Editorial

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Pharmacogenomics

The role of *SLCO1B1* genotyping in lowering cardiovascular risk

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"As one component of shared decision-making around statin therapy, *SLCO1B1* genotyping has the potential to lower ASCVD risk, particularly if delivered in a healthcare setting with decision support that promotes its timely and effective use"

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Pharmacogenomics is considered the most widely relevant and feasible genomics application in clinical medicine [1]. Growing knowledge of drug-gene associations, declining costs of genetic testing, and the emergence of clinical guidelines for using pharmacogenetic results have positioned it at the forefront of precision medicine [2]. While these factors support the implementation of pharmacogenetic testing into clinical practice, its impact on patient outcomes remains an open question. Pharmacogenetic information is only part of the complex pharmacotherapeutic process, which encompasses patient and provider characteristics, perceptions, and behaviors as well as health systems factors. Thus, the value of pharmacogenomics does not depend solely on the strength of disease-gene associations or the availability of testing, but also on how it is integrated within larger clinical pathways to promote desired patient outcomes. Here, we use the clinical scenario of statin use for atherosclerotic cardiovascular disease (ASCVD) risk reduction to illustrate the complex pathways by which pharmacogenetic testing might affect patient outcomes.

Statin therapy in practice

3-hydroxy-3-methylglutaryl coenzyme A inhibitors, or statins, are first-line drugs for reducing low-density lipoprotein cholesterol (LDL-C) levels and are proven to lower ASCVD-related events [3,4]. As a result, clinical guidelines recommend statin therapy for the prevention of ASCVD for hundreds of millions of people worldwide [5–9]. Statins are generally well-tolerated and safe [10] but an estimated 20% of users report statin-associated muscle symptoms (SAMS), which most commonly manifest as muscle pain (myalgia) or weakness (myopathy) [11,12]. Very rarely (~1 in 10,000), patients may experience more severe myopathy, including life-threatening rhabdomyolysis [13]. The messaging to patients about the risk of SAMS is complicated, given that statins can cause real myopathy, as evidenced by creatinine kinase elevations and the rare incidence of rhabdomyolysis [14,15], but blinded randomized trials have shown that the incidence of subjective muscle symptoms might not differ between patients taking statins and those taking placebo [16,17]. Moreover, patients who have previously experienced SAMS and discontinued treatment might be able to resume treatment without recurrence [18].

Compared with guideline recommendations, statin adherence rates are suboptimal [19–21]. Patients' perceived risk of SAMS is one major barrier to statin therapy, accounting for approximately two-thirds of statin declinations or discontinuations [22,23]. Prescriber management of SAMS is further complicated by the challenging, and sometimes lengthy, trial and error of statin discontinuation, rechallenge, and dose adjustment [24–27]. Disrupted or poor adherence to statins results in increased incidence of ASCVD events and mortality and resultant increased medical costs [28–31]. Shared decision-making between patient and prescriber has been identified as a way to increase patient

Table 1. Abbreviated clinical guidelines associated with *SLCO1B1* genotype and recommendations for statin therapy.

Medication	Genotype (rs4149056)	Recommendation	Ref.
The Clinical Pharmacogenetics Implementation Consortium			[37]
Simvastatin	CC	Low function/high myopathy risk: prescribe lower dose simvastatin (≤20 mg) or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance.	
	TC	Intermediate function/intermediate myopathy risk: prescribe lower dose simvastatin (≤20 mg) or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance.	
The Dutch Pharmacogenetics Working Group			[46]
Atorvastatin	CC	The risk of myopathy may be increased. Choose alternative for patients with additional SAMS risk factors (e.g., avoid simvastatin). Advise patients with no additional SAMS risk to contact physician in the event of muscle symptoms.	
	TC	The risk of myopathy can be elevated. Choose alternative for patients with additional SAMS risk factors (e.g., avoid simvastatin). Advise patients with no additional risk factors to contact physician in the event of muscle symptoms.	
Simvastatin	CC	The risk of myopathy and severe myopathy is markedly increased. Choose an alternative (e.g., atorvastatin not recommended for patients with additional SAMS risk).	
	TC	The risk of myopathy and severe myopathy is increased. Choose an alternative (e.g., atorvastatin not recommended for patients with additional SAMS risk). If alternative is not available avoid simvastatin doses exceeding 40 mg/day and advise patients to contact physician in the event of muscle symptoms.	
The French National Network of Pharmacogenetics			[47,48]
HMG-CoA Reductase Inhibitors (Statins)	CC/TC	Higher risk of myotoxicity. High dose statins, as well as OATP1B1 and/or CYP3A inhibitors should be avoided. Lower simvastatin dose to 20 mg/day plus CK surveillance or choose an alternative.	

