Impact of *SLCO1B1* Pharmacogenetic Testing on Patient and Healthcare Outcomes: A Systematic Review

Jason L. Vassy[1,2,3], Sojeong Chun[1,4], Sanjay Advani[1], Sophie A. Ludin[1,5], Jason G. Smith[1] and Elaine C. Alligood[1]

Demonstrated improvements in patient outcomes will facilitate the clinical implementation of pharmacogenetic testing. Using the association between solute carrier organic anion transporter family member 1B1 (*SLCO*1B1) and statin-associated muscle symptoms (SAMSs) as a model, we conducted a systematic review of patient outcomes after delivery of *SLCO*1B1 results. Using PubMed and Embase searches through December 19, 2017, we identified 37 eligible records reporting preliminary or final outcomes, including six studies delivering only *SLCO*1B1 results and five large healthcare system–based implementation projects of multipharmacogene panels. Two small trials have demonstrated at least short-term improvements in low-density lipoprotein cholesterol after *SLCO*1B1 testing among previously statin intolerant patients. Evidence from large implementation projects suggests that *SLCO*1B1 results may change prescribing patterns for some high-risk patients. No study has reported improvements in SAMSs or cardiovascular events or tracked the economic outcomes of *SLCO*1B1 testing. Ongoing studies should collect and report outcomes relevant to pharmacogenetics stakeholders.

The field of pharmacogenetics is one beneficiary of the past decade's accelerated pace of genomic discovery.[1,2] Hundreds of drug–gene associations have now been identified that have the potential to help prescribers and patients optimize the risk–benefit ratio of pharmacotherapy.[3] These pharmacogenetic associations could be ideal candidates for the translation of genomic discovery into patient care, because test results might have ready actionability to inform drug selection and dose[4,5] and might lend themselves to clinical decision support (CDS) interventions in the electronic health record (EHR).[6–9] Some healthcare systems in the United States and worldwide are making large investments to implement clinical pharmacogenetics programs into their healthcare delivery systems,[10–14] but most health care is still delivered in settings without the routine use of pharmacogenetic testing. Innovation generally diffuses slowly throughout medical practice,[15] and for pharmacogenetics, this lag is exacerbated in part by healthcare providers and insurers who remain unconvinced of its value in improving the health care and outcomes of patients.[16–19] Evidence that pharmacogenetic testing improves patient outcomes is needed to break this impasse.[16–19]

One well-validated drug–gene association is the interaction between simvastatin and the solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene for the risk of statin-associated muscle symptoms (SAMSs). Statins, or 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, are cholesterol-lowering medications used by >30 million Americans that have dramatically reduced the risk of cardiovascular disease (CVD) and death in the United States.[20] Statins are generally well tolerated, but up to 20% of patients describe muscle aches or weakness[21,22] and up to 1 in 10,000 experience life-threatening myopathy.[23–25] In 2008, a high-profile genome-wide association study using data from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial identified a robust association between a common genetic variant in *SLCO1B1* and simvastatin-related myopathy.[26] Each copy of the *C* minor allele at *rs4149056* (contained within the *SLCO1B1*5*, *SLCO1B1*15*, and *SLCO1B1*17* haplotypes) increased myopathy risk by a factor of 4.5, such that *CC* homozygotes had a 16.9-fold increased risk compared with *TT* homozygotes.[26] Numerous other studies have gone on to replicate the association between *SLCO1B1* and SAMSs, particularly with simvastatin.[27–30] In 2012, the Clinical Pharmacogenetics Implementation Consortium issued its first recommendations for simvastatin prescribing and dosing when a patient's *SLCO1B1* genotype is known,[31] and some early-adopter healthcare systems are now incorporating *SLCO1B1* genotyping into their clinical and research pharmacogenetics programs.[10–14]

