Supplemental Material

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *SLCO1B1*, *ABCG2*, and *CYP2C9* and statin-associated musculoskeletal symptoms

Authors:

*Rhonda M. Cooper-DeHoff[1,2], *Mikko Niemi[3,4,5], Laura B. Ramsey[6,7], Jasmine A. Luzum[8], E. Katriina Tarkiainen[3,4,5], Robert J. Straka[9], Li Gong[10], Sony Tuteja[11], Russell A. Wilke[12], Mia Wadelius[13], Eric A. Larson[12], Dan M. Roden[14,15], Teri E. Klein[10], Sook Wah Yee[16], Ronald M. Krauss[17], Richard M. Turner[18], Latha Palaniappan[19], Andrea Gaedigk[20], Kathleen M. Giacomini[16], Kelly E. Caudle[22], Deepak Voora[23]

[1]Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics and Precision Medicine, College of Pharmacy, University of Florida, Gainesville, Florida, USA
[2]Division of Cardiovascular Medicine, Department of Medicine, College of Medicine, University of Florida, Gainesville, Florida, USA
[3]Department of Clinical Pharmacology, Individualized Drug Therapy Research Program University of Helsinki, Helsinki, Finland
[4]HUS Diagnostic Center, Helsinki University Hospital, Helsinki, Finland
[5]Individualized Drug Therapy Research Program, University of Helsinki, Helsinki, Finland
[6]Divisions of Clinical Pharmacology & Research in Patient Services, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA[7]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[8]Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor,
[9]Department of Experimental and Clinical Pharmacology, University of Minnesota College of Pharmacy, Minneapolis, Minnesota, USA
[10]Department of Biomedical Data Science, School of Medicine, Stanford University, Stanford, California, USA
[11]Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
[12]Department of Internal Medicine, University of South Dakota Sanford School of Medicine, Sioux Falls, South Dakota, USA
[13]Department of Medical Sciences, Clinical Pharmacogenomics & Science for Life Laboratory, Uppsala University, Uppsala, Sweden
[14]Division of Cardiovascular Medicine and Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
[15]Department of Pharmacology and Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA
[16]Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, California, USA
[17]Departments of Pediatrics and Medicine, University of California, San Francisco, CA, USA

[18]The Wolfson Centre for Personalised Medicine, University of Liverpool, Liverpool, UK

[19]Division of Primary Care and Population Health, Stanford University School of Medicine, Stanford, CA, USA

[20]Division of Clinical Pharmacology, Toxicology, and Therapeutic Innovation, Children's Mercy Kansas City and School of Medicine, University of Missouri-Kansas City, Kansas City, MO, USA

[22]Division of Pharmaceutical Sciences, Department of Pharmacy and Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA

[23]Department of Medicine, Duke Center for Applied Genomics & Precision Medicine, Duke University School of Medicine, Durham, NC, USA

*shared first author

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

TABLE OF CONTENTS

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

CPIC UPDATES

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on www.cpicpgx.org. Information will be reviewed and updated periodically on that website.

New to this guideline:

- Updated evidence reviews for *SLCO1B1* (**Table S1**) and revised recommendation (**Table 2**)
- Addition of *CYP2C9* and *ABCG2* evidence reviews and recommendations (**Tables S2 and S3** and **Tables 3** and **4)**)
- Evidence reviews and recommendation for all statins (**Tables S1-S3 and Tables 2-6)**)
- Addition of the **Figure 1**. *SLCO1B1* recommendations with intensity and statin dose stratified by SLCO1B1 phenotype
- Evidence reviews for *HMGC4* and *CYP3A4/5* and all statins (**Tables S4** and **S5**)
- Combined recommendations for *SLCO1B1/ABCG2* and *SLCO1B1/CYP2C9* (**Tables 5** and **6**)
- Implementation resources (gene and drug resource mappings, CDS alerts, allele definition, allele frequency, allele functionality, diplotype to phenotype tables have all been updated and reformatted and are now available at https://cpicpgx.org/guidelines/cpic-guideline-for-statins/

LITERATURE REVIEW

We searched the PubMed database (1966 to July 2021) using the following keyword strategies: *SLCO1B1*: (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (SLCO1B1 OR OATP1B1) AND (myopathy OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR Rhabdomyolysis OR Myositis OR "Statin associated muscle symptoms" OR withdrawal OR intolerance OR hepatocyte uptake OR response OR reaction) NOT ("review"[Publication Type]) AND English[lang] AND ("2014/01/01"[PDAT] : "2021/07/20"[PDAT])
ABCG2: (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (ABCG2 OR BCRP) AND (myopathy

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR reaction OR Rhabdomyolysis OR Myositis OR "Statin associated muscle symptoms" OR withdrawal OR intolerance OR hepatocyte uptake OR response) NOT ("review"[Publication Type]) AND English[lang]

CYP2C9: (fluvastatin) AND (CYP2C9)

HMGCR: (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (HMGCR) AND (myopathy OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR reaction OR Rhabdomyolysis OR Myositis OR "Statin associated muscle symptoms" OR withdrawal OR intolerance OR hepatocyte uptake OR response) NOT ("review"[Publication Type]) AND English[lang]

CYP3A4/5: (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (CYP3A4 OR CYP3A5) AND (myopathy OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR reaction OR Rhabdomyolysis OR Myositis OR "Statin associated muscle symptoms" OR withdrawal OR intolerance OR hepatocyte uptake OR response) NOT ("review"[Publication Type]) AND English[lang]

Using these search terms, 1023 publications were identified. Study inclusion criteria included publications that incorporated analyses for the association between *SLCO1B1, ABCG2, CYP2C9, HMGCR, or CYP3A4/5* genotypes and statins pharmacokinetic parameters as well as clinical outcomes. Non-English manuscripts and reviews were excluded. Following the application of these inclusion and exclusion criteria, 197 publications were reviewed and included in the evidence table (**Table S1 to S5**).

AVAILABLE GENETIC TEST OPTIONS

Desirable characteristics of pharmacogenetic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (1). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables (see **Allele Definition Table**, **Allele Functionality Table** and **Allele Frequency Table** (https://cpicpgx.org/guidelines/cpic-guideline-for-statins/) adhere to these

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

allele nomenclature standards (1). Moreover, the **Allele Definition Table**, **Allele Functionality Table**, and **Allele Frequency Table** may be used to assemble lists of known functional and actionable pharmacogenetic variants and their population frequencies, which may inform decisions as to whether tests are adequately comprehensive in interrogations of alleles. Furthermore, the Association for Molecular Pathology and College of American Pathologists have published a joint recommendation for the key attributes of alleles recommended for clinical testing and a minimum set of variants that should be included in clinical genotyping assays for *CYP2C9* (2).

Commercially available genetic testing options change over time. Additional updated information can be found at the Genetic Testing Registry (GTR). The 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/.

LINKING GENETIC VARIABILITY TO VARIABILITY IN DRUG-RELATED PHENOTYPES

SLCO1B1. Both SLCO1B1 decreased and poor function phenotypes are associated with increased exposure for most statins, with greater effects of poor function phenotypes. Effects on exposure also vary by statin type (**Figure S1**). Therefore, the risk of SAMS varies based on statin type and statin dose. For simvastatin, the evidence linking SAMS to *SLCO1B1* rs4149056 (c.521T>C) is of high quality, and this association has been reproduced in retrospective studies of randomized trials and clinical practice-based cohorts (**Table S1**). This variant is present in several *SLCO1B1* star alleles including the relatively common *SLCO1B1*5* and *15* alleles. Although the association of rs4149056 with myopathy varies by statin, there is evidence supporting the role of *SLCO1B1* variants in the systemic clearance of all statins (3) (**Table S1**). Pasanen *et al*. determined that homozygous carriers of the C allele at rs4149056 (CC genotype) had substantiality greater exposure to the active simvastatin acid (AUC_{0-12}) than subjects homozygous for the ancestral T allele (4). In single-dose studies (**Figure S1**), the observed plasma AUCs of active simvastatin acid, pitavastatin, atorvastatin, pravastatin and rosuvastatin have been 221%, 162-191%, 144%, 57-130% and 62-117% higher, respectively in rs4149056

CC homozygotes than in rs4149056 TT homozygotes (**Figure S1**). Thus, the recommendations in this guideline (for *SLCO1B1*, *ABCG2* and *CYP2C9*) are based on both pharmacokinetic evidence and when available clinical evidence supporting increased risk of SAMS (see **Supplemental Material** for further detail). Further, we make note in this guideline when therapeutic recommendations are based solely on the basis of pharmacokinetic data due to the absence of clinical toxicity data related to SAMS (**Figure 1**).

Genotype at rs4149056 may also alter the desired lipid-lowering efficacy of statins (**Table S1**). Because rs4149056 influences hepatic uptake of statins, the C allele (e.g., *SLCO1B1*5* and *15*) has opposite effects on toxicity and efficacy as the presence of the minor allele attenuates the LDL-cholesterol lowering effect (because hepatic HMGCR is the rate limiting step for *de novo* cholesterol biosynthesis). Carriers of the rs4149056 C allele experience lesser LDL-cholesterol reduction when taking simvastatin (5-8) but one report suggests this may be due to poor drug adherence (9). As anticipated from the pharmacokinetic data, the effect of rs4149056 on efficacy is minimal for pravastatin (10-12), rosuvastatin (13, 14), and pitavastatin (15-19). Even for simvastatin, however, the change in LDL-cholesterol level due to rs4149056 is small (<10 mg/dl) (5), and there is no evidence that this variant impacts vascular events (20). As such, our recommendations are primarily based on this variant's effects on PK and SAMS, rather than the relationship between rs4149056 and efficacy on lowering LDL or risk of cardiovascular events.

ABCG2. *ABCG2* decreased and poor function phenotypes are associated with increased exposure to rosuvastatin, with greater exposure for the poor function phenotypes (**Table S2**). In particular, rosuvastatin levels (AUC and C_{max}) may be doubled in individuals with poor function phenotypes (21). Based on the observed increase in exposure, the risk for myopathy would also be expected to be increased (22). Nonetheless, there is only a single study directly assessing myopathy due to rosuvastatin use in individuals with decreased or poor function phenotypes which did not show any significant effect on myopathy (23). However, for efficacy, the JUPITER Trial showed an increase in lipid lowering effects of rosuvastatin in individuals with decreased and poor function phenotypes (24). Dosing based on genotype for rosuvastatin must necessarily include other considerations such as liver or renal function and ancestry (**Table 3**). The higher levels of rosuvastatin observed in individuals of Asian ancestry have been attributed

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

to higher allele frequencies of the reduced function *ABCG2* polymorphism, c.421G>A (rs2231142) (25); however, other factors may contribute to higher rosuvastatin levels in Asians (26). The effect of the *ABCG2* polymorphism, rs2231142 (c.421C>A), has also been studied for its association with pharmacokinetic, toxicity or efficacy with other statins, such as atorvastatin, pitavastatin, fluvastatin and lovastatin (**Table S2**). Except for fluvastatin, in which a single study showed a clear association of rs2231142 with exposure, the evidence for association of *ABCG2* genetic variants with exposure, response or toxicity to other statins is considered weak to moderate primarily because of small sample sizes or variation in results among studies (**Table S2**).

CYP2C9. Genetic variations in *CYP2C9* are associated with increased exposure to fluvastatin (**Table S3**), but the pharmacokinetics or pharmacodynamics of other statins are not affected. To date, studies have focused on two alleles, *CYP2C9*2* (decreased function) and *CYP2C9*3* (no function). Hirvensalo *et al.* showed that for fluvastatin the AUC was 25% and 75% greater per copy of the *CYP2C9*2* and *CYP2C9*3* variant allele, respectively. Additionally, *CYP2C9*2* and *CYP2C9*3* alleles are associated with increased risk of fluvastatin-induced adverse effects, including liver toxicity and SAMS. However, the evidence supporting increased risk of myopathy in carriers of decreased or poor function alleles of *CYP2C9* is of moderate quality and mainly based on the pharmacokinetic evidence. Genetic variation in *CYP2C9* has not been associated with fluvastatin lipid-lowering response.

CYP3A4 and *CYP3A5*. To date, studies have focused on two alleles, *CYP3A4*1B* (a promoter variant) and *CYP3A5*3* (harboring a common intronic variant causing a splice defect which leads to truncated inactive CYP3A5 protein). While neither variant has been shown to predict myopathy while on atorvastatin, Wilke *et al.* describe an association for these variants with the severity of muscle damage in a small cohort of 68 patients who reported myalgias while taking atorvastatin (27). Although significant, the effect size was modest. For patients with myalgias on atorvastatin, the median CK level was 321 units/L in carriers of the *CYP3A4*1B* allele, vs 246 units/L in non-carriers (adjusted p = 0.059), and the median CK level was 318 units/L in carriers of the *CYP3A5*3* allele, vs 246 units/L in non-carriers (adjusted p = 0.010).

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

CYP3A4 and *CYP3A5* genes are located on chromosome 7, at a locus that also contains two pseudogenes, and *CYP3A7* which is predominantly expressed *in utero* (28). Functionally, the CYP3A4 and CYP3A5 enzymes have a high degree of overlap in their substrate specificity (biological redundancy), and there is wide patient-to-patient variability (more than 10-fold variation) in their expression in adults. While *CYP3A4*1B* and *CYP3A5*3* are in strong linkage disequilibrium (D' >0.8), the *CYP3A5*3* allele is thought to be the causal variant driving the association between this locus and CK elevation during atorvastatin therapy. Because this variant only predicts the severity of how high the CK may go, it does not predict who will develop SAMS, and thus, the association may not be clinically actionable. There are additional published studies (see **Table S5**), but the overall strength of evidence for *CYP3A4/5* and statin response was rated as weak. Therefore, the current guideline does not make any recommendations regarding *CYP3A4/5* genotype at this time.