Note: TT considered reference/wild-type/normal function.
Data taken from [43,45].
CK: Creatine kinase; HMG-CoA: 3-Hydroxy-3-methylglutaryl coenzyme A; SAMS: Statin-associated muscle symptoms.

acceptance of clinical guidance [32], to ameliorate resistance to statin use [33], and is recommended as a critical component of statin therapy by some guidelines [8]. Of available options for encouraging statin adherence, one increasingly accessible approach for potentially averting SAMS prior to statin prescription or better distinguishing its cause after exposure is through the utilization of *SLCO1B1* genotyping.

SAMS & *SLCO1B1*

The most highly validated genetic association with SAMS is with the *SLCO1B1* gene. In 2008, the SEARCH Collaborative identified a significant association between clinically-confirmed SAMS and the c.521T>C variant (rs4149056; Val174Ala) in *SLCO1B1*, a functional variant that impairs hepatic uptake of statins via OATP1B1 [34,35]. This variant occurs in about 15% of European populations, but allele frequencies differ widely across ancestral groups ranging from around 1% (Oceania and Sub-Saharan Africa) to nearly 25% (South/Central America) [36,37]. Compared with TT homozygotes, TC heterozygotes and CC homozygotes had an odds ratio of 4.5 (95% CI, 2.6 to 7.7) and 16.9 (95% CI, 4.7 to 61.1) for significant SAMS, respectively [34]. This association has been widely replicated, most commonly with the use of simvastatin and variably with atorvastatin [38–42]. In sum, this evidence supports a PharmGKB Level 1A designation for the *SLCO1B1*-SAMS association [43] and clinical practice guidelines by international consortia for pharmacogenetic-guided statin therapy when a patient's *SLCO1B1* genotype is known (Table 1). The availability of these results, along with clinical recommendations, may help guide statin prescribing for many patients at heightened risk of SAMS and may offer peace of mind for patients with a normal function genotype [44].

An obvious goal of *SLCO1B1* clinical testing is the avoidance of SAMS, but how might such testing impact the already complicated clinical conversations between patients and providers about statin therapy to lower ASCVD risk? Figure 1 presents a conceptual model of the pathways through which *SLCO1B1* genotyping might work through patients, providers, and healthcare systems to impact patient health. We briefly review the literature on whether *SLCO1B1* pharmacogenetic results might work through these pathways to improve statin prescribing, patient adherence, and ASCVD prevention.

Clinical *SLCO1B1* testing

First, *SLCO1B1* testing will only improve patient outcomes if its results are available when key clinical decisions are made. Given its potential clinical benefit and scope, many early pharmacogenomics adopters have implemented *SLCO1B1* genotyping as part of preemptive multigene panels [49–51]. In this scenario, *SLCO1B1* results are available

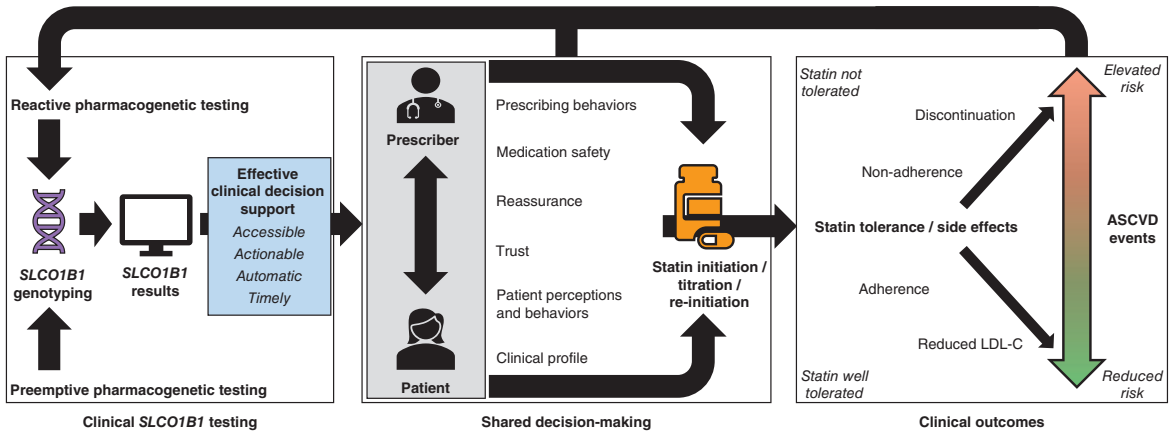

Figure 1. Pathways through which *SLCO1B1* testing might impact statin prescribing and, ultimately, downstream clinical outcomes.
ASCVD: Atherosclerotic cardiovascular disease; LDL-C: Low-density lipoprotein cholesterol.

before a clinical indication for statin therapy and could be used when a statin prescription is warranted. On the other hand, approximately a third of US institutions currently implementing pharmacogenetic testing use a reactive approach [52], whereby a prescriber orders a pharmacogenetic test either upon consideration of a medication or in response to a patient's experience of a medication-related adverse effect. A reactive approach to *SLCO1B1* genotyping is favored by some, including the French National Network of Pharmacogenetics [47,48], due to its targeted application and immediate utility in those with heightened SAMS risk or previous statin intolerance. At present, there is no evidence to support population *SLCO1B1* genotyping, despite the widespread use of statins.