Although it makes intuitive sense that the use of *SLCO1B1* testing in clinical care would help prescribers and patients avoid statin-related adverse effects, intuition might not be sufficiently persuasive to promote its widespread adoption among providers and payers. Several reviews have examined the validity of the *SLCO1B1*-SAMS association,[30,32,33] but none has reviewed the prospective outcomes of integrating *SLCO1B1* genotype

[1]Veterans Affairs (VA) VA Boston Healthcare System, Boston, Massachusetts, USA; [2]Harvard Medical School, Boston, Massachusetts, USA; [3]Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, Boston, Massachusetts, USA; [4]Massachusetts College of Pharmacy and Health Sciences University, Boston, Massachusetts, USA; [5]Cornell University, Ithaca, New York, USA. Correspondence: Jason L. Vassy (jvassy@partners.org)

Received 26 April 2018; accepted 14 August 2018; advance online publication 00 Month 2018. doi:10.1002/cpt.1223

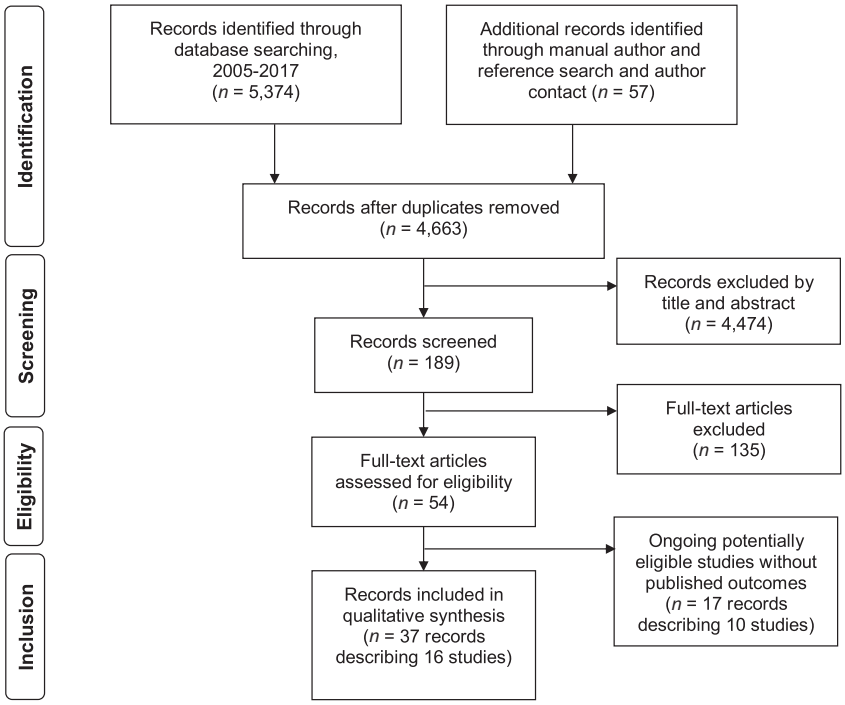

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of search results.

information into clinical care. Given the primacy of outcomes data in determining the clinical utility of pharmacogenetic testing, we performed a systematic review of studies reporting outcomes after the delivery of *SLCO1B1* results.

RESULTS

Search results

The database searches described in the Methods section yielded 5,374 unique records (**Figure 1**). Manual author and reference searches identified another 57 potentially eligible records, including one personal author communication providing unpublished results. After full-text review, we identified 37 records describing 16 eligible studies with completed or preliminary outcomes, including two nonrandomized trials and four randomized controlled trials (RCTs). **Table 1** presents the characteristics of these studies. We identified 17 records describing another 10 studies with potentially eligible study designs that have not yet reported outcomes.

