Supplemental Material

The Clinical Pharmacogenetics Implementation Consortium CPIC guideline for *SLCO1B1* and simvastatin-induced myopathy: 2014 update

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Table of Contents

CPIC Updates

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on the PharmGKB website (www.pharmgkb.org). Relevant information will be periodically reviewed and updated guidelines will be published online.

CPIC Updates in Supplement v2.0:

- **Literature review from February 2011 to December 2013.**
- **Updated *SLCO1B1* * allele nomenclature and functional status (Supplemental Table S1 and S2)**
- **Updated evidence linking *SLCO1B1* genotype to phenotype (Supplemental Table S5).**
- **Updated FDA dosing recommendations (Supplemental Table S7)**
- **Added resources to facilitate incorporation of *SLCO1B1* pharmacogenetics into an electronic health record with clinical decision support (Supplemental Table S8-S11)**

Literature Review

We searched the PubMed database (1966 to December 2013) and Ovid MEDLINE (1950 to December 2013) using several keyword strategies: SLCO1B1, SLCO1B1 AND myopathy, SLCO1B1 AND statin myopathy, SLCO1B1 AND simvastatin, SLCO1B1 AND LDL lowering, SLCO1B1 AND statin efficacy, SLCO1B1 AND statin kinetics AND human AND polymorphism, SLCO1B1 AND cardiovascular, OR SLCO1B1 AND statin uptake AND hepatocyte.

To construct tables showing *SLCO1B1* (1966-May 2010) minor allele frequency based on ancestry, the PubMed database was further searched using the following criteria: *SLCO1B1*, OATP1B1, population, rs4149056, *SLCO1B1*5*, *SLCO1B1 *15*. Studies were included if: **(A)** the race of the population was clearly indicated, **(B)** allele frequencies or minor allele

percentages for *SLCO1B1* haplotypes were reported, **(C)** the method by which *SLCO1B1* was genotyped was reliable, **(D)** the sample size was at least 20 subjects.

Gene: *SLCO1B1*

Background

SLCO1B1 (OATP1B1) function associated with the known *SLCO1B1* allelic variants is summarized in **Supplemental Table S2**. The dosing recommendations in this guideline are specific for variant alleles in which there are clear data linking the *SLCO1B1* genotype to statin-induced toxicity (*SLCO1B1*5, *15,* and **17*) (**Supplemental Table S5**). However, several other variants have been reported to be associated with reduced/increased enzyme function and/or linked to statin-induced myopathy, albeit with somewhat weaker evidence (**Supplemental Table S2**). These variants have been categorized as "possible decreased function" or "possible increased function" based on weak *in vitro* evidence suggesting the variant results in decreased/increased function but lack evidence linking these genotypes to statin-induced myopathy or as "unknown/unclear/contradictory" based on conflicting evidence.

Available Genetic Test Options

Commercially available genetic testing options change over time. Additional updated information can be found at: http://www.pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp. Furthermore, the Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr/. At the time of writing, there is one *SLCO1B1* genetic test listed in the GTR (http://www.ncbi.nlm.nih.gov/gtr/tests/509024/).

Levels of Evidence

The evidence summarized in **Supplemental Table S5** is graded using a scale based on previously published criteria (1) and applied to other CPIC guidelines(2-4):

- **High**: Evidence includes consistent results from well-designed, well-conducted studies.

- **Moderate**: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
- **Weak**: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations.

Strength of Recommendations

CPIC's dosing recommendations weigh the evidence from a combination of preclinical and clinical data. Some of the factors that are taken into account include *in vivo* clinical outcome data for statins, *in vivo* pharmacodynamic data for statins, and *in vivo* pharmacokinetic data for statins in individuals who vary by *SLCO1B1* genotype. We also consider *in vitro* pharmacodynamic and pharmacokinetic data for statins.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf): 'strong', where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; 'moderate', in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and 'optional', in which the desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action (2, 5).

'Strong' recommendation for the statement
'Moderate' recommendation for the statement
'Optional' recommendation for the statement

Incidental findings

Hepatic uptake of unconjugated bilirubin is mediated by *SLCO1B1* (6). Variation in *SLCO1B1* has been shown to alter total serum bilirubin levels (6-10) and has been associated with hyperbilirubinemia in adult Asians (11). Variants in *SLCO1B1* are also associated with increased risk for gallstone disease (rs11045819) (12), as well as hypertension (rs4149014) (13) and coronary artery disease (rs4149013) (14).

The *SLCO1B1* gene product transports many drugs and biochemicals (reviewed in details by Niemi et al, 2011). The C allele at rs4149056 is related to impaired transport of many drugs *in vitro* and *in vivo,* including for example changes in irinotecan disposition (15, 16) and clearance of the antiretroviral drug lopinavir (17). Other variants have an impact as well. For example, *SLCO1B1* rs11045819 polymorphism (c.463C>A) is associated with lower rifampin exposure in adults with pulmonary tuberculosis (18).

Other Considerations

Drug-drug interactions. Between 1998 and 2001, more than forty cases of muscle toxicity associated with the use of cerivastatin were found to be fatal. Many of these occurred within the context of gemfibrozil, a drug that strongly inhibits the cytochrome P450 (CYP) 2C8-catalyzed biotransformation of cerivastatin and also inhibits membrane transport and phase II conjugation of statins (19, 20).

The biological disposition of each statin differs on a drug-by-drug basis. Some statins undergo extensive phase I oxidation (atorvastatin, fluvastatin, lovastatin, and simvastatin), others do not (pitavastatin, pravastatin, and rosuvastatin). CYP3A4 inhibitors (e.g., azole antifungals, protease inhibitors, amiodarone, and many calcium channel blockers) increase risk of myopathy for statins metabolized by CYP3A4/5 (e.g., simvastatin, lovastatin and atorvastatin) (21).

Many statins also undergo additional modification through phase II conjugation by enzymes in the UDP-glucuronosyltransferase-1 (*UGT1*) family. This process can be altered by concomitant administration of fibric acids (22). Gemfibrozil, a fibric acid derivative, alters pharmacokinetic handling of a variety of statins. By inhibiting the glucuronidation and membrane transport of

simvastatin hydroxy-acids, gemfibrozil increases systemic exposure to active simvastatin acid (23) placing patients at increased risk for developing myopathy. Because of interactions such as these, the simvastatin package label update also recommends reducing the dose of simvastatin in patients using concomitant medications known to alter its pharmacokinetics (details in Supplemental Table 1).

The Role of Ancestry. Our guideline reflects recent recommendations from the U.S. FDA regarding the strong dose-dependence of muscle toxicity for simvastatin. For other statins, the FDA has recommended limiting the dose based upon major continental race (FDA Public Health Advisory on rosuvastatin; Media release March 2, 2005). For rosuvastatin, specifically, the FDA recommends limiting patients of Asian ancestry to a 5 mg starting dose, based upon two clinical observations: first, that patients of Asian ancestry exhibit a 2-fold increase in AUC for rosuvastatin, compared to patients of European ancestry, following single dose exposure (24) and second, that patients of Asian ancestry have greater lipid lowering efficacy at lower doses of rosuvastatin, compared to patients of European ancestry (24). As a result, the FDA has concluded that Asian Americans are one of three important groups with an elevated risk/benefit ratio (the others were patients on cyclosporine (CSA)/immune suppression and patients with severe kidney failure) (25-31).