The impact of *SLCO1B1* testing also depends on the timing, format, and persistence of result delivery. The utilization of clinical decision support (CDS) tools to bring timely pharmacogenetic results and appropriate clinical recommendations to the point of care presents the most efficient and potentially effective opportunity to impact clinical decision-making [53]. Such CDS tools have been shown to enhance clinician practices associated with both ASCVD prevention [54,55] and pharmacogenetic-guided prescribing [56,57]. Outside pharmacogenetics, Nije *et al.* [54] observed across 45 studies median increases in recommended screening and preventive services (+3.8%, e.g., blood pressure screening), clinical testing (+4.0%, e.g., lipid testing), and prescribed treatments (+2.0%, e.g., aspirin prescription) when providers were prompted by CDS tools compared with usual care. In a systematic review, Sebastian *et al.* [57] found that pharmacogenetic CDS tools often resulted in alterations to clinical management by nongenetics healthcare providers in the areas of medication switching, dose adjustment, and polypharmacy reduction. But, for many health systems, the accommodation of complex genetic data into electronic health records and CDS tools poses major challenges [1]. Common barriers include a lack of provider familiarity with pharmacogenetic result reporting and the absence of electronic health records infrastructures to facilitate the longitudinal use of pharmacogenetic information [58]. The downstream benefits of *SLCO1B1* testing may be diminished if the results are not readily available, within existing workflows, at clinically relevant moments.

Shared decision-making

Upon delivery of *SLCO1B1* results to the clinic, their translation to improved cardiovascular outcomes depends on provider and patient behaviors, perceptions, and, ideally, shared decision-making. Observational outcomes from institutions employing *SLCO1B1* genotyping, mostly via multigene panels, offer some evidence that the availability of *SLCO1B1* results lead to alterations in prescriber behaviors. O'Donnell *et al.* [56] observed no pharmacogenomically discordant prescriptions and attributed at least eight statin discontinuations as well as 69% of simvastatin and 40% of atorvastatin dose changes to the availability of pharmacogenomic results in 547 patients over a 3-year period. In a primary care cohort of 200 patients, van der Wouden *et al.* [59] observed high prescriber adherence (83%) to Dutch Pharmacogenetics Working Group [46] guidelines for both atorvastatin (28/33) and simvastatin (2/3) in patients with an actionable *SLCO1B1* genotype. A small pilot from the eMERGE Network, however, showed that only 46% (11/24) of clinical alerts associated with *SLCO1B1* genotype and guidance for simvastatin prescribing were followed by a timely and clinically recommended action [60]. The varied findings are

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attributable to myriad factors, including a lack of provider preparedness [61], concerns about reimbursement, and most cited, a lack of evidence for clinical utility [62].

SLCO1B1 results can serve as an important complement to this conversation, offering important information about ASCVD implications, SAMS risk, and a straightforward segue to medication selection. Findings from Lanting *et al.* [63] noted that patients who underwent panel-based testing (*SLCO1B1* included) generally found the results comforting (89%), useful (92%) and value-added (91%) when considering pharmacotherapy. When discussed with their doctors, only 71% of patients scored conversations about pharmacogenetic testing as 'very good,' whereas 13% scored them as 'very bad'. Reasons for dissatisfaction included patients' difficulty understanding the implications of their results and their perception that their providers were not well-informed. Simplification of results and recommendations, enhanced patient personalization, and improvements in provider knowledge and training around pharmacogenetics are important for bridging this gap [63,64]. When considering the impact of panel-based pharmacogenetic reporting (including statins) on downstream adherence, Christian *et al.* [65] found patients were 2.43 (OR, 95% CI, 1.03 to 5.74, $p < 0.05$) times more likely to have lower composite adherence rates when prescribed medications that were highly incongruent with their genetic risk (e.g., red light vs green light). While the impact of *SLCO1B1* genotyping alone was not discerned, these findings suggest its potential to aid overall patient adherence to medications as part of a broader testing strategy. Overall, these results support the promise of *SLCO1B1* genotyping, to better inform shared selection of the right medication, at the right dose, at the right time – with fewer trials of dose adjustment, switching or discontinuation.