HMGCR. *HMGCR* encodes for HMG-CoA reductase, the target of statins. Variations in *HMGCR* (e.g., rs1724484A>T and rs17238540T>G) have been shown to be associated with LDL-c response (see **Table S4**) but with very limited and weak data to support. Thus, the current guideline does not make recommendation regarding *HMGCR* and statin lipid response.

LEVELS OF EVIDENCE

The evidence summarized in **Supplemental Table S1-S3** is graded using a scale modified slightly from Valdes et al. (29)

> 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.

STRENGTH OF DOSING RECOMMENDATIONS

CPIC's dosing recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data (**Supplemental Tables S1-S3**) as well as on some existing disease-specific consensus guidelines (30). Some of the factors that are considered in evaluating the evidence supporting dosage recommendations include: *in vivo* clinical outcome data for statins, *in vivo* pharmacokinetic and pharmacodynamic data for statins, *in vitro* enzyme/transporter activity of expressed wild-type or variant-containing gene, *in vitro* enzyme activity from tissues isolated from individuals of known genotypes, *in vivo* pre-clinical pharmacokinetic and pharmacodynamic studies, and *in vitro* studies of protein stability.

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 four categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents (31):

Strong recommendation for the statement: "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects."

Moderate recommendation for the statement: "There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects."

Optional recommendation for the statement: "The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action."

No recommendation: "There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time."

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 (32, 33).

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

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) (34).

Many statins also undergo additional modification through phase II conjugation by enzymes of the UDP-glucuronosyltransferase-1 (UGT1) family. This process can be altered by concomitant administration of fibric acids (35). Gemfibrozil, a fibric acid derivative, alters pharmacokinetic parameters of a variety of statins. By inhibiting the glucuronidation and membrane transport of simvastatin hydroxy-acids, gemfibrozil increases systemic exposure to active simvastatin acid (36) placing patients at increased risk for developing myopathy. Because of interactions such as these, all the statin package labels recommend reducing the dose of statins in patients using concomitant medications known to alter its pharmacokinetics.

The Role of Ancestry. There is some evidence that Asian Americans are one of three important groups with an elevated risk/benefit ratio for use of some statins compared to other ancestry groups; the other important groups were patients on cyclosporine (CSA)/immune suppression and patients with severe kidney failure) (37-43).Geographic differences in allele frequency for *SLCO1B1* rs4149056 (c.521T>C) do not appear to contribute to this sensitivity in Asians (44). 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 (45). For simvastatin, ancestry-dependent differences in *SLCO1B1* variant frequency carry an undefined impact on outcome.

Other Limitations. The pharmacokinetic predictors of SAMS are well understood (5, 36, 46-61). 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

11

precursors (i.e., isoprenoids) can lead to mitochondrial dysfunction, and programmed cell death (62-65). 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.

Because rs4149056 (c.521T>C) can be inherited in combination with other *SLCO1B1* variants that carry a protective effect, the C allele 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) (66). Therefore, altered drug kinetics and increased risk for severe drug toxicity may still occur in the absence of a c.521 C allele, and a c.521TT genotype at rs4149056 does not necessarily imply the absence of other potentially function-altering variant(s) in *SLCO1B1*. Allele and variant function are available on PharmVar.org as well as CPIC's **_SLCO1B1_Allele Functionality Table** (67, 68).

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN EHR WITH CDS

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (69-73). See https://cpicpgx.org/guidelines/cpic-guideline-for-statins/ for resources to support the adoption of CPIC guidelines within an EHR. Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating the use of *SLCO1B1, ABCG2* and *CYP2C9* genotype results to guide statin use in an EHR.

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (74, 75). 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**). 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". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (69, 76).

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. To facilitate this process, CPIC is providing gene-specific information figures and tables that include full diplotype to phenotype tables, diagram(s) that illustrate how pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems for genes relevant to the CPIC guideline (see https://cpicpgx.org/guidelines/cpic-guideline-for-statins/).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC provides gene-drug specific tables that offer guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for drugs relevant to the CPIC guideline (see https://cpicpgx.org/guidelines/cpic-guideline-for-statins/).

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0
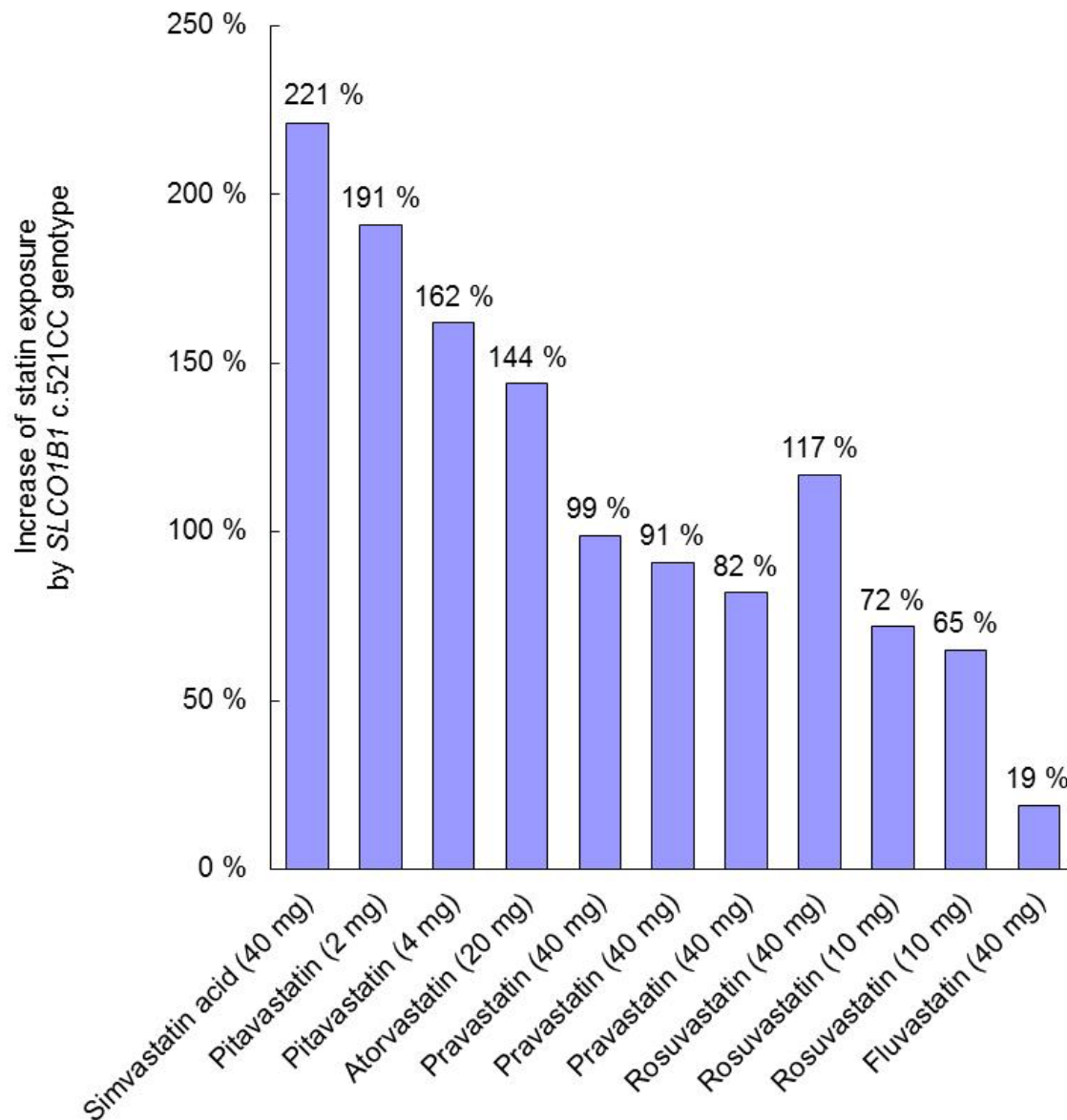
FIGURE S1. PHARMACOKINETIC IMPACT OF RS4149056 GENOTYPE FOR SEVERAL STATINS. Effect of the *SLCO1B1* c.521T>C variant (rs4149056) on plasma exposure (*i.e.,* area under the concentration-time curve) for different statins, CC vs TT. This summary figure represents a composite of single-dose data from the following references: Pasanen *et al* (4), Ieiri *et al* (18), Lee *et al*. (77), Niemi *et al* (78), Pasanen *et al* (79), Choi *et al* (80), Deng *et al* (17), Ho *et al* (81).

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

Portions of this figure have been reproduced from reference (82) (Niemi *et al*) with permission from the author (MN), the publisher, the American Society for Pharmacology and Experimental Therapeutics (ASPET), and *Pharmacological Reviews*.

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

TABLE S1. EVIDENCE LINKING SLCO1B1 GENOTYPE WITH STATIN PHENOTYPE

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major Findings	References	Level of Evidence
Atorvastatin			
In vitro	SLCO1B1 is the major atorvastatin uptake transporter. The average contribution to atorvastatin uptake was *SLCO1B1* > SLCO1B3 >> OATP2B1 > NTCP.	Vildhede, *et al.* (2014) (83)	Weak
In vitro	*SLCO1B1* rs4149056 (c.521T>C, *5) reduces atorvastatin transport activity by decreasing OATP1B1 function due to sorting errors in transporter localization	Kameyama, *et al.* (2005) (84)	Weak
Clinical	*SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased risk of atorvastatin-induced myopathy.	Puccetti, *et al.* (2010) (85) Brunham, *et al.* (2012) (86) Santos, *et al.* (2012) (87) Hou, *et al.* (2015) (88) Hubacek, *et al.* (2015) (89) Mirosevic, *et al.* (2015) (90) Liu, *et al.* (2017) (91) Xiang, *et al.* (2018) (92) Du, *et al.* (2018) (93) Ramakumari, *et al.* (2018) (94) Mori, *et al.* (2019) (95) Linskey, *et al.* (2020) (96) Turner, *et al.* (2020) (97)	Moderate
Clinical	*SLCO1B1* rs4149056 (c.521T>C) C allele is not significantly associated with an increased risk of atorvastatin-induced liver tox.	Fukunaga, *et al.* (2016) (98)	Weak

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

Clinical	*SLCO1B1* rs4149056 (c.521T>C) C polymorphism affects the pharmacokinetics of atorvastatin (higher AUC and Cmax).	Pasanen, *et al.* (2007) (79) Lee, *et al.* (2010) (99) DeGorter, *et al.* (2013) (22) Daka, *et al.* (2015) (100) Birmingham, *et al.* (2015) (101) Leon-Cachon, *et al.* (2016) (102) Rajput, *et al.* (2017) (103) Wang, *et al.* (2017) (104) Woo, *et al.* (2017) (105) Lee, *et al.* (2019) (106) Mori, *et al.* (2019) (95) Turner, *et al.* (2020) (97)	High
Clinical	Individuals with the *SLCO1B1* rs4149056 (c.521T>C) C allele showed an attenuated total-cholesterol-lowering effect compared with those homozygous for the c.521T allele.	Tachibana-Iimori, *et al.* (2004) (107) Drogari, *et al.* (2014) (108) Giannakopoulou, *et al.* (2014) (109) Meyer, *et al.* (2015) (110) Prado, et al. (2015) (111) Mladenovska, *et al.* (2017) (112) Du, *et al.* (2018) (93)	Weak
Clinical	The *SLCO1B1* rs4149056 (c.521T>C) is associated with higher likelihood of dose decrease or switching during statin therapy.	de Keyser, *et al.* (2014) (113)	Moderate
In vitro	*SLCO1B1* rs2306283 (c.388A>G, *1b) did not alter the activity of OATP1B1 significantly.	Kameyama, *et al.* (2005) (84)	Weak
Clinical	*SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with risk of myotoxicity in individuals that received atorvastatin.	Liu, *et al.* (2017) (91) Du, *et al.* (2018) (93)	Moderate
Clinical	*SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with atorvastatin pharmacokinetics.	Birmingham, *et al.* (2015) (101) Lee, *et al.* (2019) (106)	Moderate
Clinical	*SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with atorvastatin efficacy.	Drogari, *et al.* (2014) (108) Prado, *et al.* (2015) (111) Kadam, *et al.* (2016) (114) Mladenovska, *et al.* (2017) (112)	Weak