Geographic differences in allele frequency for rs4149056 in *SLCO1B1* do not appear to contribute to this race discrepancy (24). For rosuvastatin, this difference appears to be at least partly attributable to variability in efflux transporters such as *ABCG2*, as well as gene-gene and gene-environment interactions not yet defined(32). For simvastatin, race-dependent differences in *SLCO1B1* variant frequency carry an undefined impact on outcome. Because there is great variability in the distribution of this variant by race (33), we present a summary in **Supplemental Table 3** and details in **Supplemental Table 4**.

Other Limitations. The pharmacokinetic predictors of statin-induced myopathy are well understood (23, 34-50). Pharmacodynamic predictors have been less well characterized. Although the cellular mechanism linking statins to skeletal muscle damage still remains somewhat obscured, the weight of the evidence suggests that statin-mediated reduction in the

levels of critical cholesterol precursors (i.e., isoprenoids) can lead to mitochondrial dysfunction, and programmed cell death (51-54). While inherited variability in the prenylation of key mitochondrial oxygen transport proteins may drive a subclinical form of myopathy that becomes overtly manifest after exposure to statin, there is only limited evidence supporting the clinical utility of genotyping pharmacodynamic variants.

Genotype at rs4149056 (PK variability) may also alter the desired lipid-lowering effects of statins (55, 56). Because rs4149056 influences hepatic uptake of statins, the minor allele has opposite effects on toxicity and efficacy; i.e., the presence of the minor allele attenuates the LDL-lowering effect (because the liver is the primary site for *de novo* cholesterol biosynthesis). Carriers of the rs4149056 C allele are more likely to experience decreased efficacy with regard to LDL-lowering when taking simvastatin (35, 57-59) compared to other statins such as atorvastatin (60) or fluvastatin (61). As anticipated from the kinetic data, the effect of rs4149056 on efficacy is minimal for pravastatin (62-64), rosuvastatin (65, 66), and pitavastatin (67-71). Even for simvastatin, however, the change in LDL level due to rs4149056 is small (<10 mg/dl) (35), and there is no evidence that this variant impacts vascular events. As such, we do not make recommendations based upon the relationship between rs4149056 and efficacy.

We also do not make recommendations based upon gain of function alleles (72). Because rs4149056 can be inherited in combination with other *SLCO1B1* variants that carry a protective effect, the C allele at rs4149056 should not be assumed to confer risk with 100% certainty. Like all drug-gene-outcome relationships reviewed by CPIC, it is anticipated that these guidelines will be updated as more variants (both common and rare) are increasingly characterized, e.g., through deep re-sequencing.

In the interim, a clear limitation is that rare and *de novo* variants are often not tested for within currently available genotyping tests, if discovered, it may be unclear how to act upon such results. Yet, rare exonic variants in *SLCO1B1* have been shown to have clinical impact (e.g., methotrexate clearance) (73). Therefore, altered drug kinetics and increased risk for severe drug toxicity may still occur in the absence of a C allele at rs4149056, and a TT genotype at rs4149056 does not imply the absence of another potentially deleterious variant in *SLCO1B1*.

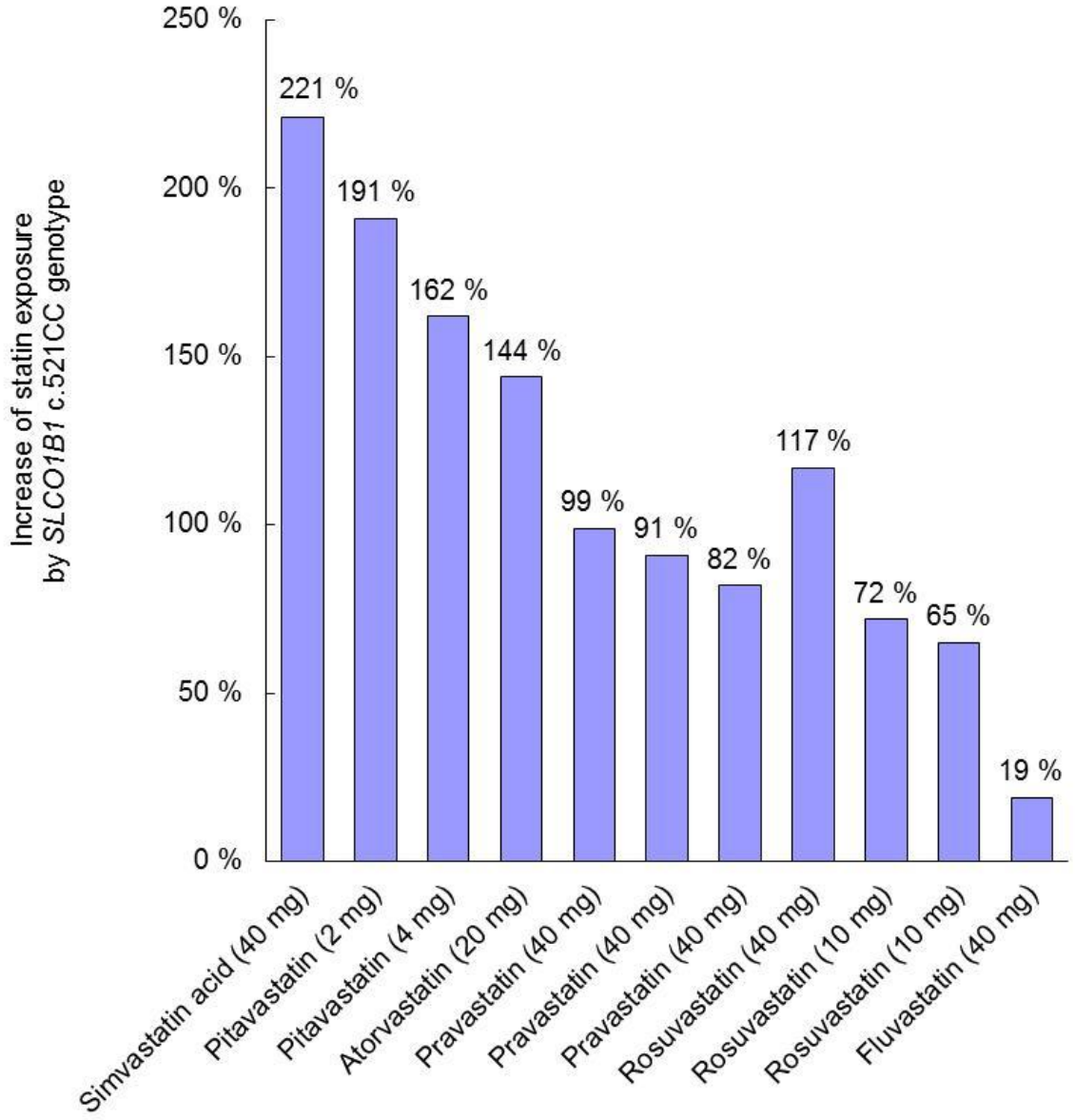
Resources to Incorporate Pharmacogenetics into an EHR with CDS

Use of clinical decision support (CDS) tools within electronic health records (EHRs) can assist clinicians to use genetic information to optimize drug therapy (74-78). Supplementary material provides new resources from CPIC to support the adoption of CPIC guidelines within an EHR. Based on the capabilities of various EHRs and local preferences, we recognize approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating the use of SLCO1B1 genotype results to guide simvastatin dosing in any EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. First, pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (79). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level." Second, results should be entered as standardized and discrete terms to facilitate using them to provide point of care CDS (80, 81). Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. Point-of-care CDS should be designed to effectively remind clinicians of prescribing implications at any time after the test result is entered into the EHR. Guidance to achieve these objectives is provided in diagrams that illustrate how *SLCO1B1* pharmacogenetic test results could be entered into an EHR (**Supplemental Figure S2**) and be used for point-of-care CDS (**Supplemental Figure S3**). **Supplemental Tables S8** and **S9** provide a cross-reference to widely used nomenclature systems for the drug and the gene, respectively.