Clinical outcomes

No studies have demonstrated that *SLCO1B1* testing prevents ASCVD events [66], but small clinical trials have reported intermediate outcomes through which such improvement in patient end points might occur. In a pilot trial of 58 statin-nonadherent patients, Li *et al.* [67] noted that patients receiving *SLCO1B1* results had more statin prescriptions (55 vs 20%, $p < 0.001$) and greater self-reported statin use (47 vs 15%, $p < 0.001$) after 4 months, as well as greater, but nonsignificant, reductions in LDL-C (-12.4 ± 45.5 vs 6.3 ± 37.8 mg/dL, $p = 0.059$) compared with controls after 1 year. Peyser *et al.* [68], found that statin-intolerant patients randomized to receive Genotype Informed Statin Therapy (n = 83) received more statin prescriptions (55 vs 38%, $p = 0.04$) and had lower LDL-C (131.9 ± 42.0 vs 144.4 ± 43.0 mg/dL, $p = 0.048$) compared with controls (n = 76) after 3 months. Lower LDL-C levels persisted in Genotype Informed Statin Therapy recipients at similar magnitudes after 8 months, but differences were not statistically significant (128.6 ± 37.9 vs 141.0 ± 44.4 mg/dL, $p = 0.12$). Additionally, no differences in self-reported adherence rates between arms were observed after either 3 ($p = 0.96$) or 8 ($p = 0.57$) months. In a recent randomized trial of timely preemptive testing in 408 statin-naive patients, we [69] found no evidence that *SLCO1B1* testing worsened ASCVD prevention in intervention patients compared with controls, as measured by statin initiation (13 vs 11%) and change in LDL-C levels (Δ-1.1 ± 2.4 vs -2.2 ± 2.5 mg/dL, noninferiority $p < 0.001$) after 12 months. As such, there is some assurance that *SLCO1B1* genotyping does not result in unintended harms and to date may provide short term improvements in statin initiations and LDL-C reductions when administered as a single gene test.

In the absence of more definitive trial results, modeling studies make important contributions to the question of whether *SLCO1B1* testing can improve outcomes such as ASCVD, either alone or as part of a preemptive pharmacogenetic panel. Shi *et al.* [70] modeled statin-related adverse events (AEs) averted and improvements in quality-adjusted life days for genotype-tailored therapy in the year following a statin prescription. Projections approximated the avoidance of between 3 and 26 AEs and the addition of between 1 and 9 quality-adjusted life days per 1000 Black and white patients, respectively. In a hypothetical cohort of 10,000 patients over 50 years Zhu *et al.* [71], concluded that preemptive panel testing (including *SLCO1B1*) led to greater numbers of quality-adjusted life-years (QALY) and was more cost-effective than both reactive (6.2 vs 5.9 QALYs; USD$/QALY = 64,921) and no testing (6.2 vs 5.9 QALYS; USD$/QALY = 86,227) scenarios at a willingness to pay threshold of $100,000 USD/QALY. Slightly more statin-related AEs were observed in the pharmacogenetic testing scenarios (4.9% preemptive, 4.3% reactive and 3.2% usual care), though cardiovascular-related death occurred less frequently for both preemptive (39.8%) and reactive (46.4%) testing compared with usual care (48.5%). Dong *et al.* [72] evaluated utility and costs associated with multigene (*SLCO1B1* included), single-gene, and no testing in 300,000 acute coronary syndrome patients. At 12-months, multigene testing resulted in fewer statin-related AEs (195) and statin discontinuations (53) compared with single-gene testing and usual care. Fewer numbers of cardiovascular-related events and greater cost–effectiveness was observed for multigene testing across all timeframes (12- and 24-month, and

lifetime). While *SLCO1B1* testing did not play a dominant role in these simulations, its potential value within the milieu of cardiovascular disease management is intriguing and requires further study.

Conclusion

The association between *SLCO1B1* and SAMS is well-established, and existing evidence supports the idea that, at least in the short term, its clinical translation can improve patient outcomes. As one component of shared decision-making around statin therapy, *SLCO1B1* genotyping has the potential to lower ASCVD risk, particularly if delivered in a healthcare setting with decision support that promotes its timely and effective use. Additional considerations not described here may moderate the use of *SLCO1B1* results in specific patient populations, including those with nongenetic SAMS risk factors and in individuals from non-European populations. The overall rarity of severe SAMS and the healthcare system factors needed to support optimal utility make it difficult to implement *SLCO1B1* genotyping as a single test. However, its potential within the broader framework of multigene testing and its likely contributions to overall patient health remains encouraging and inspires continued appraisal.

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