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

		Du, *et al.* (2018) (93)	
Fluvastatin			
Clinical	Presence of the *SLCO1B1*14* allele is associated with enhanced lipid-lowering efficacy for fluvastatin.	Couvert, *et al.* (2008) (115)	Moderate
Clinical	The *SLCO1B1* rs4149056 (c.521T>C) C variant is associated with decreased lipid- lowering response to fluvastatin.	Couvert, *et al.* (2008) (115) Meyer, *et al.* (2015) (110) Xiang, *et al.* (2018) (116)	Weak
In vitro	The uptake of fluvastatin was not influenced by *SLCO1B1* rs4149056 (c.521T>C) at concentrations >1 uM	Deng, *et al.* (2008) (117) Xiang, *et al.* (2020 (118)	Moderate
In vitro	The *SLCO1B1* rs4149056 (c.521T>C) C variant is associated with reduced uptake of both fluvastatin enantiomers (3R,5S-fluvastatin and 3S,5R-fluvastatin).	Hirvensalo, *et al.* (2019) (119)	Moderate
Clinical	Fluvastatin PK did not differ between subjects with different *SLCO1B1* rs4149056 (c.521T>C) genotypes.	Niemi, *et al.* (2006) (120) Zhou, *et al.* (2012) (121) Hirvensalo, *et al.* (2019) (119) Mori, *et al.* (2019) (95) Xiang, et al. (2020) (118)	Weak
Clinical	*SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with lipid-lowering response to fluvastatin.	Couvert, *et al.* (2008) (115) Xiang, *et al.* (2018) (116)	Weak
Lovastatin			
Clinical	*SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased concentration of lovastatin acid but have no significant effect on lovastatin lactone.	Tornio, *et al.* (2015) (122) Zhao, *et al.* (2017) (123)	Weak
Clinical	*SLCO1B1* rs2306283 (c.388A>G) is not associated with concentration of lovastatin acid and lovastatin lactone.	Tornio, *et al.* (2015) (122) Zhao, *et al.* (2017) (123)	Weak
Clinical	*SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased risk of statin-induced myopathy + rhabdomyolysis.	Lu, *et al.* (2021)(124)	Moderate
Pitavastatin			
Clinical	*SLCO1B1* SNP rs4149056 (c.521T>C) did not affect the lipid-lowering efficacy of pitavastatin.	Yang, *et al.* (2010) (125)	Moderate

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

Clinical	*SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased AUC and decreased clearance of pitavastatin.	Chung, *et al.* (2005) (126) Ieiri, *et al.* (2007) (127) Deng, *et al.* (2008) (117) Oh, *et al.* (2013) (128) Zhou, *et al.* (2013) (129) Mori, *et al.* (2019) (95)	High
Clinical	*SLCO1B1* SNP rs2306283 (c.388A>G) did not affect the lipid-lowering efficacy of pitavastatin.	Yang, *et al.* (2010) (125)	Moderate
Clinical	Pitavastatin AUC and Cmax increased for carriers of the *SLCO1B1* rs2306283 (c.388A>G) polymorphism.	Wen, *et al.* (2010) (130)	Weak
Simvastatin			
In vitro	*SLCO1B1* rs4149056 (c.521T>C) is the key SNP determining the functional properties of *SLCO1B1**5, *15 allelic proteins and that decreased activities of these variant proteins are mainly caused by a sorting error produced by this SNP. Reduced transport function for *SLCO1B1**15 as compared with *1a.	Iwai, *et al.* (2004) (131) Kameyama, *et al.* (2005) (84) Ho, *et al.* (2006) (132)	Moderate
Clinical	*SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased risk of simvastatin-induced myopathy.	Link, *et al.* (2008) (133) Brunham, *et al.* (2012) (86) Hubacek, *et al.* (2015) (89) Liu, *et al.* (2017) (91) Shek, *et al.* (2017) (134) Bakar, *et al.* (2018) (135) Flores-Unzueta, *et al.* (2018) (136) Xiang, *et al.* (2018) (92) Carr, *et al.* (2019) (137) C. Thambiah, *et al.* (2019) (138)	High
Clinical	*SLCO1B1**17 is associated with an increased risk of simvastatin-induced myopathy.	Chan, *et al.* (2019) (139)	Weak
Clinical	*SLCO1B1* rs4149056 C (c.521T>C) polymorphism markedly affects the pharmacokinetics of active simvastatin acid, but has no significant effect on parent simvastatin.	Pasanen, *et al.* (2006) (4) Zhou, *et al.* (2013) (140) Tsamandouras, *et al.* (2014) (141)	High

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

		Birmingham, *et al.* (2015) (101) Choi, *et al.* (2015) (142) Luzum, *et al.* (2015) (143) Hasunuma, *et al.* (2016) (144) Jiang, *et al.* (2017) (145) Wagner, *et al.* (2018) (146) Ogungbenro, *et al.* (2019) (147)	
Clinical	Individuals with the *SLCO1B1* rs4149056 (c.521T>C) C allele showed an attenuated lipid-lowering effect compared with those homozygous for the 521T allele. The effect size may be small.	Tachibana-Iimori, *et al.* (2004) (107) Bailey, *et al.* (2010) (148) Hopewell, *et al.* (2013) (149) Giannakopoulou, *et al.* (2014) (109) Dou, *et al.* (2015) (150) Li, *et al.* (2015) (151) Meyer, *et al.* (2015) (110) Kitzmiller, *et al.* (2017) (152) Oni-Orisan, *et al.* (2018) (153) Kaewboonlert, *et al.* (2018) (154) Wu, *et al.* (2018) (155)	High
Clinical	Individuals with the rs4149056 C (c.521T>C) allele may be more likely to have dose decrease or switch.	De Keyser, *et al.* (2014) (113)	Weak
Clinical	*SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with risk of myotoxicity in individuals that received atorvastatin, simvastatin.	Liu, *et al.* (2017) (91)	Weak
Clinical	*SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with simvastatin or simvastatin acid pharmacokinetics.	Birmingham, *et al.* (2015) (101)	Weak
Clinical	*SLCO1B1* rs2306283 (c.388A>G) is not significantly associated with the lipid-lowering effect of simvastatin.	Kaewboonlert, *et al.* (2018) (154) Wu, *et al.* (2018) (155)	Weak
Statin			
Clinical	*SLCO1B1* rs2900478 is associated with a statistically significant though clinically negligible, lipid-lowering effect of statin.	Postmus, *et al.* (2014) (20)	Moderate

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

Clinical	*SLCO1B1**5 (rs4149056) (c.521T>C) is associated with an increased risk of statin-induced myopathy.	Voora, *et al.* (2009) (156) Hubacek, *et al.* (2015) (89) Khine, *et al.* (2016) (157) Bakar, *et al.* (2018) (135) C. Thambiah, *et al.* (2019) (138) Floyd, *et al.* (2019) (158)	Weak
Clinical	Presence of the *SLCO1B1* rs4149056 (c.521T>C) 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) (156) Carr, *et al.* (2013) (159)	Moderate
Clinical	*SLCO1B1* rs4149056 (c.521T>C) C allele is associated with an increased LDL-C levels in statin-treated patients.	Li, *et al.* (2015) (151)	Moderate
Clinical	*SLCO1B1* rs2306283 (c.388A>G) is not associated with an increased LDL-C levels in statin-treated patients.	Li, *et al.* (2015) (151)	Moderate
Clinical	Genetically guided statin therapy improves patients' perceptions of statins, more statin prescriptions, and lower LDL-C.	Li, *et al.* (2014) (160) Peyser, *et al.* (2018) (161)	Weak

TABLE S2. EVIDENCE LINKING ABCG2 GENOTYPE WITH STATIN PHENOTYPE

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major Findings	References	Level of Evidence
Clinical	*ABCG2* rs2231142 (c.421C>A) CA genotype is found to be more frequent in statin-intolerant cases.	Shek, *et al.* (2017) (134)	Weak
Clinical	*ABCG2* rs2231142 (c.421C>A) is associated with simvastatin-induced liver symptoms.	Shek, *et al.* (2018) (162)	Moderate
Clinical	*ABCG2* rs2231142 (c.421C>A) may be associated with statin-induced muscle symptoms.	Chan, *et al.* (2019) (139)	Weak
Clinical	*ABCG2* rs2231142 (c.421C>A) A allele carriers had higher AUC(0-t) and Cmax of simvastatin acid as compared with those carrying the CC genotype. It did not affect simvastatin lactone concentration.	Keskitalo, *et al.* (2009) (163) Birmingham, *et al.* (2015) (101) Choi, *et al.* (2015) (142)	Weak
Clinical	*ABCG2* rs2231142 (c.421C>A) is not significantly associated with the lipid-lowering effect of simvastatin.	Bailey, *et al.* (2010) (148)	High
In vitro	Rosuvastatin is a substrate of SLCO1B1, SLCO1B3, and SLCO2B1 in sinusoidal uptake and of MRP2, MDR1, and ABCG2 in biliary excretion. SLCO1B1 as well as NTCP plays an important role in rosuvastatin uptake into human hepatocytes.	Kitamura, *et al.* (2018) (164)	Moderate
In vitro	Rosuvastatin is transported efficiently by ABCG2 and suggest that ABCG2 plays a significant role in the disposition of rosuvastatin.	Huang, *et al.* (2006) (165)	High
Clinical	*ABCG2* rs2231142 (c.421C>A) is not significantly associated with high SIM risk.	Sreter, *et al.* (2017) (166) Bai, *et al.* (2019) (23)	Moderate
Clinical	*ABCG2* rs2231142 (c.421C>A) is associated with greater LDL response to rosuvastatin.	Tomlinson, *et al.* (2010) (167)	Moderate

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

		Lee, *et al.* (2013) (168) Kim, *et al.* (2017) (169) Kim, *et al.* (2019) (170)	
Clinical	*ABCG2* SNP rs2199936 is significantly associated with absolute LDL-C reduction. (rs2231142 (421C>A) is in LD with rs2199936 in the HapMap (CEU, r2=0.81)).	Chasman, *et al.* (2012) (171)	High
Clinical	*ABCG2* rs2231142 (c.421C>A) is significantly associated with rosuvastatin exposure. Genotypes AC + AA are associated with increased exposure to rosuvastatin compared to CC.	Zhang, *et al.* (2006) (172) Keskitalo, *et al.* (2009) (21) Zhou, *et al.* (2013) (173) DeGorter, *et al.* (2013) (22) Lee, *et al.* (2013) (168) Birmingham, *et al.* (2015) (174) Birmingham, *et al.* (2015) (101) Wan, *et al.* (2015) (175) Kim, *et al.* (2019) (170) Liu, *et al.* (2016) (176) Kashihara, *et al.* (2017) (177) Bai, *et al.* (2019) (23) Soko, *et al.* (2019) (178) Zhang, *et al.* (2020) (179)	High
Clinical	*ABCG2* rs2231142 (c.421C>A) A allele is not significantly associated with an increased risk of atorvastatin-induced liver tox.	Fukunaga, *et al.* (2016) (98)	Weak
Clinical	*ABCG2* rs2231142 (c.421C>A) A allele is significantly associated with an increased risk of atorvastatin-induced adverse events.	Mirosevic Skvrce, *et al.* (2015) (90)	Moderate

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

Clinical	*ABCG2* rs2231142 (c.421C>A) is significantly associated with atorvastatin exposure.	Keskitalo, *et al.* (2009) (21) DeGorter, *et al.* (2013) (22) Birmingham, *et al.* (2015) (101) Tsamandouras, *et al.* (2017) (180) Lee, *et al.* (2019) (106)	Weak
Clinical	In vitro study showed that *ABCG2* affect atorvastatin transport.	Keskitalo, *et al.* (2009) (21)	High
Clinical	*ABCG2* rs2231142 (c.421C>A) is not associated with atorvastatin response.	Prado, *et al.* (2018) (181)	Moderate
Clinical	*ABCG2* rs2231142 (c.421C>A) is not associated with decreased clearance of pravastatin.	Ho, *et al.* (2007) (182) Keskitalo, *et al.* (2009) (163) Lu, *et al.* (2016) (183)	Moderate
In vitro	Pitavastatin acid is a substrate of *ABCG2*, whereas the lactone form is not. *ABCG2* is involved in the biliary excretion of pitavastatin.	Fujino, *et al.* (2005) (184) Hirano, *et al.* (2005) (185)	Moderate
Clinical	*ABCG2* rs2231142 (c.421C>A) is not significantly associated with concentration of pitavastatin.	Ieiri, *et al.* (2007) (127) Oh, *et al.* (2013) (128)	Moderate
Clinical	*ABCG2* rs2231142 (c.421C>A) AA genotype is associated with higher fluvastatin AUC.	Keskitalo, *et al.* (2009) (163)	High
Clinical	*ABCG2* rs2231142 (c.421C>A) is associated with greater odds of developing fluvastatin-induced adverse effects (liver and muscle toxicity).	Mirosevic, *et al.* (2013) (186)	Moderate
Clinical	*ABCG2* rs2231142 (c.421C>A) is not associated with concentration of lovastatin acid and lovastatin lactone.	Zhao, *et al.* (2017) (123)	Weak

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

TABLE S3. EVIDENCE LINKING CYP2C9 GENOTYPE WITH STATIN PHENOTYPE

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major Findings	References	Level of Evidence
In vitro	Fluvastatin is metabolized in human liver by several enzymes, with CYP2C9 being the most important, followed by CYP3A4 and CYP2C8.	Fischer, *et al.* (1999) (187) Toda, *et al.* (2009) (188) Hirvensalo, *et al.* (2019) (119)	High
In vitro	Fluvastatin is a potent inhibitor of *CYP2C9*.	Transon, *et al.* (1996) (189) Cohen, *et al.* (2000) (190)	Moderate
In vitro	*CYP2C9*2, *3* were associated with reduced clearance of fluvastatin enantiomers in vitro.	Hirvensalo, *et al.* (2019) (119)	Moderate
In vitro	Fluvastatin and lovastatin increased *CYP2C9* protein level in endothelial cells.	Bertrand-Thiebault, *et al.* (2007) (191)	Weak
Clinical	*CYP2C9*2, *3* are not significantly associated with lipid-lowering response to fluvastatin.	Kirschheiner, *et al.* (2003) (192) Xiang, *et al.* (2018) (116)	Weak
Clinical	*CYP2C9*3 affected the pharmacokinetics of both fluvastatin enantiomers. *CYP2C9*3 associated with significantly increased area under the plasma concentration-time curve (AUC) of both 3R,5S-fluvastatin and 3S,5R-fluvastatin.	Kirschheiner, *et al.* (2003) (192) Toda, *et al.* (2009) (188) Zhou, *et al.* (2012) (121) Hirvensalo, *et al.* (2019) (119) Xiang, *et al.* (2020) (118)	High
Clinical	*CYP2C9*2 influences the pharmacokinetics of the fluvastatin (affect the AUC of both fluvastatin enantiomers).	Fischer, *et al.* (1999) (187)	Moderate