To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript**). **Supplemental Table S10** further translates results into a coded

diplotype/phenotype summary, priority result notification, and sample interpretative result text. The result tables provide summary genotype/phenotype terms, example text for documentation in the EHR and point-of-care alerts. Finally, sample point-of-care alert text that corresponds to the workflow described in **Supplemental Figure S3** is provided in **Supplemental Table S11**.



Supplemental Figure S1. Pharmacokinetic impact of rs4149056 genotype for several statins. Effect of the *SLCO1B1* c.521T>C variant (rs4149056) on plasma exposure (*i.e.* area under the concentration-time curve) for different statins, CC vs TT. This summary figure represents a composite of single-dose data from the following references: Pasanen *et al* (82), Ieiri *et al* (70), Lee *et al*. (83), Niemi *et al* (84), Pasanen *et al* (85), Choi *et al* (86), Deng *et al* (69), Ho *et al* (87).

Portions of this figure have been reproduced from reference (88) (Niemi *et al*) with permission from the author (MN), the publisher, the American Society for Pharmacology and Experimental Therapeutics (ASPET), and *Pharmacological Reviews.*

Supplemental Table S1. Genotypes that constitute the * alleles for *SLCO1B1*.

Allele	Constituted by genotypes at:
*1A	Wild-type at all loci
*1B	rs2306283 G allele (A ancestral) (c.388A>G, p.N130D)
*2	rs56101265 C allele (T ancestral) (c.217T>C, p.F73L)
*3	rs56061388 C allele (T ancestral) (c.245T>C, p.V82A); rs72559745 (c.467A>G, p.Q156G)
*4	rs11045819 A allele (C ancestral) (c.463C>A, p.P155T)
*5	rs4149056 C allele (T ancestral) (c.521T>C, p.V174A)
*6	rs55901008 C allele (T ancestral) (c.1058T>C, p.I353T)
*7	rs56387224 G allele (A ancestral) (c.1294A>G, p.N432D)
*8	rs72559748 G allele (A ancestral) (c.1385A>G, p.D462G)
*9	rs59502379 C allele (G ancestral) (c.1463G>C, p.G488A)
*10	rs56199088 G allele (A ancestral) (c.1964A>G, p.D655G)
*11	rs55737008 G allele (A ancestral) (c.2000A>G, p.E667G)
*12	rs56101265 C allele (T ancestral); rs56199088 G allele (A ancestral)
*13	rs56061388 C allele (T ancestral); rs55737008 G allele (A ancestral); rs72559745 G allele (A ancestral)
*14	rs2306283 G allele (A ancestral); rs11045819 A allele (C ancestral)
*15	rs2306283 G allele (A ancestral); rs4149056 C allele (T ancestral)
*16	rs2306282 G allele (A ancestral) (c.452A>G, p.N151S)
*17	rs4149015 A allele (G ancestral; g.-11187G>A); rs2306283 G allele (A ancestral); rs4149056 C allele (T ancestral)
*18	rs2306283 G allele (A ancestral); rs11045818 A allele (G ancestral) (c.411G>A, p.S137=); rs11045819 A allele (C ancestral); rs4149057 C allele (T ancestral) (c.571T>C, p.L191=); rs72559746 G allele (T ancestral) (c.578T>G, p.L193R)
*19	rs4149057 C allele (T ancestral); rs34671512 C allele (A ancestral) (c.1929A>C, p.L643F)
*20	rs2306283 G allele (A ancestral); rs2291075 T allele (C ancestral) (c.597C>T, p.F199=); rs34671512 C allele (A ancestral)
*21	rs4149015 A allele (G ancestral); rs2306283 G allele (A ancestral); rs2291075 T allele (C ancestral)
*22	rs34671512 C allele (A ancestral)
*23	rs373327528 A allele (G ancestral) (c.315G>A, p.G71R)
*24	rs2306283 G allele (A ancestral); rs11045852 G allele (A ancestral) (c.733A>G, p.I245V)
*25	rs2306283 G allele (A ancestral); rs11045819 A allele (C ancestral); rs11045852 G allele (A ancestral) (c.733A>G, p.I245V); rs11045853 A allele (G ancestral) (c.758G>A, p.R253G)
*26	rs142965323 A allele (G ancestral) (c.1309G>A, p.G437R)
*27	rs2306283 G allele (A ancestral); rs59113707 G allele (C ancestral) (c.1200C>G, p.F400L)

*28	rs2306283 G allele (A ancestral); rs11045852 G allele (A ancestral) (c.733A>G, p.I245V); rs11045853 A allele (G ancestral)
*29	rs2306283 G allele (A ancestral); rs140790673 T allele (C ancestral) (c.2045C>T, p.S682F)
*30	rs2306283 G allele (A ancestral); rs79135870 G allele (A ancestral) (c.664A>G, p.I222V)
*31	rs2306283 G allele (A ancestral); rs59502379 C allele (G ancestral)
*32	rs2306283 G allele (A ancestral); rs11045819 A allele (C ancestral); rs11045852 G allele (A ancestral)
*33	rs139257324 T allele (C ancestral) (c.169C>T, p.R57W); rs2306283 G allele (A ancestral); rs11045852 G allele (A ancestral); rs11045853 A allele (G ancestral)
*34	rs200995543 T allele (C ancestral) (c.2032C>T, p.H678Y)
*35	rs2306283 G allele (A ancestral); rs34671512 C allele (A ancestral)
*36	chr12:21355487(hg19) G allele (T ancestral) (c.1198T>G, p.F400V)

See http://www.pharmgkb.org/gene/PA134865839#tabview=tab4&subtab=31 for updates on *SLCO1B1* alleles and nomenclature. Bases reported on the positive chromosomal strand.

Supplemental Table S2. Association between allelic variants and SLCO1B1 (OATP1B1) function

Functional Status	Alleles	References
Normal function[a]	*1a, *1b	Mwinyi *et al*. (2004) (89) Kameyama *et al*. (2005)(90) Lee *et al*. (2005) (83) Katz *et al*. (2006) (91) Tirona *et al*. (2011) (92)
Decreased function	*5, *15, *17	See Supplemental Table S5
Possible decreased function	*2, *3, *6, *9, *10, *23, *31	Tirona *et al*. (2001)(92) Tirona *et al*. (2003) (93) Ho *et al*. (2006) (8) Katz *et al*. (2006) (91) Niemi *et al*. (2011)(88) Ramsey *et al*. (2012) (94)[b]
Possible increased function	*14, *35	Ramsey *et al*. (2012) (94)[b] Nies *et al*. (2013) (95)
Unknown/unclear/contradictory evidence	*4, *7, *8, *11, *12, *13, *16, *18, *19, *20, *21, *22, *24, *25, *26, *27, *28, *29, *30, *32, *33, *34, *36	Tirona *et al*. (2001)(92) Michalski *et al*. (2002) (96) Tirona *et al*. (2003) (93) Ho *et al*. (2006) (8) Katz *et al*. (2006) (91) Seithel *et al*. (2008) (97) Niemi *et al*. (2011)(88)

[a]An important caveat for all genotyping tests is that the decision to assign an allele a "wild-type" status is based upon a genotyping test that interrogates only the most common and already-proven sites of functional variation. In human DNA, it is always possible that a new, previously undiscovered (and therefore un-interrogated) site of variation may confer loss-of-function in an individual, and thus lead to the rare possibility of a non-functional allele being erroneously called as "wild-type"

[b]Transport function was tested for methotrexate, and may not be generalizable to statins. *23 was observed only once in 700 patients, but in vitro transport assays showed little/no function. *31 was observed only in patients of African ancestry, and in vitro transport assays showed little/no function for this haplotype also. *14 and *35 were associated with higher methotrexate clearance in patients, but were not tested for in vitro transport function.

