Study participants. Generalized Estimating Equations (GEEs) were used to adjust mean differences, 95% confidence interval estimates, and *p*-values for clustering by provider. *Confidence interval and *p*-value derived from model-based standard error estimate. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

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