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

		Kirschheiner, *et al.* (2003) (192) Hirvensalo, *et al.* (2019) (119)	
Clinical	*CYP2C9*2* or **3* allele is associated with greater odds of developing fluvastatin-induced adverse effects (liver and muscle toxicity).	Mirosevic, *et al.* (2013) (186)	Moderate
Unknown	Statins, *CYP2C9* genotypes are not significantly associated with muscle tox or lipid response to statins (simvastatin, fluvastatin, rosuvastatin).	Zuccaro, *et al.* (2007) (193)	Weak
Clinical	A case with liver cirrhosis who experienced fluvastatin-induced fatal rhabdomyolysis. This patient had been treated with simvastatin (20 mg/day) for coronary artery disease and was switched to fluvastatin (20 mg/day) 10 days before admission.	Baek, *et al.* (2011) (194)	Weak
Clinical	*CYP2C9*3* is not associated with LDL response to rosuvastatin.	Bailey, *et al.* (2010) (148)	Moderate
Clinical	*CYP2C9*3* allele is associated with an increased concentration of pitavastatin.	Zhou, *et al.* (2013) (129)	Weak

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

TABLE S4. EVIDENCE LINKING HMGCR GENOTYPE WITH STATIN PHENOTYPE

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major Findings	References	Level of Evidence
Clinical	Multiple cases of statin-related immune-mediated necrotizing myopathy (SINAM) were described. Many are positive for anti-HMGCR antibody, but there are exceptions.	Mygland, *et al.* (2014) (195) Ong, *et al.* (2017) (196) Karunaratne, *et al.* (2018) (197) Pitlick, *et al.* (2019) (198)	Weak
Clinical	*HMGCR* haplotypes H2 and H7 were associated with attenuated reduction of LDL cholesterol when treated with simvastatin. Tag SNP rs17238540 and rs17244841 were also associated with altered LDL-C response.	Krauss, *et al.* (2008) (199)	Weak
	Carriers of both *HMGCR* H2/H7 haplotype and LDLR L5 haplotype had significantly attenuated statin-mediated changes in LDLC and LDLR in comparison to either noncarriers or carriers of individual haplotypes. This effect is more evident in African-Americans than in European-Americans.	Mangravite, *et al.* (2010) (200)	Weak
	HMGCR ScrF I polymorphism is associated with vLDL-C lowering effect by simvastatin.	Ying, *et al.* (2007) (201)	Weak
In vitro	*HMGCR* variant rs3846662 influenced *HMGCR* alternative splicing. Greater upregulation of *HMGCR*v_1 in vitro was significantly correlated with reduced statin response (smaller reductions of plasma total and low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B).	Medina, *et al.* (2008) (202)	Weak
Clinical	*HMGCR* variants rs17238540 and rs17244841 were significantly associated with a smaller reduction in total cholesterol and LDL cholesterol following pravastatin therapy.	Chasman, *et al.* (2004) (203)	Weak

		Polisecki, *et al.* (2008) (204)	
Clinical	*HMGCR* variants rs17238540, rs17244841 were not associated with lipid response to fluvastatin.	Singer, *et al.* (2007) (205)	Weak
Clinical	Multiple cases of statin-related immune-mediated necrotizing myopathy (SINAM) were described. All are previously atorvastatin treated. All are positive for anti-*HMGCR* antibody.	Nichols, *et al.* (2015) (206) De Cock, *et al.* (2018) (207) Woolley, *et al.* (2018) (208) Sharma, *et al.* (2019) (209)	Weak
In vitro	Atorvastatin had no significant effect on LRP or *HMGCR* mRNA levels in circulating mononuclear cells.	Pocathikorn, *et al.* (2010) (210)	Weak
Clinical	*HMGCR* variants rs17238540 and rs17244841 were significantly associated with reduction in total cholesterol and LDL-c levels.	Thompson, *et al.* (2009) (211) Poduri, *et al.* (2010) (212) Kirac, *et al.* (2017) (213)	Weak
Clinical	*HMGCR* variant rs17671591 is associated with greater plasma LDL-C reductions after therapy with atorvastatin.	Cuevas, *et al.* (2016) (214)	Weak
Clinical	*HMGCR* rs3846662 was associated with LDL lowering response to atorvastatin.	Chung, *et al.* (2012) (215) Yue, *et al.* (2016) (216)	Weak
Clinical	*HMGCR* variants (rs10474433, rs17671591, rs6453131) were associated with statin response by with smaller effect than the ApoE variants.	Thompson, *et al.* (2009) (211)	Weak
In vitro	Atorvastatin insensitivity is associated with upregulation of HMGCR and SCD.	Lettiero, *et al.* (2018) (217)	Weak

TABLE S5. EVIDENCE LINKING CYP3A4/5 GENOTYPE WITH STATIN PHENOTYPE

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major Findings	References	Level of Evidence
Clinical	*CYP3A5*3/*3* genotype (6986A>G) is associated with simvastatin-induced muscle symptoms.	Shek, *et al.* (2017) (134) Liu, *et al.* (2017) (91)	Weak
Clinical	*CYP3A5*3/*3* genotype (6986A>G) is more frequent in statin-intolerant cases.	Shek, *et al.* (2018) (162)	Weak
Clinical	*CYP3A5*3/*3* genotype (6986A>G) is associated with simvastatin-induced liver symptoms.	Shek, *et al.* (2017) (134)	Weak
Clinical	When simvastatin-intolerant patients were switched to rosuvastatin, serious side effect were not observed and many of them carry *CYP3A5*3/*3*.	Shek, *et al.* (2018) (162)	Weak
Clinical	*CYP3A4* rs2740574 (G>A) G allele is associated with smaller risk of a dose decrease or switch to another drug during simvastatin and atorvastatin therapy.	Becker, *et al.* (2010) (218)	Weak
Clinical	*CYP3A4*22* is associated with lower statin dose (atorvastatin, simvastatin, or lovastatin).	Wang, *et al.* (2011) (219)	Weak
Clinical	*CYP3A5*3* is associated with cholesterol response to simvastatin.	Kivisto, *et al.* (2004) (220) Fiegenbaum, *et al.* (2005) (221) Hu, *et al.* (2013) (222) Kolovou, *et al.* (2014) (223) Kitzmiller, *et al.* (2017) (152)	Weak

Clinical	*CYP3A4*22* is associated with cholesterol response to simvastatin.	Elens, *et al.* (2011) (224) Ragia, *et al.* (2015) (225) Kitzmiller, *et al.* (2017) (152)	Weak
Clinical	*CYP3A4*1G* is not associated with cholesterol response to simvastatin.	Gao, *et al.* (2008) (226) Hu, *et al.* (2013) (222)	Weak
Clinical	*CYP3A4*1B* is not associated with cholesterol response to simvastatin.	Fiegenbaum, *et al.* (2005) (221)	Weak
Clinical	*CYP3A4*4* is not associated with LDL lowering response to simvastatin but may affect percentage reductions in total cholesterol and triglycerides.	Wang, *et al.* (2005) (227)	Weak
Clinical	*CYP3A5*3* may be associated with higher simvastatin concentration.	Kim, *et al.* (2007) (228) Kitzmiller, *et al.* (2014) (229) Choi, *et al.* (2015) (142) Luzum, *et al.* (2015) (143)	Weak
Clinical	*CYP3A4*22* is associated with higher plasma simvastatin concentration compared to *CYP3A4*1/*1.	Kitzmiller, *et al.* (2014) (229) Luzum, *et al.* (2015) (143)	Weak
Clinical	*CYP3A5*3* is not significantly associated with risk of myotoxicity in individuals that received rosuvastatin.	Liu, *et al.* (2017) (91) Ramakumari, *et al.* (2018) (94)	Weak
Clinical	Patients with *CYP3A5*1* allele achieved LDL cholesterol target more frequently as compared to patients with *CYP3A5*3/*3 when treated with rosuvastatin.	Bailey, *et al.* (2010) (148)	Weak
Clinical	*CYP3A5*3* is not significantly associated with risk of myotoxicity in individuals that received atorvastatin, however it may affect the severity of myotoxicity (magnitude of serum CK elevation).	Wilke, *et al.* (2005) (27) Liu, *et al.* (2017) (91) Ramakumari, *et al.* (2018) (94)	Weak
Clinical	*CYP3A4*22* is not significantly associated with adverse events in individuals that received atorvastatin.	Mirosevic, *et al.* (2015) (90)	Weak
Clinical	*CYP3A5*3* is significantly associated with atorvastatin efficacy.	Kivisto, *et al.* (2004) (220)	Weak

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

		Thompson, *et al.* (2005) (230) Willrich, *et al.* (2008) (231) Rosales, *et al.* (2012) (232) Drogari, *et al.* (2014) (108) Wei, *et al.* (2015) (233)	
Clinical	*CYP3A4*22* is not significantly associated with atorvastatin efficacy.	Drogari, *et al.* (2014) (108) Ragia, *et al.* (2015) (225)	Weak
Clinical	*CYP3A4* rs2740574 G allele may be associated with a greater reduction in serum total cholesterol and LDL-c.as compared to AA when treated with atorvastatin.	Kajinami, *et al.* (2004) (234) Rosales, *et al.* (2012) (232)	Weak
Clinical	*CYP3A4* rs2242480 is associated with lipid-lowering efficacy of atorvastatin.	Gao, *et al.* (2008) (226) Peng, *et al.* (2018) (235)	Weak
Clinical	*CYP3A4* rs2242480 is associated with lower AUC and greater clearance when treated with atorvastatin.	He, *et al.* (2014) (236)	Weak
Clinical	*CYP3A5* genotype has minimal effects on the pharmacokinetic parameters of atorvastatin.	Shin, *et al.* (2011) (237)	Weak
Clinical	*CYP3A5*3* is associated with enhanced lovastatin lipid lowering efficacy.	Kivisto, *et al.* (2004) (220)	Weak
Clinical	*CYP3A5*3* is not significantly associated with lipid lowering efficacy to fluvastatin.	Kivisto, *et al.* (2004) (220)	Weak
Clinical	*CYP3A5*3* is not significantly associated with lipid lowering efficacy to pravastatin.	Kivisto, *et al.* (2004) (220)	Weak

CPIC guidelines for *SLCO1B1* and statin-induced myopathy- Supplement v3.0

REFERENCES

(1) Kalman, L.V. *et al.* Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. *Clin Pharmacol Ther* **99**, 172-85 (2016).

(2) Pratt, V.M. *et al.* Recommendations for Clinical CYP2C9 Genotyping Allele Selection: A Joint Recommendation of the Association for Molecular Pathology and College of American Pathologists. *J Mol Diagn*, (2019).

(3) Niemi, M. Transporter pharmacogenetics and statin toxicity. *Clin Pharmacol Ther* **87**, 130-3 (2010).

(4) Pasanen, M.K., Neuvonen, M., Neuvonen, P.J. & Niemi, M. SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. *Pharmacogenet Genomics* **16**, 873-9 (2006).

(5) Generaux, G.T., Bonomo, F.M., Johnson, M. & Doan, K.M. Impact of SLCO1B1 (OATP1B1) and ABCG2 (BCRP) genetic polymorphisms and inhibition on LDL-C lowering and myopathy of statins. *Xenobiotica* **41**, 639-51 (2011).

(6) Kaddurah-Daouk, R. *et al.* Enteric microbiome metabolites correlate with response to simvastatin treatment. *PLoS One* **6**, e25482 (2011).

(7) Ho, R.H. & Kim, R.B. Transporters and drug therapy: implications for drug disposition and disease. *Clinical pharmacology and therapeutics* **78**, 260-77 (2005).

(8) Campana, C. *et al.* Efficacy and pharmacokinetics of simvastatin in heart transplant recipients. *Ann Pharmacother* **29**, 235-9 (1995).

(9) Donnelly, L.A. *et al.* Common nonsynonymous substitutions in SLCO1B1 predispose to statin intolerance in routinely treated individuals with type 2 diabetes: a go-DARTS study. *Clin Pharmacol Ther* **89**, 210-6 (2011).

(10) Ho, R.H. *et al.* Effect of drug transporter genotypes on pravastatin disposition in European- and African-American participants. *Pharmacogenetics and genomics* **17**, 647-56 (2007).

(11) Igel, M. *et al.* Impact of the SLCO1B1 polymorphism on the pharmacokinetics and lipid-lowering efficacy of multiple-dose pravastatin. *Clinical pharmacology and therapeutics* **79**, 419-26 (2006).

(12) Niemi, M. *et al.* Acute effects of pravastatin on cholesterol synthesis are associated with SLCO1B1 (encoding OATP1B1) haplotype *17. *Pharmacogenetics and genomics* **15**, 303-9 (2005).

(13) Bailey, K.M. *et al.* Hepatic metabolism and transporter gene variants enhance response to rosuvastatin in patients with acute myocardial infarction: the GEOSTAT-1 Study. *Circulation Cardiovascular genetics* **3**, 276-85 (2010).

(14) Choi, J.H., Lee, M.G., Cho, J.Y., Lee, J.E., Kim, K.H. & Park, K. Influence of OATP1B1 genotype on the pharmacokinetics of rosuvastatin in Koreans. *Clinical pharmacology and therapeutics* **83**, 251-7 (2008).