Supplemental Table S3. Observed frequencies for select *SLCO1B1* alleles[a] within major race/ethnic or geographic groups.

Allele	Functional Status	Caucasian	South/Central American	African	Middle Eastern	Asian	SW Asian	Oceania
*1A	normal/ wild type[b]	50%	37%	17%	49%	27%	47%	34%
*1B	normal/ wild type[b]	22%	39%	78%	31%	60%	46%	66%
*5	variant/ reduced function	1%	0%	0%	5%	0%	0%	0%
*15	variant/ reduced function	14%	24%	3%	15%	13%	6%	0%

[a]Average allele frequencies are presented based upon the actual numbers of subjects with each allele reported in multiple studies, and grouped according to major race/ethnic or geographic groups (see Supplemental Table 4 for references and constitution of the race/ethnic/geographic groups).

[b]An important caveat for all genotyping tests is that the decision to assign "wild-type" status is based upon a genotyping test that interrogates only the most common and already-proven sites of functional variation. In human DNA, it is always possible that new, previously undiscovered (and therefore un-interrogated) site of variation may confer loss-of-function in an individual, and thus lead to the rare possibility of a non-functional allele being erroneously called as "wild-type."

Supplemental Table S4. Detailed distribution of *SLCO1B1* allele frequency by race, ethnicity, or geographic groups.

Race/ethnic/geographic groups group	Race/ethnicity/geographic location as reported in source document	Haplotype frequency (%)				Total pts	alleles observed					Total alleles	Source
		*1A	*1B	*5	*15/*16/*17		*1A	*1B	*5	*15/*16/*17	other		
African	American	22%	76%	0%	1%	38	17	58	0	1	0	76	(87)
African	North African	34%	48%	2%	16%	29	20	28	1	9	0	58	(33)
African	Sub-Saharan Africa	21%	77%	0%	2%	105	44	162	0	4	0	210	(33)
African	Ugandan	22%	70%	0%	3%	109	48	153	0	7	10	218	(98)
African	Tanzanian	13%	84%	0%	3%	366	97	614	0	21	0	732	(99)
Asian	Japanese	35%	54%	1%	10%	267	188	287	4	55	0	534	(100)
Asian	Japanese	33%	46%	0%	18%	120	78	110	0	44	8	240	(101)
Asian	Malays	17%	70%	0%	13%	35	12	49	0	9	0	70	(83)
Asian	Korean	31%	46%	0%	23%	24	15	22	0	11	0	48	(102)
Asian	Chinese	19%	71%	0%	11%	94	35	133	0	20	0	188	(103)
Asian	Malays	12%	79%	0%	9%	97	23	153	0	18	0	194	(103)
Asian	Korean	29%	60%	0%	12%	200	115	238	0	47	0	400	(86)
Asian	Korean	18%	62%	0%	18%	81	29	101	0	29	3	162	(15)
Asian	Chinese	26%	60%	0%	14%	111	58	133	0	31	0	222	(104)
Asian	Chinese	22%	69%	1%	8%	106	46	146	3	17	0	212	(105)
Asian	Korean	26%	60%	0%	14%	469	247	560	0	131	0	938	(105)
Asian	Vietnamese	21%	63%	0%	16%	104	44	130	0	34	0	208	(105)
Asian	East Asian	25%	63%	0%	12%	239	120	301	0	57	0	478	(33)
Asian	Japanese	36%	47%	0%	17%	177	128	166	0	60	0	354	(106)
Asian	Japanese	33%	49%	0%	18%	80	52	79	0	29	0	160	(107)
Asian	Chinese	25%	64%	0%	12%	96	47	122	0	23	0	192	(108)
Asian	Malays	19%	71%	0%	9%	96	37	137	0	18	0	192	(108)
Asian	Chinese	30%	59%	0%	11%	32	19	38	0	7	0	64	(109)
Asian	Chinese	33%	59%	0%	9%	35	23	41	0	6	0	70	(83)
Caucasian		47%	31%	1%	21%	36	34	22	1	15	0	72	(83)
Caucasian	German	49%	33%	1%	11%	250	245	165	5	55	30	500	(110)
Caucasian	Finnish	11%	2%	3%	17%	468	100	21	25	161	629	936	(111)

Caucasian	American	61%	25%	1%	14%	69	84	34	1	19	0	138	(87)
Caucasian	German	58%	25%	3%	15%	99	114	49	5	30	0	198	(112)
Caucasian	European	56%	26%	2%	16%	151	169	79	6	48	0	302	(33)
Caucasian	German	60%	9%	3%	12%	276	333	48	17	66	88	552	(98)
Caucasian	Turkish	52%	22%	1%	9%	78	82	34	2	15	24	156	(98)
Caucasian	French	53%	14%	2%	15%	185	196	52	8	56	58	370	(113)
Caucasian	Dutch	57%	27%	1%	15%	1885	2148	1022	27	572	0	3770	(114)
Caucasian	Canadian	50%	5%	0%	18%	41	41	4	0	15	22	82	(115)
Caucasian	German	56%	35%	3%	7%	236	263	163	12	34	0	472	(99)
Middle East		49%	31%	5%	15%	133	130	83	13	40	0	266	(33)
Oceanic		34%	66%	0%	0%	28	19	37	0	0	0	56	(33)
South/Central American		37%	39%	0%	24%	64	47	50	0	31	0	128	(33)
SW Asian	Indian	46%	47%	0%	7%	35	32	33	0	5	0	70	(83)
SW Asian	Indian	41%	56%	2%	2%	93	76	104	3	3	0	186	(103)
SW Asian	South/Central Asian	52%	39%	0%	9%	192	200	150	0	34	0	384	(33)
SW Asian	Indian	44%	50%	0%	6%	96	85	96	0	11	0	192	(108)

Supplemental Table S5. Evidence linking genotype with phenotype

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major findings	References	Level of evidence*
Association of *SLCO1B*1 genotype with simvastatin disposition in vitro			
In vitro	rs4149056 is the key SNP determining the functional properties of *SLCO1B1*5*, **15* and **15*+C1007G allelic proteins and that decreased activities of these variant proteins are mainly caused by a sorting error produced by this SNP.	Kameyama *et al*. (2005) (116)	Low
In vitro	Comparable transport of rosuvastatin between OATP1B1*1a and *1b, but significantly decreased transport by OATP1B1*5 and OATP1B1*15 in HeLa cells.	Ho *et al*. (2006) (8)	Low
In vitro	Reduced transport function for OATP1B1*15 as compared with *1a. Similar transport activity was found for OATP1B1*1a and *1b in HEK293 cells.	Iwai *et al*. (2004) (117)	Low
In vitro	Similar transport activity was found for OATP1B1*1a and *1b using E1S as substrate in HEK293 cells. No reduced activity seen for *5.	Nozawa *et al*. (2002) (100)	Low
Association of *SLCO1B1* genotype with myalgia or myopathy			
Clinical	*SLCO1B1* rs4149056 C allele carriage is strongly associated with an increased risk of **simvastati**n-induced myopathy.	Link *et al*. (2008) (118) Brunham et al. (2011) (119)	High
Clinical	Presence of the *SLCO1B1*5* (rs4149056 C) allele is associated with increased risk of composite adverse events when treated with statins (**atorvastatin**, **pravastatin** or **simvastatin**) in patients with hypercholesterolemia	Voora *et al*. (2009) (120) Carr *et al*. (2013) (121)	High

Clinical	No increased risk of myalgia identified among patients receiving **rosuvastatin** who carried either rs4363657C or rs4149056C allele for *SLCO1B1*	Danik *et al*. (2013) (122)	Moderate
Clinical	*SLCO1B1* rs4149056 genotype influences susceptibility to myopathy in response to **simvastatin** but not **atorvastatin**.	Brunham *et al*. (2012)(123)	Low
Clinical	*SLCO1B1* haplotypes are not associated with **atorvastatin**-induced myalgia	Santos *et al*. (2012)(124)	Low
Clinical	There was no association between the C allele of rs4149056 and myopathy in **rosuvastatin**-treated subjects (O.R. 0.65, 95% C.I. 0.24–1.01, beta-coefficient 0.29, p = 0.099) but there was an association between the rs4149056 C allele and myopathy for atorvastatin-treated subjects (O.R. 2.7, 95% C.I. 1.3–4.9, beta-coefficient 1.56, p < 0.001).	Puccetti *et al*. (2010) (125)	Low
Association of *SLCO1B1* genotype with pharmacokinetics of simvastatin			
Preclinical, in vivo	There were no significant effects on **simvastatin** pharmacokinetics in healthy Chinese volunteers by SNPs in *SLCO1B1* c.388 A > G, *SLCO1B1* c.521 T > C, *SLCO1B1* g.11187 G > A, *SLCO1B1* c.571 T > C and *SLCO1B1* c.597 C > T.	Zhou *et al*. (2013) (126)	Moderate
Preclinical, in vivo	*SLCO1B1* rs4149056C polymorphism markedly affects the pharmacokinetics of active **simvastatin** acid, but has no significant effect on parent simvastatin.	Pasanen *et al*. (2006) (82)	Moderate
Association of *SLCO1B1* genotype with lipid-lowering effects			
Clinical	*SLCO1B1* variant alleles (rs4149056, rs11045819) and other gene variants involved in statin pharmacokinetics had small effects (<1% per allele) on lipid-lowering response to statin therapy.	Fu *et al*. (2013) (127) Hopewell *et al*. (2013) (128)	High
Clinical	SNPs in *SLCO1B1* (rs4149056; rs436365; rs12317268) were associated with reduced LDL-C in patients receiving **rosuvastatin**.	Chasman *et al*. (2012) (129)	Moderate
Clinical	The *SLCO1B1* rs4149056C variant allele significantly decreased LDL-C and TC lowering response to **pravastatin**.	Akao *et al*. (2012) (130) Takane *et al*. (2006) (131) Zhang W *et al*. (2007) (132)	High

Clinical	*SLCO1B1* rs4149056C genotype was not associated with **rosuvastatin** response as measured by frequency of patients reaching LDL-C target.	Bailey *et al*. (2010) (65)	Moderate
Clinical	*SLCO1B1* SNPs rs2306283 and rs4149056C did not affect the lipid-lowering efficacy of **pitavastatin**.	Yang *et al*. (2010) (68)	Moderate
Clinical	Presence of the *SLCO1B1*14* allele was associated with enhanced lipid-lowering efficacy for **fluvastatin**.	Couvert *et al*. (2009) (61)	Moderate
Clinical	Patients receiving **pravastatin**, **atorvastatin**, and **simvastatin** who carried the rs4149056C allele showed an attenuated total-cholesterol-lowering effect compared with those homozygous for the rs4149056C allele (-22.3+/-8.7% vs. -16.5+/-10.5%, $p<0.05$).	Tachibana-Iimori *et al*. (2004) (133)	Moderate
Clinical	rs4149056 CC genotype is associated with increased cholesterol synthesis rate when exposed to **atorvastatin**, **fluvastatin**, **pravastatin**, **rosuvastatin** and **simvastatin** as compared to rs4149056 TT genotype.	Pasanen *et al*. (2008) (134)	Moderate

Supplemental Table S6. Impact of rs4149056 (V174A) on the pharmacokinetics of various statins

Study	Patients	Treatment	Primary Endpoint(s)	Additional Finding(s)
Nishizato *et al.* (2003) (101)	N=23 healthy Japanese volunteers	Pravastatin 10 mg	Patients with the compound N130D + V174A variant had reduced total and non-renal pravastatin clearance, as compared with patients with the N130D variant.	OATP-C single-nucleotide polymorphisms, including V174A, are likely associated with altered pravastatin pharmacokinetics (PK).
Mwinyi *et al.* (2004) (43)	N=30 healthy white males	Pravastatin 40 mg	Pravastatin AUC and C_{max} increased for V174A carriers compared to WT or N130D carriers.	OATP-C variant haplotypes alter pravastatin disposition. Whereas V174A expression delayed hepatocellular uptake of pravastatin, N130D expression seemed to accelerate OATP-C-dependent uptake of the drug.
Niemi *et al.* (2004) (44)	N=41 healthy Finnish volunteers	Pravastatin 40 mg	Pravastatin AUC increased with V174A and -11187G>A variant alleles compared to WT.	Carriers of the compound N130D + V174A variants, as well as carriers of the compound N130D + V174A + -1187G>A, also had higher pravastatin AUC compared with WT.
Chung *et al.* (2005) (102)	N=24 healthy Korean volunteers	Pitavastatin 1-8 mg	Pitavastatin AUC and C_{max} increased for carriers of the compound N130D + V174A variant versus patients with WT or N130D alleles alone.	No significant differences were found according to genotype in terms of dose-normalized AUC or C_{max} values of pitavastatin lactone
Lee *et al.* (2005) (83)	N=36 white, 36 Chinese, 35 Malay, and 35 Asian-Indian subjects living in Singapore, Singapore	Rosuvastatin 40 mg	Rosuvastatin AUC's were 2.36, 2.00, and 1.68 times higher in Chinese, Malay, and Asian-Indian subjects; respectively, compared with White subjects.	SLCO1B1 genotypes did not account for the observed PK differences between Asians and White subjects.
Igel *et al.* (2006) (63)	N=16 healthy volunteers, including 8 carriers of an SLCO1B1 variant haplotype and 8 control subjects	Pravastatin 40 mg orally daily for three weeks	Pravastatin AUC and C_{max} were significantly higher in patients with V174A alleles compared to controls. Patients with the compound N130D + V174A variant, and patients with the triplotype -11187G>A + N130D + V174A, also had higher pravastatin AUC and C_{max}	Despite considerably higher plasma pravastatin concentrations in carriers of an SLCO1B1 variant haplotype, there was no significant difference in the lipid-lowering efficacy of pravastatin between the variant haplotype and control groups.