(15) Wen, J. & Xiong, Y. OATP1B1 388A>G polymorphism and pharmacokinetics of pitavastatin in Chinese healthy volunteers. *J Clin Pharm Ther* **35**, 99-104 (2010).

(16) Yang, G.P. *et al.* Lack of effect of genetic polymorphisms of SLCO1B1 on the lipid-lowering response to pitavastatin in Chinese patients. *Acta Pharmacol Sin* **31**, 382-6 (2010).

(17) Deng, J.W. *et al.* The effect of SLCO1B1*15 on the disposition of pravastatin and pitavastatin is substrate dependent: the contribution of transporting activity changes by SLCO1B1*15. *Pharmacogenetics and genomics* **18**, 424-33 (2008).

(18) Ieiri, I. *et al.* SLCO1B1 (OATP1B1, an uptake transporter) and ABCG2 (BCRP, an efflux transporter) variant alleles and pharmacokinetics of pitavastatin in healthy volunteers. *Clinical pharmacology and therapeutics* **82**, 541-7 (2007).

(19) Chung, J.Y. *et al.* Effect of OATP1B1 (SLCO1B1) variant alleles on the pharmacokinetics of pitavastatin in healthy volunteers. *Clinical pharmacology and therapeutics* **78**, 342-50 (2005).

(20)   Postmus, I. *et al.* Pharmacogenetic meta-analysis of genome-wide association studies of LDL cholesterol response to statins. *Nat Commun* **5**, 5068 (2014).

(21)   Keskitalo, J.E., Zolk, O., Fromm, M.F., Kurkinen, K.J., Neuvonen, P.J. & Niemi, M. ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. *Clin Pharmacol Ther* **86**, 197-203 (2009).

(22)   DeGorter, M.K. *et al.* Clinical and pharmacogenetic predictors of circulating atorvastatin and rosuvastatin concentrations in routine clinical care. *Circ Cardiovasc Genet* **6**, 400-8 (2013).

(23)   Bai, X. *et al.* Effects of SLCO1B1 and GATM gene variants on rosuvastatin-induced myopathy are unrelated to high plasma exposure of rosuvastatin and its metabolites. *Acta Pharmacol Sin* **40**, 492-9 (2019).

(24)   Chu, A.Y. *et al.* Differential Genetic Effects on Statin-Induced Changes Across Low-Density Lipoprotein-Related Measures. *Circ Cardiovasc Genet* **8**, 688-95 (2015).

(25)   Benet, L.Z. & Wu, H.F. Understanding the Potential Interethnic Difference in Rosuvastatin Pharmacokinetics. *J Pharm Sci* **106**, 2231-3 (2017).

(26)   Sugiyama, Y., Maeda, K. & Toshimoto, K. Is Ethnic Variability in the Exposure to Rosuvastatin Explained Only by Genetic Polymorphisms in OATP1B1 and BCRP or Should the Contribution of Intrinsic Ethnic Differences in OATP1B1 Be Considered? *J Pharm Sci* **106**, 2227-30 (2017).

(27)   Wilke, R.A., Moore, J.H. & Burmester, J.K. Relative impact of CYP3A genotype and concomitant medication on the severity of atorvastatin-induced muscle damage. *Pharmacogenet Genomics* **15**, 415-21 (2005).

(28)   Kuehl, P. *et al.* Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet* **27**, 383-91 (2001).

(29)   Valdes, R., Payne, D.A. & Linder, M.W. Laboratory analysis and application of pharmacogenetics to clinical practice. *The National Academy of Clinical Biochemistry (NACB) - Laboratory Medicine Practice Guidelines* 2010.

(30)   Grundy, S.M. *et al.* 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* **73**, 3168-209 (2019).

(31)   Adolescents, P.o.A.G.f.A.a. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services.   1-166 (2011).

(32)   Backman, J.T., Kyrklund, C., Neuvonen, M. & Neuvonen, P.J. Gemfibrozil greatly increases plasma concentrations of cerivastatin. *Clin Pharmacol Ther* **72**, 685-91 (2002).

(33)   Ronaldson, K.J., O'Shea, J.M. & Boyd, I.W. Risk factors for rhabdomyolysis with simvastatin and atorvastatin. *Drug safety : an international journal of medical toxicology and drug experience* **29**, 1061-7 (2006).

(34)   Rowan, C. *et al.* Rhabdomyolysis reports show interaction between simvastatin and CYP3A4 inhibitors. *Pharmacoepidemiol Drug Saf* **18**, 301-9 (2009).

(35)   Schneck, D.W. *et al.* The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* **75**, 455-63 (2004).

(36)   Backman, J.T., Kyrklund, C., Kivisto, K.T., Wang, J.S. & Neuvonen, P.J. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clinical pharmacology and therapeutics* **68**, 122-9 (2000).

(37)   Neuvonen, P.J., Niemi, M. & Backman, J.T. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clinical pharmacology and therapeutics* **80**, 565-81 (2006).

(38)   Hermann, M., Asberg, A., Christensen, H., Holdaas, H., Hartmann, A. & Reubsaet, J.L. Substantially elevated levels of atorvastatin and metabolites in cyclosporine-treated renal transplant recipients. *Clinical pharmacology and therapeutics* **76**, 388-91 (2004).

(39)   Stein, C.M., Sadeque, A.J., Murray, J.J., Wandel, C., Kim, R.B. & Wood, A.J. Cyclosporine pharmacokinetics and pharmacodynamics in African American and white subjects. *Clinical pharmacology and therapeutics* **69**, 317-23 (2001).

(40)   Capone, D., Stanziale, P., Gentile, A., Imperatore, P., Pellegrino, T. & Basile, V. Effects of simvastatin and pravastatin on hyperlipidemia and cyclosporin blood levels in renal transplant recipients. *Am J Nephrol* **19**, 411-5 (1999).

(41)   Lepre, F., Rigby, R., Hawley, C., Saltissi, D., Brown, A. & Walsh, Z. A double-blind placebo controlled trial of simvastatin for the treatment of dyslipidaemia in renal allograft recipients. *Clin Transplant* **13**, 520-5 (1999).

(42)   Pflugfelder, P.W., Huff, M., Oskalns, R., Rudas, L. & Kostuk, W.J. Cholesterol-lowering therapy after heart transplantation: a 12-month randomized trial. *J Heart Lung Transplant* **14**, 613-22 (1995).

(43)   Vanhaecke, J., Van Cleemput, J., Van Lierde, J., Daenen, W. & De Geest, H. Safety and efficacy of low dose simvastatin in cardiac transplant recipients treated with cyclosporine. *Transplantation* **58**, 42-5 (1994).

(44)   Lee, E. *et al.* Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther* **78**, 330-41 (2005).

(45)   Feng, Q., Wilke, R.A. & Baye, T.M. Individualized risk for statin-induced myopathy: current knowledge, emerging challenges and potential solutions. *Pharmacogenomics* **13**, 579-94 (2012).

(46)   Brunham, L.R. *et al.* Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. *Pharmacogenomics J*, (2011).

(47)   Giorgi, M.A., Caroli, C., Arazi, H.C. & Di Girolamo, G. Pharmacogenomics and adverse drug reactions: the case of statins. *Expert Opin Pharmacother* **12**, 1499-509 (2011).

(48)   He, Y.J. *et al.* Rifampicin alters atorvastatin plasma concentration on the basis of SLCO1B1 521T>C polymorphism. *Clin Chim Acta* **405**, 49-52 (2009).

(49)   Kalliokoski, A. & Niemi, M. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol* **158**, 693-705 (2009).

(50)   Neuvonen, P.J., Backman, J.T. & Niemi, M. Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. *Clin Pharmacokinet* **47**, 463-74 (2008).

(51)   Suwannakul, S. *et al.* Pharmacokinetic interaction between pravastatin and olmesartan in relation to SLCO1B1 polymorphism. *J Hum Genet* **53**, 899-904 (2008).

(52)   Pasanen, M.K., Fredrikson, H., Neuvonen, P.J. & Niemi, M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. *Clinical pharmacology and therapeutics* **82**, 726-33 (2007).

(53)   Hermann, M. *et al.* Exposure of atorvastatin is unchanged but lactone and acid metabolites are increased several-fold in patients with atorvastatin-induced myopathy. *Clinical pharmacology and therapeutics* **79**, 532-9 (2006).

(54)   Mwinyi, J., Johne, A., Bauer, S., Roots, I. & Gerloff, T. Evidence for inverse effects of OATP-C (SLC21A6) 5 and 1b haplotypes on pravastatin kinetics. *Clinical pharmacology and therapeutics* **75**, 415-21 (2004).

(55)   Niemi, M. *et al.* High plasma pravastatin concentrations are associated with single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide-C (OATP-C, SLCO1B1). *Pharmacogenetics* **14**, 429-40 (2004).

(56)   Backman, J.T., Kyrklund, C., Neuvonen, M. & Neuvonen, P.J. Gemfibrozil greatly increases plasma concentrations of cerivastatin. *Clinical pharmacology and therapeutics* **72**, 685-91 (2002).

(57) Hamelin, B.A. & Turgeon, J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. *Trends Pharmacol Sci* **19**, 26-37 (1998).

(58) Rehman, M.A. *et al.* Effects of simvastatin in hyperlipidemic renal transplant patients receiving cyclosporine. *Transplantation* **60**, 397-9 (1995).

(59) Arnadottir, M., Eriksson, L.O., Germershausen, J.I. & Thysell, H. Low-dose simvastatin is a well-tolerated and efficacious cholesterol-lowering agent in ciclosporin-treated kidney transplant recipients: double-blind, randomized, placebo-controlled study in 40 patients. *Nephron* **68**, 57-62 (1994).

(60) Arnadottir, M., Eriksson, L.O., Thysell, H. & Karkas, J.D. Plasma concentration profiles of simvastatin 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without ciclosporin. *Nephron* **65**, 410-3 (1993).

(61) Ide, T., Sasaki, T., Maeda, K., Higuchi, S., Sugiyama, Y. & Ieiri, I. Quantitative population pharmacokinetic analysis of pravastatin using an enterohepatic circulation model combined with pharmacogenomic Information on SLCO1B1 and ABCC2 polymorphisms. *Journal of clinical pharmacology* **49**, 1309-17 (2009).

(62) Werner, M., Sacher, J. & Hohenegger, M. Mutual amplification of apoptosis by statin-induced mitochondrial stress and doxorubicin toxicity in human rhabdomyosarcoma cells. *Br J Pharmacol* **143**, 715-24 (2004).

(63) Sacher, J., Weigl, L., Werner, M., Szegedi, C. & Hohenegger, M. Delineation of myotoxicity induced by 3-hydroxy-3-methylglutaryl CoA reductase inhibitors in human skeletal muscle cells. *J Pharmacol Exp Ther* **314**, 1032-41 (2005).

(64) Dirks, A.J. & Jones, K.M. Statin-induced apoptosis and skeletal myopathy. *Am J Physiol Cell Physiol* **291**, C1208-12 (2006).

(65) Maggo, S.D., Kennedy, M.A. & Clark, D.W. Clinical implications of pharmacogenetic variation on the effects of statins. *Drug safety : an international journal of medical toxicology and drug experience* **34**, 1-19 (2011).

(66) Ramsey, L.B. *et al.* Rare versus common variants in pharmacogenetics: SLCO1B1 variation and methotrexate disposition. *Genome research*, (2011).

(67) CPIC. *CPIC guideline for statins and SLCO1B1, ABCG2 and CYP2C9.* <https://cpicpgx.org/guidelines/cpic-guideline-for-statins/>. Accessed August 1, 2021 2021.

(68) PharmGKB. PGx Gene-specific Information Tables.

(69) Shuldiner, A.R. *et al.* The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation. *Clin Pharmacol Ther* **94**, 207-10 (2013).

(70) Wilke, R.A. *et al.* The emerging role of electronic medical records in pharmacogenomics. *Clin Pharmacol Ther* **89**, 379-86 (2011).

(71) Peterson, J.F. *et al.* Electronic health record design and implementation for pharmacogenomics: a local perspective. *Genetics in medicine : official journal of the American College of Medical Genetics* **15**, 833-41 (2013).

(72) Gottesman, O. *et al.* The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. *Genetics in medicine : official journal of the American College of Medical Genetics* **15**, 761-71 (2013).

(73) Kullo, I.J., Jarvik, G.P., Manolio, T.A., Williams, M.S. & Roden, D.M. Leveraging the electronic health record to implement genomic medicine. *Genetics in medicine : official journal of the American College of Medical Genetics* **15**, 270-1 (2013).

(74) Hicks, J.K. *et al.* A clinician-driven automated system for integration of pharmacogenetic interpretations into an electronic medical record. *Clin Pharmacol Ther* **92**, 563-6 (2012).

(75)   Hoffman, J.M. *et al.* Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *J Am Med Inform Assoc* **23**, 796-801 (2016).

(76)   Pulley, J.M. *et al.* Operational Implementation of Prospective Genotyping for Personalized Medicine: The Design of the Vanderbilt PREDICT Project. *Clin Pharmacol Ther* **92**, 87-95 (2012).

(77)   Lee, E. *et al.* Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther* **78**, 330-41 (2005).

(78)   Niemi, M., Pasanen, M.K. & Neuvonen, P.J. SLCO1B1 polymorphism and sex affect the pharmacokinetics of pravastatin but not fluvastatin. *Clinical pharmacology and therapeutics* **80**, 356-66 (2006).

(79)   Pasanen, M.K., Fredrikson, H., Neuvonen, P.J. & Niemi, M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. *Clin Pharmacol Ther* **82**, 726-33 (2007).

(80)   Choi, J.H., Lee, M.G., Cho, J.Y., Lee, J.E., Kim, K.H. & Park, K. Influence of OATP1B1 genotype on the pharmacokinetics of rosuvastatin in Koreans. *Clin Pharmacol Ther* **83**, 251-7 (2008).

(81)   Ho, R.H. *et al.* Effect of drug transporter genotypes on pravastatin disposition in European- and African-American participants. *Pharmacogenet Genomics* **17**, 647-56 (2007).

(82)   Niemi, M., Pasanen, M.K. & Neuvonen, P.J. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol Rev* **63**, 157-81 (2011).

(83)   Vildhede, A. *et al.* Hepatic uptake of atorvastatin: influence of variability in transporter expression on uptake clearance and drug-drug interactions. *Drug Metab Dispos* **42**, 1210-8 (2014).

(84)   Kameyama, Y., Yamashita, K., Kobayashi, K., Hosokawa, M. & Chiba, K. Functional characterization of SLCO1B1 (OATP-C) variants, SLCO1B1*5, SLCO1B1*15 and SLCO1B1*15+C1007G, by using transient expression systems of HeLa and HEK293 cells. *Pharmacogenet Genomics* **15**, 513-22 (2005).

(85)   Puccetti, L., Ciani, F. & Auteri, A. Genetic involvement in statins induced myopathy. Preliminary data from an observational case-control study. *Atherosclerosis* **211**, 28-9 (2010).

(86)   Brunham, L.R. *et al.* Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. *Pharmacogenomics J* **12**, 233-7 (2012).

(87)   Santos, P.C. *et al.* SLCO1B1 haplotypes are not associated with atorvastatin-induced myalgia in Brazilian patients with familial hypercholesterolemia. *Eur J Clin Pharmacol* **68**, 273-9 (2012).

(88)   Hou, Q., Li, S., Li, L., Li, Y., Sun, X. & Tian, H. Association Between SLCO1B1 Gene T521C Polymorphism and Statin-Related Myopathy Risk: A Meta-Analysis of Case-Control Studies. *Medicine (Baltimore)* **94**, e1268 (2015).

(89)   Hubacek, J.A. *et al.* SLCO1B1 polymorphism is not associated with risk of statin-induced myalgia/myopathy in a Czech population. *Med Sci Monit* **21**, 1454-9 (2015).

(90)   Mirosevic Skvrce, N., Macolic Sarinic, V., Simic, I., Ganoci, L., Muacevic Katanec, D. & Bozina, N. ABCG2 gene polymorphisms as risk factors for atorvastatin adverse reactions: a case-control study. *Pharmacogenomics* **16**, 803-15 (2015).

(91)   Liu, J.E. *et al.* SLCO1B1 521T > C polymorphism associated with rosuvastatin-induced myotoxicity in Chinese coronary artery disease patients: a nested case-control study. *Eur J Clin Pharmacol* **73**, 1409-16 (2017).

(92)   Xiang, Q. *et al.* Association between SLCO1B1 T521C polymorphism and risk of statin-induced myopathy: a meta-analysis. *Pharmacogenomics J* **18**, 721-9 (2018).

(93)   Du, Y., Wang, S., Chen, Z., Sun, S., Zhao, Z. & Li, X. Association of SLCO1B1 Polymorphisms and Atorvastatin Safety and Efficacy: A Meta-analysis. *Curr Pharm Des* **24**, 4044-50 (2018).

(94)   Ramakumari, N., Indumathi, B., Katkam, S.K. & Kutala, V.K. Impact of pharmacogenetics on statin-induced myopathy in South-Indian subjects. *Indian Heart J* **70 Suppl 3**, S120-S5 (2018).

(95)   Mori, D. *et al.* Effect of OATP1B1 genotypes on plasma concentrations of endogenous OATP1B1 substrates and drugs, and their association in healthy volunteers. *Drug Metab Pharmacokinet* **34**, 78-86 (2019).

(96)   Linskey, D.W. *et al.* Association of SLCO1B1 c.521T>C (rs4149056) with discontinuation of atorvastatin due to statin-associated muscle symptoms. *Pharmacogenet Genomics* **30**, 208-11 (2020).

(97)   Turner, R.M. *et al.* A Genome-wide Association Study of Circulating Levels of Atorvastatin and Its Major Metabolites. *Clin Pharmacol Ther* **108**, 287-97 (2020).

(98)   Fukunaga, K., Nakagawa, H., Ishikawa, T., Kubo, M. & Mushiroda, T. ABCB1 polymorphism is associated with atorvastatin-induced liver injury in Japanese population. *BMC Genet* **17**, 79 (2016).

(99)   Lee, Y.J., Lee, M.G., Lim, L.A., Jang, S.B. & Chung, J.Y. Effects of SLCO1B1 and ABCB1 genotypes on the pharmacokinetics of atorvastatin and 2-hydroxyatorvastatin in healthy Korean subjects. *Int J Clin Pharmacol Ther* **48**, 36-45 (2010).

(100)   Daka, A. *et al.* Effects of single nucleotide polymorphisms and haplotypes of the SLCO1B1 gene on the pharmacokinetic profile of atorvastatin in healthy Macedonian volunteers. *Pharmazie* **70**, 480-8 (2015).

(101)   Birmingham, B.K. *et al.* Impact of ABCG2 and SLCO1B1 polymorphisms on pharmacokinetics of rosuvastatin, atorvastatin and simvastatin acid in Caucasian and Asian subjects: a class effect? *Eur J Clin Pharmacol* **71**, 341-55 (2015).

(102)   Leon-Cachon, R.B.R. *et al.* A pharmacogenetic pilot study reveals MTHFR, DRD3, and MDR1 polymorphisms as biomarker candidates for slow atorvastatin metabolizers. *BMC Cancer* **16**, 74 (2016).

(103)   Rajput, T.A., Naveed, A.K., Farooqi, Z.R. & Khan, S. Effects of two functionally important SLCO1B1 gene polymorphisms on pharmacokinetics of atorvastatin. *Pak J Pharm Sci* **30**, 1363-70 (2017).

(104)   Wang, Y. *et al.* The effect of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and 2-hydroxyatorvastatin in healthy Chinese people. *Pharmazie* **72**, 365-8 (2017).

(105)   Woo, H.I., Kim, S.R., Huh, W., Ko, J.W. & Lee, S.Y. Association of genetic variations with pharmacokinetics and lipid-lowering response to atorvastatin in healthy Korean subjects. *Drug Des Devel Ther* **11**, 1135-46 (2017).

(106)   Lee, N. *et al.* Microdosing clinical study to clarify pharmacokinetic and pharmacogenetic characteristics of atorvastatin in Japanese hypercholesterolemic patients. *Drug Metab Pharmacokinet* **34**, 387-95 (2019).

(107)   Tachibana-Iimori, R. *et al.* Effect of genetic polymorphism of OATP-C (SLCO1B1) on lipid-lowering response to HMG-CoA reductase inhibitors. *Drug Metab Pharmacokinet* **19**, 375-80 (2004).

(108)   Drogari, E., Ragia, G., Mollaki, V., Elens, L., Van Schaik, R.H. & Manolopoulos, V.G. POR*28 SNP is associated with lipid response to atorvastatin in children and adolescents with familial hypercholesterolemia. *Pharmacogenomics* **15**, 1963-72 (2014).

(109)   Giannakopoulou, E. *et al.* No impact of SLCO1B1 521T>C, 388A>G and 411G>A polymorphisms on response to statin therapy in the Greek population. *Mol Biol Rep* **41**, 4631-8 (2014).

(110)   Meyer zu Schwabedissen, H.E. *et al.* Function-impairing polymorphisms of the hepatic uptake transporter SLCO1B1 modify the therapeutic efficacy of statins in a population-based cohort. *Pharmacogenet Genomics* **25**, 8-18 (2015).

(111) Prado, Y., Saavedra, N., Zambrano, T., Lagos, J., Rosales, A. & Salazar, L.A. SLCO1B1 c.388A>G Polymorphism Is Associated with HDL-C Levels in Response to Atorvastatin in Chilean Individuals. *Int J Mol Sci* **16**, 20609-19 (2015).

(112) Mladenovska, K. *et al.* Influence of SLCO1B1 polymorphisms on atorvastatin efficacy and safety in Macedonian subjects. *Pharmazie* **72**, 288-95 (2017).

(113) de Keyser, C.E. *et al.* The SLCO1B1 c.521T>C polymorphism is associated with dose decrease or switching during statin therapy in the Rotterdam Study. *Pharmacogenet Genomics* **24**, 43-51 (2014).

(114) Kadam, P., Ashavaid, T.F., Ponde, C.K. & Rajani, R.M. Genetic determinants of lipid-lowering response to atorvastatin therapy in an Indian population. *J Clin Pharm Ther* **41**, 329-33 (2016).

(115) Couvert, P. *et al.* Association between a frequent allele of the gene encoding OATP1B1 and enhanced LDL-lowering response to fluvastatin therapy. *Pharmacogenomics* **9**, 1217-27 (2008).

(116) Xiang, Q. *et al.* The association between the SLCO1B1, apolipoprotein E, and CYP2C9 genes and lipid response to fluvastatin: a meta-analysis. *Pharmacogenet Genomics* **28**, 261-7 (2018).

(117) Deng, J.W. *et al.* The effect of SLCO1B1*15 on the disposition of pravastatin and pitavastatin is substrate dependent: the contribution of transporting activity changes by SLCO1B1*15. *Pharmacogenet Genomics* **18**, 424-33 (2008).

(118) Xiang, Q. *et al.* The influence of genetic polymorphisms in drug metabolism enzymes and transporters on the pharmacokinetics of different fluvastatin formulations. *Asian J Pharm Sci* **15**, 264-72 (2020).

(119) Hirvensalo, P. *et al.* Enantiospecific Pharmacogenomics of Fluvastatin. *Clin Pharmacol Ther* **106**, 668-80 (2019).

(120) Niemi, M., Pasanen, M.K. & Neuvonen, P.J. SLCO1B1 polymorphism and sex affect the pharmacokinetics of pravastatin but not fluvastatin. *Clin Pharmacol Ther* **80**, 356-66 (2006).

(121) Zhou, Q., Ruan, Z.R., Yuan, H. & Zeng, S. CYP2C9*3(1075A>C), MDR1 G2677T/A and MDR1 C3435T are determinants of inter-subject variability in fluvastatin pharmacokinetics in healthy Chinese volunteers. *Arzneimittelforschung* **62**, 519-24 (2012).

(122) Tornio, A., Vakkilainen, J., Neuvonen, M., Backman, J.T., Neuvonen, P.J. & Niemi, M. SLCO1B1 polymorphism markedly affects the pharmacokinetics of lovastatin acid. *Pharmacogenet Genomics* **25**, 382-7 (2015).

(123) Zhao, G. *et al.* Effect of polymorphisms in CYP3A4, PPARA, NR1I2, NFKB1, ABCG2 and SLCO1B1 on the pharmacokinetics of lovastatin in healthy Chinese volunteers. *Pharmacogenomics* **18**, 65-75 (2017).

(124) Lu, B. *et al.* Effect of SLCO1B1 T521C on Statin-Related Myotoxicity With Use of Lovastatin and Atorvastatin. *Clin Pharmacol Ther* **110**, 733-40 (2021).

(125) Yang, G.P. *et al.* Lack of effect of genetic polymorphisms of SLCO1B1 on the lipid-lowering response to pitavastatin in Chinese patients. *Acta Pharmacol Sin* **31**, 382-6 (2010).

(126) Chung, J.Y. *et al.* Effect of OATP1B1 (SLCO1B1) variant alleles on the pharmacokinetics of pitavastatin in healthy volunteers. *Clin Pharmacol Ther* **78**, 342-50 (2005).

(127) Ieiri, I. *et al.* SLCO1B1 (OATP1B1, an uptake transporter) and ABCG2 (BCRP, an efflux transporter) variant alleles and pharmacokinetics of pitavastatin in healthy volunteers. *Clin Pharmacol Ther* **82**, 541-7 (2007).

(128) Oh, E.S., Kim, C.O., Cho, S.K., Park, M.S. & Chung, J.Y. Impact of ABCC2, ABCG2 and SLCO1B1 polymorphisms on the pharmacokinetics of pitavastatin in humans. *Drug Metab Pharmacokinet* **28**, 196-202 (2013).

(129) Zhou, Q., Chen, Q.X., Ruan, Z.R., Yuan, H., Xu, H.M. & Zeng, S. CYP2C9*3(1075A > C), ABCB1 and SLCO1B1 genetic polymorphisms and gender are determinants of inter-subject variability in pitavastatin pharmacokinetics. *Pharmazie* **68**, 187-94 (2013).

(130) Wen, J. & Xiong, Y. OATP1B1 388A>G polymorphism and pharmacokinetics of pitavastatin in Chinese healthy volunteers. *J Clin Pharm Ther* **35**, 99-104 (2010).

(131) Iwai, M., Suzuki, H., Ieiri, I., Otsubo, K. & Sugiyama, Y. Functional analysis of single nucleotide polymorphisms of hepatic organic anion transporter OATP1B1 (OATP-C). *Pharmacogenetics* **14**, 749-57 (2004).

(132) Ho, R.H. *et al.* Drug and bile acid transporters in rosuvastatin hepatic uptake: function, expression, and pharmacogenetics. *Gastroenterology* **130**, 1793-806 (2006).

(133) Group, S.C. *et al.* SLCO1B1 variants and statin-induced myopathy--a genomewide study. *N Engl J Med* **359**, 789-99 (2008).