Niemi *et al.* (2006) (135)	N=32 healthy Finnish volunteers	Pravastatin 40 mg and fluvastatin 40 mg	Pravastatin AUC, C_{max} increased for men homozygous for V174A compared to men who were carriers for V174A or WT. Women who were WT had significantly higher Pravastatin AUC, C_{max} than men who were WT. Fluvastatin PK did not differ between subjects with different SLCO1B1 genotypes or between the sexes.	SLCO1B1 polymorphism alters PK of pravastatin but not fluvastatin, which suggests that fluvastatin does not rely on OATP1B1 for hepatic uptake. Patient gender may affect pravastatin PK.
Pasanen *et al.* (2006) (111)	N=4 healthy Caucasian volunteers	Simvastatin 40 mg	Simvastatin acid AUC and C_{max} increased for V174A carriers vs. WT	The V174A variant may increase risk for myopathy as well as reduce lipid-lowering effects due to decreased hepatic uptake.
Ho *et al.* (2007) (87)	N=107 healthy volunteers (69 European-American and 38 African-Americans)	Pravastatin 40 mg	Pravastatin AUC, C_{max} increased in heterozygous carriers of the compound N130D + V174A variant and in N130D + V174A homozygotes	European-Americans had significantly higher pravastatin AUC and C_{max} than African-Americans.
Ieiri *et al.* (2007) (70)	N=38 healthy Japanese volunteers	Pitavastatin 2 mg	Pitavastatin AUC, Cmax increased for N130D or compound N130D+ V174A heterozygotes, and for compound N130D+ V174A homozygotes	Pitavastatin lactone PK were not altered by SLCO1B1 genotype.
Pasanen *et al.* (2007) (85)	N=32 healthy volunteers	Atorvastatin 20 mg and rosuvastatin 10 mg	AUC and C_{max} for atorvastatin, 2-hydroxyatorvastatin, and rosuvastatin were increased in patients with the V174A variant.	Unexpectedly, SLCO1B1 polymorphism has a larger effect on the PK of atorvastatin than rosuvastatin.
Choi *et al.* (2008) (86)	N=30 Korean volunteers	Rosuvastatin 10 mg	Rosuvastatin AUC increased for compound N130D + V174A homozygotes, compound N130D + V174A carriers, and N130D carriers compared with WT. C_{max} increased for compound N130D + V174A homozygotes compared to other groups.	Rosuvastatin-lactone PK were similar among the three groups.
Deng *et al.* (2008) (69)	N=11 healthy Korean volunteers	Pravastatin 40 mg or Pitavastatin 4 mg	Pitavastatin AUC and Cmax increased more than pravastatin for compound N130D + V174A homozygotes compared with WT	Uptake into oocytes overexpressing the compound N130D + V174A allele was decreased for pitavastatin more so than pravastatin. Fluvastatin was unaffected.
Suwannakul *et al.* (2008) (40)	N=10 healthy Japanese volunteers	Pravastatin 10 mg (+ olmesartan 10 mg)	Pravastatin PK not significantly affected for N130D homozygotes, versus carriers of the compound N130D + V174A variant and/or versus N130D + V174A homozygotes	Co-administration of olmesartan + pravastatin did not affect PK based on SLCO1B1 genotype.

He *et al.*(2009) (37)	N=16 healthy Chinese volunteers	Atorvastatin 40 mg (+ rifampicin 600 mg)	When combined with concomitant rifampicin, Atorvastatin AUC increased among V174A carriers and WT patients compared to V174A homozygotes	Rifampicin PK not affected by variation in SLCO1B1 genotype.
Ide *et al.* (2009) (50)	N=57 healthy Japanese male volunteers	Pravastatin	Relative bioavailability F(rel) increased for pravastatin in carriers of the compound N130D + V174A variant, and in homozygotes, versus WT.	Since compound N130D + V174A genotype alters $F_{(rel)}$, OATP1B1 is one of the determinants of systemic exposure to pravastatin.
Wen *et al.* (2010) (67)	N=18 healthy Chinese volunteers	Pitavastatin 2 mg	Pitavastatin AUC, C_{max} increased with N130D carriers compared to wild type (WT).	Pitavastatin CL was reduced in N130D carriers. No differences according to genotype were observed in $T_{1/2}$ and $T_{max.}$
Lee *et al.* (2010) (136)	N=290 Korean volunteers	Atorvastatin 20 mg	Mean AUC of atorvastatin and 2-hydroxyatorvastatin was larger for compound N130D + V174A homozygotes (n = 3), than for N130D + V174A carriers (n = 8), and also larger than patients with WT. No PK difference with atorvastatin lactone was found.	This study showed the compound N130D + V174A variant may be associated with individual difference in the AUC of atorvastatin.
Marciante *et al.* (2011) (137)	185 cases of rhabdomyolysis compared to 732 controls	Cerivastatin at various doses	Permutation test results suggested an association between cerivastatin-associated rhabdomyolysis and SLCO1B1variants (P=0.002), but not CYP2C8 variants (P=0.073) or UGTs (P=0.523). The V174A allele was associated with risk of rhabdomyolysis (odds ratio: 1.89; 95% confidence interval: 1.40-2.56).	In transfected cells, V174A allele reduced cerivastatin transport by 40% compared with the reference transporter (P<0.001).

Supplemental Table S7. FDA Dosing Recommendations for Simvastatin, posted in 2013

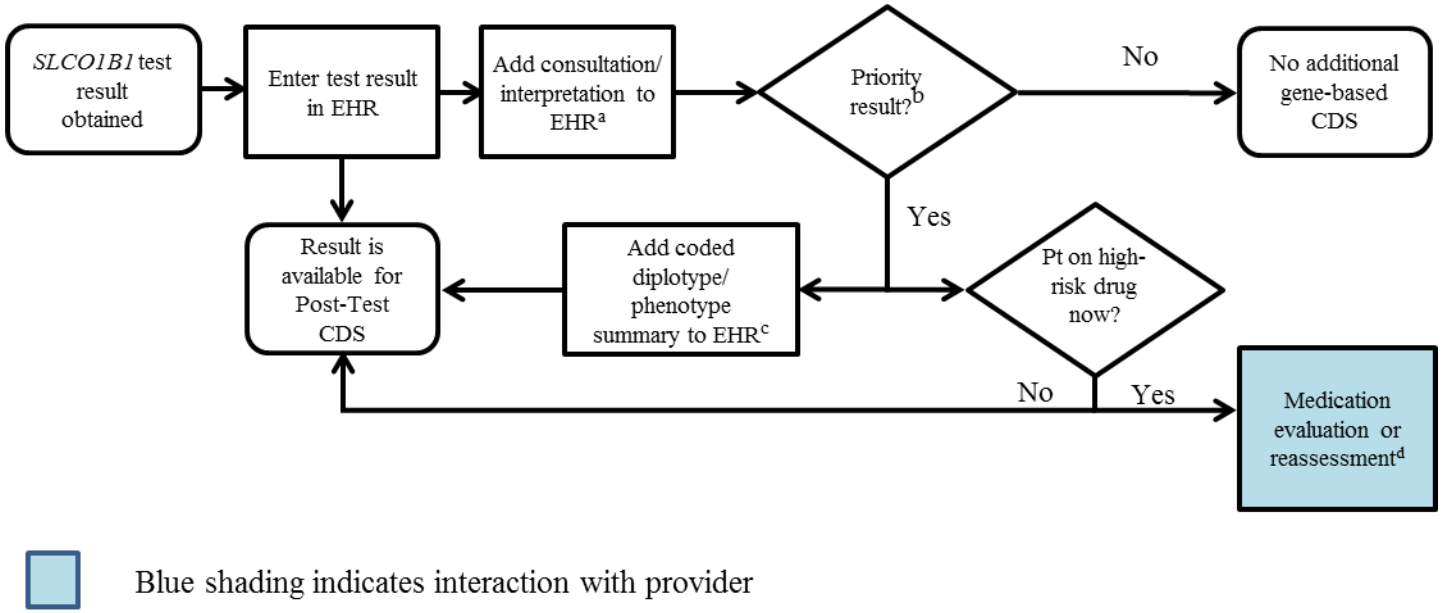
Warning(s) Regarding 80 mg Simvastatin	Simvastatin Contraindicated	Maximum Simvastatin Dose	
		Max 10 mg daily (20 mg dose is contraindicated)	**Max 20 mg daily** (40 mg dose is contraindicated)
• Simvastatin 80 mg should not be started in new patients • It is acceptable to continue simvastatin 80 mg daily in patients who have been taking it for 12 months or more without side effects • Switch patients requiring a drug that interacts with simvastatin to an alternative statin with less potential for drug-drug interaction • Patients unable to achieve their LDL-C goal utilizing the 40 mg dose should not be titrated to the 80 mg dose, but should be placed on alternative LDL-C lowering treatments	• Itraconazole, Ketoconazole, Posaconazole, Voriconazole • Erythromycin, Clarithromycin, Telithromycin • HIV Protease inhibitors • Boceprevir, Telaprevir • Nefazodone • Gemfibrozil • Cyclosporine • Danazol	• Verapamil • Diltiazem • Dronedarone	• Amiodarone • Amlodipine • Ranolazine • Lomitapide*
*For patients with homozygous familial hypercholesterolemia (HoFH) taking lomitapide, do not exceed 20 mg simvastatin daily, except for patients with HoFH who have taken 80 mg simvastatin chronically for ≥12 months without muscle toxicity, who should not exceed 40 mg of simvastatin daily when lomitapide is prescribed concomitantly			