(134) Shek, A.B. *et al.* Simvastatin intolerance genetic determinants: some features in ethnic Uzbek patients with coronary artery disease. *Arch Med Sci Atheroscler Dis* **2**, e68-e75 (2017).

(135) Bakar, N.S., Neely, D., Avery, P., Brown, C., Daly, A.K. & Kamali, F. Genetic and Clinical Factors Are Associated With Statin-Related Myotoxicity of Moderate Severity: A Case-Control Study. *Clin Pharmacol Ther* **104**, 178-87 (2018).

(136) Flores-Unzueta, S. *et al.* Simvastatin-related myopathy in shift workers: a report of two cases. *Drug Metab Pers Ther* **33**, 153-6 (2018).

(137) Carr, D.F. *et al.* Genomewide Association Study of Statin-Induced Myopathy in Patients Recruited Using the UK Clinical Practice Research Datalink. *Clin Pharmacol Ther* **106**, 1353-61 (2019).

(138) S, C.T. *et al.* A pilot study on the association between SLCO1B1 RS4363657 polymorphism and muscle adverse events in adults with newly diagnosed dyslipidaemia who were prescribed a statin: the Malaysian primary health care cohort. *Biomarkers* **24**, 659-65 (2019).

(139) Chan, J.C.M., Ng, M.H., Wong, R.S.M. & Tomlinson, B. A case of simvastatin-induced myopathy with SLCO1B1 genetic predisposition and co-ingestion of linagliptin and Stevia rebaudiana. *J Clin Pharm Ther* **44**, 381-3 (2019).

(140) Zhou, Q., Ruan, Z.R., Jiang, B., Yuan, H. & Zeng, S. Simvastatin pharmacokinetics in healthy Chinese subjects and its relations with CYP2C9, CYP3A5, ABCB1, ABCG2 and SLCO1B1 polymorphisms. *Pharmazie* **68**, 124-8 (2013).

(141) Tsamandouras, N. *et al.* Identification of the effect of multiple polymorphisms on the pharmacokinetics of simvastatin and simvastatin acid using a population-modeling approach. *Clin Pharmacol Ther* **96**, 90-100 (2014).

(142) Choi, H.Y. *et al.* Impact of CYP2D6, CYP3A5, CYP2C19, CYP2A6, SLCO1B1, ABCB1, and ABCG2 gene polymorphisms on the pharmacokinetics of simvastatin and simvastatin acid. *Pharmacogenet Genomics* **25**, 595-608 (2015).

(143) Luzum, J.A. *et al.* Individual and Combined Associations of Genetic Variants in CYP3A4, CYP3A5, and SLCO1B1 With Simvastatin and Simvastatin Acid Plasma Concentrations. *J Cardiovasc Pharmacol* **66**, 80-5 (2015).

(144) Hasunuma, T. *et al.* Absence of ethnic differences in the pharmacokinetics of moxifloxacin, simvastatin, and meloxicam among three East Asian populations and Caucasians. *Br J Clin Pharmacol* **81**, 1078-90 (2016).

(145) Jiang, F. *et al.* The influences of SLCO1B1 and ABCB1 genotypes on the pharmacokinetics of simvastatin, in relation to CYP3A4 inhibition. *Pharmacogenomics* **18**, 459-69 (2017).

(146) Wagner, J.B. *et al.* Impact of SLCO1B1 Genotype on Pediatric Simvastatin Acid Pharmacokinetics. *J Clin Pharmacol* **58**, 823-33 (2018).

(147) Ogungbenro, K., Wagner, J.B., Abdel-Rahman, S., Leeder, J.S. & Galetin, A. A population pharmacokinetic model for simvastatin and its metabolites in children and adolescents. *Eur J Clin Pharmacol* **75**, 1227-35 (2019).

(148)   Bailey, K.M. *et al.* Hepatic metabolism and transporter gene variants enhance response to rosuvastatin in patients with acute myocardial infarction: the GEOSTAT-1 Study. *Circ Cardiovasc Genet* **3**, 276-85 (2010).

(149)   Hopewell, J.C. *et al.* Impact of common genetic variation on response to simvastatin therapy among 18 705 participants in the Heart Protection Study. *Eur Heart J* **34**, 982-92 (2013).

(150)   Dou, Y., Zhu, X., Wang, Q., Tian, X., Cheng, J. & Zhang, E. Meta-Analysis of the SLCO1B1 c.521T>C Variant Reveals Slight Influence on the Lipid-Lowering Efficacy of Statins. *Ann Lab Med* **35**, 329-35 (2015).

(151)   Li, J.H., Suchindran, S., Shah, S.H., Kraus, W.E., Ginsburg, G.S. & Voora, D. SLCO1B1 genetic variants, long-term low-density lipoprotein cholesterol levels and clinical events in patients following cardiac catheterization. *Pharmacogenomics* **16**, 449-58 (2015).

(152)   Kitzmiller, J.P., Luzum, J.A., Dauki, A., Krauss, R.M. & Medina, M.W. Candidate-Gene Study of Functional Polymorphisms in SLCO1B1 and CYP3A4/5 and the Cholesterol-Lowering Response to Simvastatin. *Clin Transl Sci* **10**, 172-7 (2017).

(153)   Oni-Orisan, A. *et al.* Characterization of Statin Low-Density Lipoprotein Cholesterol Dose-Response Using Electronic Health Records in a Large Population-Based Cohort. *Circ Genom Precis Med* **11**, e002043 (2018).

(154)   Kaewboonlert, N., Thitisopee, W., Sirintronsopon, W., Porntadavity, S. & Jeenduang, N. Lack of association between SLCO1B1 polymorphisms and lipid-lowering response to simvastatin therapy in Thai hypercholesterolaemic patients. *J Clin Pharm Ther* **43**, 647-55 (2018).

(155)   Wu, X. *et al.* Associations of the SLCO1B1 Polymorphisms With Hepatic Function, Baseline Lipid Levels, and Lipid-lowering Response to Simvastatin in Patients With Hyperlipidemia. *Clin Appl Thromb Hemost* **24**, 240S-7S (2018).

(156)   Voora, D. *et al.* The SLCO1B1*5 genetic variant is associated with statin-induced side effects. *J Am Coll Cardiol* **54**, 1609-16 (2009).

(157)   Khine, H., Yuet, W.C., Adams-Huet, B. & Ahmad, Z. Statin-associated muscle symptoms and SLCO1B1 rs4149056 genotype in patients with familial hypercholesterolemia. *Am Heart J* **179**, 1-9 (2016).

(158)   Floyd, J.S. *et al.* Pharmacogenomics of statin-related myopathy: Meta-analysis of rare variants from whole-exome sequencing. *PLoS One* **14**, e0218115 (2019).

(159)   Carr, D.F. *et al.* SLCO1B1 genetic variant associated with statin-induced myopathy: a proof-of-concept study using the clinical practice research datalink. *Clin Pharmacol Ther* **94**, 695-701 (2013).

(160)   Li, J.H. *et al.* Genetically guided statin therapy on statin perceptions, adherence, and cholesterol lowering: a pilot implementation study in primary care patients. *J Pers Med* **4**, 147-62 (2014).

(161)   Peyser, B. *et al.* Effects of Delivering SLCO1B1 Pharmacogenetic Information in Randomized Trial and Observational Settings. *Circ Genom Precis Med* **11**, e002228 (2018).

(162)   Shek, A.B. *et al.* Personalized rosuvastatin therapy in problem patients with partial statin intolerance. *Arch Med Sci Atheroscler Dis* **3**, e83-e9 (2018).

(163)   Keskitalo, J.E., Pasanen, M.K., Neuvonen, P.J. & Niemi, M. Different effects of the ABCG2 c.421C>A SNP on the pharmacokinetics of fluvastatin, pravastatin and simvastatin. *Pharmacogenomics* **10**, 1617-24 (2009).

(164)   Kitamura, S., Maeda, K., Wang, Y. & Sugiyama, Y. Involvement of multiple transporters in the hepatobiliary transport of rosuvastatin. *Drug Metab Dispos* **36**, 2014-23 (2008).

(165)   Huang, L., Wang, Y. & Grimm, S. ATP-dependent transport of rosuvastatin in membrane vesicles expressing breast cancer resistance protein. *Drug Metab Dispos* **34**, 738-42 (2006).

(166) Sreter, K.B., Barisic, B. & Popovic-Grle, S. Pharmacogenomics and tailored polypharmacy: an 80-year-old lady with rosuvastatin-associated rhabdomyolysis and maprotiline-related Ogilvie's syndrome. *Int J Clin Pharmacol Ther* **55**, 442-8 (2017).

(167) Tomlinson, B. *et al.* ABCG2 polymorphism is associated with the low-density lipoprotein cholesterol response to rosuvastatin. *Clin Pharmacol Ther* **87**, 558-62 (2010).

(168) Lee, H.K., Hu, M., Lui, S., Ho, C.S., Wong, C.K. & Tomlinson, B. Effects of polymorphisms in ABCG2, SLCO1B1, SLC10A1 and CYP2C9/19 on plasma concentrations of rosuvastatin and lipid response in Chinese patients. *Pharmacogenomics* **14**, 1283-94 (2013).

(169) Kim, T.E. *et al.* The Effect of Genetic Polymorphisms in SLCO2B1 on the Lipid-Lowering Efficacy of Rosuvastatin in Healthy Adults with Elevated Low-Density Lipoprotein. *Basic Clin Pharmacol Toxicol* **121**, 195-201 (2017).

(170) Kim, Y. *et al.* Influence of OATP1B1 and BCRP polymorphisms on the pharmacokinetics and pharmacodynamics of rosuvastatin in elderly and young Korean subjects. *Sci Rep* **9**, 19410 (2019).

(171) Chasman, D.I., Giulianini, F., MacFadyen, J., Barratt, B.J., Nyberg, F. & Ridker, P.M. Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. *Circ Cardiovasc Genet* **5**, 257-64 (2012).

(172) Zhang, W. *et al.* Role of BCRP 421C>A polymorphism on rosuvastatin pharmacokinetics in healthy Chinese males. *Clin Chim Acta* **373**, 99-103 (2006).

(173) Zhou, Q., Ruan, Z.R., Yuan, H., Xu, D.H. & Zeng, S. ABCB1 gene polymorphisms, ABCB1 haplotypes and ABCG2 c.421c > A are determinants of inter-subject variability in rosuvastatin pharmacokinetics. *Pharmazie* **68**, 129-34 (2013).

(174) Birmingham, B.K. *et al.* Rosuvastatin pharmacokinetics and pharmacogenetics in Caucasian and Asian subjects residing in the United States. *Eur J Clin Pharmacol* **71**, 329-40 (2015).

(175) Wan, Z. *et al.* Marked Alteration of Rosuvastatin Pharmacokinetics in Healthy Chinese with ABCG2 34G>A and 421C>A Homozygote or Compound Heterozygote. *J Pharmacol Exp Ther* **354**, 310-5 (2015).

(176) Liu, M. *et al.* Effects of Polymorphisms in NR1H4, NR1I2, SLCO1B1, and ABCG2 on the Pharmacokinetics of Rosuvastatin in Healthy Chinese Volunteers. *J Cardiovasc Pharmacol* **68**, 383-90 (2016).

(177) Kashihara, Y. *et al.* Small-Dosing Clinical Study: Pharmacokinetic, Pharmacogenomic (SLCO2B1 and ABCG2), and Interaction (Atorvastatin and Grapefruit Juice) Profiles of 5 Probes for OATP2B1 and BCRP. *J Pharm Sci* **106**, 2688-94 (2017).

(178) Soko, N.D., Chimusa, E., Masimirembwa, C. & Dandara, C. An African-specific profile of pharmacogene variants for rosuvastatin plasma variability: limited role for SLCO1B1 c.521T>C and ABCG2 c.421A>C. *Pharmacogenomics J* **19**, 240-8 (2019).

(179) Zhang, D. *et al.* Effects of ABCG2 and SLCO1B1 gene variants on inflammation markers in patients with hypercholesterolemia and diabetes mellitus treated with rosuvastatin. *Eur J Clin Pharmacol* **76**, 939-46 (2020).

(180) Tsamandouras, N., Guo, Y., Wendling, T., Hall, S., Galetin, A. & Aarons, L. Modelling of atorvastatin pharmacokinetics and the identification of the effect of a BCRP polymorphism in the Japanese population. *Pharmacogenet Genomics* **27**, 27-38 (2017).

(181) Prado, Y., Zambrano, T. & Salazar, L.A. Transporter genes ABCG2 rs2231142 and ABCB1 rs1128503 polymorphisms and atorvastatin response in Chilean subjects. *J Clin Pharm Ther* **43**, 87-91 (2018).

(182) Ho, R.H. *et al.* Effect of drug transporter genotypes on pravastatin disposition in European- and African-American participants. *Pharmacogenet Genomics* **17**, 647-56 (2007).

(183) Lu, X.F., Zhou, Y., Bi, K.S. & Chen, X.H. Mixed effects of OATP1B1, BCRP and NTCP polymorphisms on the population pharmacokinetics of pravastatin in healthy volunteers. *Xenobiotica* **46**, 841-9 (2016).

(184) Fujino, H., Saito, T., Ogawa, S. & Kojima, J. Transporter-mediated influx and efflux mechanisms of pitavastatin, a new inhibitor of HMG-CoA reductase. *J Pharm Pharmacol* **57**, 1305-11 (2005).