Supplemental Table S8. Drug(s) that pertain to this guideline.

Drug or Ingredient	Source	Code Type	Code
Simvastatin	RxNorm	RxCUI	36567
Simvastatin	DrugBank	Accession Number	DB00641
Simvastatin	ATC	ATC Code	C10AA01
Simvastatin	PharmGKB	PharmGKB ID	PA451363

Supplemental Table S9. Gene(s) that pertain to this guideline

Gene Symbol	Source	Code Type	Code
SLCO1B1	HGNC	Symbol	SLCO1B1
SLCO1B1	HGNC	HGNC ID	HGNC10959
SLCO1B1	NCBI	Gene ID	10599
SLCO1B1	Ensembl	Ensembl ID	ENSG00000134538
SLCO1B1	PharmGKB	PharmGKB ID	PA134865839



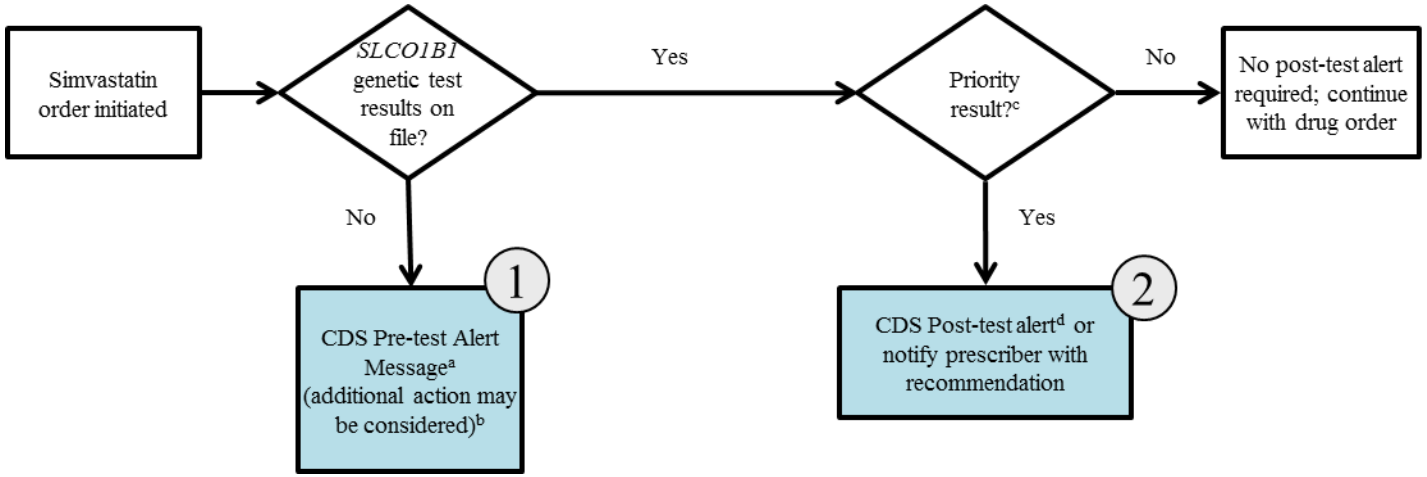
Supplemental Figure S2. *SLCO1B1* Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR

[a]See **Supplementary Table S10** for diplotype/phenotype specific example

[b]"Priority result" is defined as a genetic test result that necessitates a change in drug, drug dose, or drug monitoring now or potentially in the future.

[c]Documentation in the EHR is institution specific. Optimally, the phenotype and/or genotype are available in the EHR to permanently inform prescribing decisions. See **Supplementary Table S10** for genotype/phenotype-specific summaries.

[d]See supplement section "Other Considerations" for discussion regarding use of simvastatin using the information of a patient's *SLCO1B1* genotype test result.



Note: Circled numerals refer to ***Supplementary Table 11***

Supplemental Figure S3. *SLCO1B1* Genotype and Simvastatin: Point of Care Clinical Decision Support

[a]See **Supplementary Table S11** for diplotype/phenotype specific pre-test alert example.

[b]Additional actions may include ordering a pharmacogenetic test, preventing the clinician from ordering the medication or allowing the clinician to cancel out of the alert.

[c]Priority result defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

[d]See **Supplementary Table S11** for diplotype/phenotype specific post-test alert example.

Translation table:

Supplemental Table S10. Example Implementation of this Guideline: Pharmacogenetic Diplotype/Phenotype Summary Entries[a]

Diplotype Test Result for *SLCO1B1*	Coded Diplotype/Phenotype Summary[b]	EHR Priority Result Notation[c]	Consultation (Interpretation) Text Provided with Test Result[d]
*1a/*1a	None	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a wild type (normal function) allele. Based on the genotype result, this patient is predicted to have normal SLCO1B1 function. This means that there is no reason to adjust the dose of most medications that are affected by SLCO1B1 (including simvastatin) on the basis of SLCO1B1 genetic status. Please consult a clinical pharmacist for more specific information about how SLCO1B1 function influences drug dosing.
*1b/*1b	None	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a wild type (normal function) allele. Based on the genotype result, this patient is predicted to have normal SLCO1B1 function. This means that there is no reason to adjust the dose of most medications that are affected by SLCO1B1 (including simvastatin) on the basis of SLCO1B1 genetic status. Please consult a clinical pharmacist for more specific information about how SLCO1B1 function influences drug dosing.
*1a/*1b	None	Normal/Routine/ Low Risk	This result signifies that the patient has two copies of a wild type (normal function) allele. Based on the genotype result, this patient is predicted to have normal SLCO1B1 function. This means that there is no reason to adjust the dose of most medications that are affected by SLCO1B1 (including simvastatin) on the basis of SLCO1B1 genetic status. Please consult a clinical pharmacist for more specific information about how SLCO1B1 function influences drug dosing.
*1a/*5	SLCO1B1 - Intermediate Function	Abnormal/Priority / High Risk	This result signifies that the patient has one copy of a wild type (normal function) allele (*1a) and one copy of a decreased function allele (*5). Based on the genotype result, this patient is predicted to have intermediate SLCO1B1 function. This patient may be at risk for an adverse response to medications that are affected by SLCO1B1. To avoid an untoward drug response, dose adjustments may be necessary for medications affected by SLCO1B1. If simvastatin is prescribed to a patient with intermediate SLCO1B1 function, there is an increased risk for developing simvastatin-associated myopathy; such patients may need a lower starting dose of simvastatin or an alternate statin agent. Please consult a