(185) Hirano, M., Maeda, K., Matsushima, S., Nozaki, Y., Kusuhara, H. & Sugiyama, Y. Involvement of BCRP (ABCG2) in the biliary excretion of pitavastatin. *Mol Pharmacol* **68**, 800-7 (2005).

(186) Mirosevic Skvrce, N., Bozina, N., Zibar, L., Barisic, I., Pejnovic, L. & Macolic Sarinic, V. CYP2C9 and ABCG2 polymorphisms as risk factors for developing adverse drug reactions in renal transplant patients taking fluvastatin: a case-control study. *Pharmacogenomics* **14**, 1419-31 (2013).

(187) Fischer, V. *et al.* The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor fluvastatin: effect on human cytochrome P-450 and implications for metabolic drug interactions. *Drug Metab Dispos* **27**, 410-6 (1999).

(188) Toda, T., Eliasson, E., Ask, B., Inotsume, N. & Rane, A. Roles of different CYP enzymes in the formation of specific fluvastatin metabolites by human liver microsomes. *Basic Clin Pharmacol Toxicol* **105**, 327-32 (2009).

(189) Transon, C., Leemann, T. & Dayer, P. In vitro comparative inhibition profiles of major human drug metabolising cytochrome P450 isozymes (CYP2C9, CYP2D6 and CYP3A4) by HMG-CoA reductase inhibitors. *Eur J Clin Pharmacol* **50**, 209-15 (1996).

(190) Cohen, L.H., van Leeuwen, R.E., van Thiel, G.C., van Pelt, J.F. & Yap, S.H. Equally potent inhibitors of cholesterol synthesis in human hepatocytes have distinguishable effects on different cytochrome P450 enzymes. *Biopharm Drug Dispos* **21**, 353-64 (2000).

(191) Bertrand-Thiebault, C., Masson, C., Siest, G., Batt, A.M. & Visvikis-Siest, S. Effect of HMGCoA reductase inhibitors on cytochrome P450 expression in endothelial cell line. *J Cardiovasc Pharmacol* **49**, 306-15 (2007).

(192) Kirchheiner, J. *et al.* Influence of CYP2C9 polymorphisms on the pharmacokinetics and cholesterol-lowering activity of (-)-3S,5R-fluvastatin and (+)-3R,5S-fluvastatin in healthy volunteers. *Clin Pharmacol Ther* **74**, 186-94 (2003).

(193) Zuccaro, P., Mombelli, G., Calabresi, L., Baldassarre, D., Palmi, I. & Sirtori, C.R. Tolerability of statins is not linked to CYP450 polymorphisms, but reduced CYP2D6 metabolism improves cholesteraemic response to simvastatin and fluvastatin. *Pharmacol Res* **55**, 310-7 (2007).

(194) Baek, S.D. *et al.* Fatal rhabdomyolysis in a patient with liver cirrhosis after switching from simvastatin to fluvastatin. *J Korean Med Sci* **26**, 1634-7 (2011).

(195) Mygland, A., Ljostad, U. & Krossnes, B.K. Persisting weakness after withdrawal of a statin. *BMJ Case Rep* **2014**, (2014).

(196) Ong, S.G. & Ding, H.J. Patient with statin-associated immune-mediated necrotizing myopathy presenting with subcutaneous edema, persistent bulbar weakness and absent anti-HMGCR. *Int J Rheum Dis* **20**, 2175-8 (2017).

(197) Karunaratne, K., Amiras, D., Pickering, M.C., Hofer, M. & Viegas, S. Autoimmune necrotising myopathy and HMGCR antibodies. *Pract Neurol* **18**, 151-5 (2018).

(198) Pitlick, M. & Ernste, F. Anti-HMGCR myopathy presenting with acute systolic heart failure. *BMJ Case Rep* **12**, (2019).

(199) Krauss, R.M. *et al.* Variation in the 3-hydroxyl-3-methylglutaryl coenzyme a reductase gene is associated with racial differences in low-density lipoprotein cholesterol response to simvastatin treatment. *Circulation* **117**, 1537-44 (2008).

(200) Mangravite, L.M. *et al.* Combined influence of LDLR and HMGCR sequence variation on lipid-lowering response to simvastatin. *Arterioscler Thromb Vasc Biol* **30**, 1485-92 (2010).

(201) Ying, S., Sun, Y.M., Liu, X.M., An, C.Y. & Gao, Y.Y. Effect of ScrF I polymorphism in the 2nd intron of the HMGCR gene on lipid-lowering response to simvastatin in Chinese diabetic patients. *Biochem Biophys Res Commun* **363**, 395-8 (2007).

(202) Medina, M.W., Gao, F., Ruan, W., Rotter, J.I. & Krauss, R.M. Alternative splicing of 3-hydroxy-3-methylglutaryl coenzyme A reductase is associated with plasma low-density lipoprotein cholesterol response to simvastatin. *Circulation* **118**, 355-62 (2008).

(203) Chasman, D.I., Posada, D., Subrahmanyan, L., Cook, N.R., Stanton, V.P., Jr. & Ridker, P.M. Pharmacogenetic study of statin therapy and cholesterol reduction. *JAMA : the journal of the American Medical Association* **291**, 2821-7 (2004).

(204) Polisecki, E. *et al.* Genetic variation at the LDL receptor and HMG-CoA reductase gene loci, lipid levels, statin response, and cardiovascular disease incidence in PROSPER. *Atherosclerosis* **200**, 109-14 (2008).

(205) Singer, J.B. *et al.* Genetic analysis of fluvastatin response and dyslipidemia in renal transplant recipients. *J Lipid Res* **48**, 2072-8 (2007).

(206) Nichols, L., Pfeifer, K., Mammen, A.L., Shahnoor, N. & Konersman, C.G. An Unusual Case of Statin-Induced Myopathy: Anti-HMGCoA Necrotizing Autoimmune Myopathy. *J Gen Intern Med* **30**, 1879-83 (2015).

(207) De Cock, E., Hannon, H., Moerman, V. & Schurgers, M. Statin-induced myopathy: a case report. *Eur Heart J Case Rep* **2**, yty130 (2018).

(208) Woolley, M., Stebbings, S. & Highton, J. Statin-associated immune-mediated necrotising myopathy: a New Zealand case series showing possible overrepresentation in Pacific Islanders. *Intern Med J* **48**, 32-6 (2018).

(209) Sharma, P., Timilsina, B., Adhikari, J., Parajuli, P., Dhital, R. & Tachamo, N. Statin-induced necrotizing autoimmune myopathy: an extremely rare adverse effect from statin use. *J Community Hosp Intern Med Perspect* **9**, 503-6 (2019).

(210) Pocathikorn, A., Taylor, R.R. & Mamotte, C.D. Atorvastatin increases expression of low-density lipoprotein receptor mRNA in human circulating mononuclear cells. *Clin Exp Pharmacol Physiol* **37**, 471-6 (2010).

(211) Thompson, J.F. *et al.* Comprehensive whole-genome and candidate gene analysis for response to statin therapy in the Treating to New Targets (TNT) cohort. *Circ Cardiovasc Genet* **2**, 173-81 (2009).

(212) Poduri, A., Khullar, M., Bahl, A., Sehrawat, B.S., Sharma, Y. & Talwar, K.K. Common variants of HMGCR, CETP, APOAI, ABCB1, CYP3A4, and CYP7A1 genes as predictors of lipid-lowering response to atorvastatin therapy. *DNA Cell Biol* **29**, 629-37 (2010).

(213) Kirac, D. *et al.* HMGCR and ApoE mutations may cause different responses to lipid lowering statin therapy. *Cell Mol Biol (Noisy-le-grand)* **63**, 43-8 (2017).

(214) Cuevas, A. *et al.* HMGCR rs17671591 SNP Determines Lower Plasma LDL-C after Atorvastatin Therapy in Chilean Individuals. *Basic Clin Pharmacol Toxicol* **118**, 292-7 (2016).

(215) Chung, J.Y. *et al.* Effect of HMGCR variant alleles on low-density lipoprotein cholesterol-lowering response to atorvastatin in healthy Korean subjects. *J Clin Pharmacol* **52**, 339-46 (2012).

(216) Yue, Y.H. *et al.* Gene Polymorphisms Affect the Effectiveness of Atorvastatin in Treating Ischemic Stroke Patients. *Cell Physiol Biochem* **39**, 630-8 (2016).

(217) Lettiero, B., Inasu, M., Kimbung, S. & Borgquist, S. Insensitivity to atorvastatin is associated with increased accumulation of intracellular lipid droplets and fatty acid metabolism in breast cancer cells. *Sci Rep* **8**, 5462 (2018).

(218) Becker, M.L., Visser, L.E., van Schaik, R.H., Hofman, A., Uitterlinden, A.G. & Stricker, B.H. Influence of genetic variation in CYP3A4 and ABCB1 on dose decrease or switching during simvastatin and atorvastatin therapy. *Pharmacoepidemiol Drug Saf* **19**, 75-81 (2010).

(219) Wang, D., Guo, Y., Wrighton, S.A., Cooke, G.E. & Sadee, W. Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs. *Pharmacogenomics J* **11**, 274-86 (2011).

(220) Kivisto, K.T. *et al.* Lipid-lowering response to statins is affected by CYP3A5 polymorphism. *Pharmacogenetics* **14**, 523-5 (2004).

(221) Fiegenbaum, M. *et al.* The role of common variants of ABCB1, CYP3A4, and CYP3A5 genes in lipid-lowering efficacy and safety of simvastatin treatment. *Clin Pharmacol Ther* **78**, 551-8 (2005).

(222) Hu, M., Mak, V.W., Xiao, Y. & Tomlinson, B. Associations between the genotypes and phenotype of CYP3A and the lipid response to simvastatin in Chinese patients with hypercholesterolemia. *Pharmacogenomics* **14**, 25-34 (2013).

(223) Kolovou, G. *et al.* Impact of CYP3A5 Gene Polymorphism on Efficacy of Simvastatin. *Open Cardiovasc Med J* **8**, 12-7 (2014).

(224) Elens, L. *et al.* Novel CYP3A4 intron 6 single nucleotide polymorphism is associated with simvastatin-mediated cholesterol reduction in the Rotterdam Study. *Pharmacogenet Genomics* **21**, 861-6 (2011).

(225) Ragia, G. *et al.* No effect of CYP3A4 intron 6 C>T polymorphism (CYP3A4*22) on lipid-lowering response to statins in Greek patients with primary hypercholesterolemia. *Drug Metab Pers Ther* **30**, 43-8 (2015).

(226) Gao, Y., Zhang, L.R. & Fu, Q. CYP3A4*1G polymorphism is associated with lipid-lowering efficacy of atorvastatin but not of simvastatin. *Eur J Clin Pharmacol* **64**, 877-82 (2008).

(227) Wang, A. *et al.* Ile118Val genetic polymorphism of CYP3A4 and its effects on lipid-lowering efficacy of simvastatin in Chinese hyperlipidemic patients. *Eur J Clin Pharmacol* **60**, 843-8 (2005).

(228) Kim, K.A., Park, P.W., Lee, O.J., Kang, D.K. & Park, J.Y. Effect of polymorphic CYP3A5 genotype on the single-dose simvastatin pharmacokinetics in healthy subjects. *J Clin Pharmacol* **47**, 87-93 (2007).

(229) Kitzmiller, J.P., Luzum, J.A., Baldassarre, D., Krauss, R.M. & Medina, M.W. CYP3A4*22 and CYP3A5*3 are associated with increased levels of plasma simvastatin concentrations in the cholesterol and pharmacogenetics study cohort. *Pharmacogenet Genomics* **24**, 486-91 (2014).

(230) Thompson, J.F. *et al.* An association study of 43 SNPs in 16 candidate genes with atorvastatin response. *Pharmacogenomics J* **5**, 352-8 (2005).

(231) Willrich, M.A. *et al.* CYP3A53A allele is associated with reduced lowering-lipid response to atorvastatin in individuals with hypercholesterolemia. *Clin Chim Acta* **398**, 15-20 (2008).

(232) Rosales, A., Alvear, M., Cuevas, A., Saavedra, N., Zambrano, T. & Salazar, L.A. Identification of pharmacogenetic predictors of lipid-lowering response to atorvastatin in Chilean subjects with hypercholesterolemia. *Clin Chim Acta* **413**, 495-501 (2012).

(233) Wei, K.K. & Zhang, L.R. Interactions between CYP3A5*3 and POR*28 polymorphisms and lipid lowering response with atorvastatin. *Clin Drug Investig* **35**, 583-91 (2015).

(234) Kajinami, K., Brousseau, M.E., Ordovas, J.M. & Schaefer, E.J. CYP3A4 genotypes and plasma lipoprotein levels before and after treatment with atorvastatin in primary hypercholesterolemia. *Am J Cardiol* **93**, 104-7 (2004).

(235) Peng, C. *et al.* Polymorphisms in CYP450 Genes and the Therapeutic Effect of Atorvastatin on Ischemic Stroke: A Retrospective Cohort Study in Chinese Population. *Clin Ther* **40**, 469-77 e2 (2018).

(236) He, B.X., Shi, L., Qiu, J., Zeng, X.H. & Zhao, S.J. The effect of CYP3A4*1G allele on the pharmacokinetics of atorvastatin in Chinese Han patients with coronary heart disease. *J Clin Pharmacol* **54**, 462-7 (2014).

(237) Shin, J., Pauly, D.F., Pacanowski, M.A., Langaee, T., Frye, R.F. & Johnson, J.A. Effect of cytochrome P450 3A5 genotype on atorvastatin pharmacokinetics and its interaction with clarithromycin. *Pharmacotherapy* **31**, 942-50 (2011).