			clinical pharmacist for more specific information about how SLCO1B1 function influences drug dosing.
*1a/*15	SLCO1B1 - Intermediate Function	Abnormal/Priority /High Risk	This result signifies that the patient has one copy of a wild type (normal function) allele (*1a) and one copy of a decreased function allele (*15). Based on the genotype result, this patient is predicted to have intermediate SLCO1B1 function. This patient may be at risk for an adverse response to medications that are affected by SLCO1B1. If simvastatin is prescribed to a patient with intermediate SLCO1B1 function, there is an increased risk for developing simvastatin-associated myopathy; such patients may need a lower starting dose of simvastatin or an alternate statin agent. Please consult a clinical pharmacist for more specific information about how SLCO1B1 function influences drug dosing.
*1a/*17	SLCO1B1 - Intermediate Function	Abnormal/Priority /High Risk	This result signifies that the patient has one copy of a wild type (normal function) allele (*1a) and one copy of a decreased function allele (*17). Based on the genotype result, this patient is predicted to have intermediate SLCO1B1 function. This patient may be at risk for an adverse response to medications that are affected by SLCO1B1. If simvastatin is prescribed to a patient with intermediate SLCO1B1 function, there is an increased risk for developing simvastatin-associated myopathy; such patients may need a lower starting dose of simvastatin or an alternate statin agent. Please consult a clinical pharmacist for more specific information about how SLCO1B1 function influences drug dosing.
*1b/*5	SLCO1B1 - Intermediate Function	Abnormal/Priority /High Risk	This result signifies that the patient has one copy of a wild type (normal function) allele (*1b) and one copy of a decreased function allele (*5). Based on the genotype result, this patient is predicted to have intermediate SLCO1B1 function. This patient may be at risk for an adverse response to medications that are affected by SLCO1B1. If simvastatin is prescribed to a patient with intermediate SLCO1B1 function, there is an increased risk for developing simvastatin-associated myopathy; such patients may need a lower starting dose of simvastatin or an alternate statin agent. Please consult a clinical pharmacist for more specific information about how SLCO1B1 function influences drug dosing.
*1b/*15	SLCO1B1 - Intermediate Function	Abnormal/Priority /High Risk	This result signifies that the patient has one copy of a wild type (normal function) allele (*1b) and one copy of a decreased function allele (*15). Based on the genotype result, this patient is predicted to have intermediate SLCO1B1 function. This patient may be at risk for an adverse response to medications that are affected by SLCO1B1. If simvastatin is prescribed to a patient with intermediate SLCO1B1 function, there is an increased risk for developing simvastatin-associated myopathy; such patients may need a lower starting dose of simvastatin or an alternate statin agent. Please consult a clinical pharmacist for more specific information about how SLCO1B1 function influences drug dosing.
*1b/*17	SLCO1B1 - Intermediate Function	Abnormal/Priority /High Risk	This result signifies that the patient has one copy of a wild type (normal function) allele (*1b) and one copy of a decreased function allele (*17). Based on the genotype result, this

			patient is predicted to have intermediate SLCO1B1 function. This patient may be at risk for an adverse response to medications that are affected by SLCO1B1. If simvastatin is prescribed to a patient with intermediate SLCO1B1 function, there is an increased risk for developing simvastatin-associated myopathy; such patients may need a lower starting dose of simvastatin or an alternate statin agent and creatine kinase levels may need to be monitored routinely. Please consult a clinical pharmacist for more specific information about how SLCO1B1 function influences drug dosing.
*5/*5	SLCO1B1 - Low Function	Abnormal/Priority /High Risk	This result signifies that the patient has two copies of a decreased function allele. Based on the genotype result, this patient is predicted to have low SLCO1B1 function. This patient may be at a high risk for an adverse response to medications that are affected by SLCO1B1. If simvastatin is prescribed to a patient with low SLCO1B1 function, there is a high risk of developing simvastatin-associated myopathy; such patients may need a lower starting dose of simvastatin or an alternate statin agent, and creatine kinase levels may need to be monitored routinely. Please consult a clinical pharmacist for more specific information about how SLCO1B1 function influences drug dosing.
*5/*15	SLCO1B1 - Low Function	Abnormal/Priority /High Risk	
*5/*17	SLCO1B1 - Low Function	Abnormal/Priority /High Risk	
*15/*15	SLCO1B1 - Low Function	Abnormal/Priority /High Risk	
*15/*17	SLCO1B1 - Low Function	Abnormal/Priority /High Risk	
*17/*17	SLCO1B1 - Low Function	Abnormal/Priority /High Risk	

This table is provided to show examples of how a test result could be translated into discrete fields within an EHR, including a brief interpretation that summarized the result. The information presented here is consistent with the guideline but may need to be adapted to a given EHR's design and capabilities. Various EHRs or organizations may require different terms, and so different options are provided.

[a]A more comprehensive table of genotype/phenotype EHR entries for possible diplotype combinations of all variants listed in **Supplemental Table S2** is available at PharmGKB http://www.pharmgkb.org/guideline/PA166105005.

[b]The coded diplotype/phenotype summary is used to store an interpretation of the test result. This is a design decision that may differ among sites.

[c]For this example, a priority result is defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

[d]The specific wording of the interpretive text may differ among sites.

Supplemental Table S11. Example Implementation of this Guideline: Point of Care Clinical Decision Support

Flow Chart Reference Point (See Supplemental Figure S3)	CDS Context, Relative to Genetic Testing	Trigger Condition	CDS Alert Text[a]
1	Pre-Test	No *SLCO1B1* result on file	*SLCO1B1* diplotype may be important for simvastatin side effects. An *SLCO1B1* genotype does not appear to have been ordered for this patient. Use of an alternative statin or dose may be recommended. Please consult a clinical pharmacist[b] for more information.
2	Post-Test	SLCO1B1 - Intermediate Function	Based on the genotype result, this patient is predicted to have intermediate SLCO1B1 function and may be at increased risk for developing simvastatin-associated myopathy. Consider starting with a lower dose of simvastatin (20 mg/day for adults) or choosing an alternate statin agent. Monitor creatine kinase levels routinely. Please consult a clinical pharmacist[b] for more information.
2	Post-Test	SLCO1B1 – Low Function	Based on the genotype result, this patient is predicted to have low SLCO1B1 function and may be at high risk for developing simvastatin-associated myopathy. Consider starting with a lower dose of simvastatin (20 mg/day for adults) or choosing an alternate statin agent. Monitor creatine kinase levels routinely. Please consult a clinical pharmacist[b] for more information.

[a]The specific wording of the alert text may differ among sites.

[b]Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.

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