Five pilot studies and one RCT have studied the delivery of *SLCO1B1* results specifically,[34–43] all but one of which were conducted by investigators at Duke University.[34–40,42,43] Three of the Duke pilot studies involved pharmacists in the identification of patients for *SLCO1B1* genotyping and/or the formulation of medication recommendations on the basis of *SLCO1B1* results.[34–38,40] A fourth Duke study, a pilot nonrandomized trial, enrolled 58 patients with prior statin nonadherence and studied the impact of *SLCO1B1* results delivery on statin prescriptions and medication adherence, compared with concurrent controls.[39] This pilot trial informed the design of a larger trial, the only published RCT designed specifically to examine the clinical impact of *SLCO1B1* testing. In this RCT by Voora and colleagues,[42,43] 167 patients with prior statin intolerance were randomly allocated to *SLCO1B1* results delivery to patients and providers at baseline vs. at study end. The study was powered to detect a one-point difference in the primary outcome of a medication adherence scale; secondary outcomes included low-density lipoprotein cholesterol (LDL-C) at 3 and 8 months, the Brief Pain Inventory, and the Short Form Health Survey quality-of-life measure.[42,43]

In addition, five large healthcare system–based pharmacogenetics implementation projects of multigene panels, including *SLCO1B1*, have reported preliminary or final results: four in the United States (1,200 Patients Project[11,44–49]; INdiana GENomics Implementation: an Opportunity for the UnderServed (INGENIOUS)[13,50,51]; the Marshfield Clinic[12,52]; and the RIGHT protocol[8,11,12,53–56]) and one from La Paz University Hospital in Spain[10] (**Table 1**). Most of these projects are using passive or active CDS in the EHR to support prescriber use of pharmacogenetic results in several different clinically actionable pharmacogenes. The remaining studies identified by our search included smaller single-arm intervention studies of multigene panels[11,49,57–65] and one pilot RCT of genome sequencing[66,67] (**Table 1**).

Study quality and risk of bias

The included studies generally had poor to moderate quality and risk of bias (**Table S1**). Most intervention studies experienced poor comparability on the Newcastle–Ottawa Scale because of the absence of a comparator group.

Reported outcomes

Review of the outcomes reported in the eligible studies led to the conceptual model of patient and healthcare outcomes shown in

Table 1 Characteristics of eligible studies

Study/institution	Design (country)	Population (*n*)	Genotype(s) reported	Experimental intervention	Decision support	Control group (*n*)
1,200 Patients Project[a11,44–49]	Intervention study (United States)	Patients aged ≥65 years receiving care from 1 of 17 providers at eight primary or specialty care clinics (**1,108**)	*ABCB1*, *ADD1*, *ADRB1*, *AGT*, *CACNA1C*, *CYP3A4*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *GNB3*, *GRK4*, *KIF6*, *LDLR*, *LTC4S*, *REN*, ***SLCO1B1***, *VKORC1*	• Genotyping of prospectively enrolled cohort • PGx results available to participating providers in institutional PGx CDS system • At participants' office visits, providers alerted verbally or by chart flagging to PGx results	• CDS system outside EHR, including green/yellow/red alerts with clinical summaries and interpretation • Providers could query CDS system for information for other drugs by name or by disease	—
AltheaDx[61,63]	Intervention study (United States)	Patients at several long-term care facilities taking five or more medications (**132**)	*COMT*, *CYP1A2*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4/CYP3A5*, *F2*, *F5*, *HTR2A*, *HTR2C*, *MTHFR*, *OPRM1*, *SLC6A2*, *SLC6A4*, ***SLCO1B1***, *VKORC1*	• Potential drug–drug, drug–environment, and drug–gene interactions reported to physicians • Internal medication management assessment by pharmacists	Reports listed commonly used medications categorized as "use as directed" or "use with caution and/or increased monitoring"	—
Duke University 1[39]	Nonrandomized trial (United States)	Primary care patients with a history of statin nonadherence (**58**)	***SLCO1B1***	PGx results available to providers through EHR and to patients through patient portal	• Genotype-specific information about patient's myopathy risk • Recommendations for statin prescribing	Concurrent controls: patients with prior statin prescription but without statin use in prior 3 months (**59**)
Duke University 2[40]	Intervention study (United States)	Patients receiving new or recurrent simvastatin prescriptions from pharmacists at five community pharmacies (**19**)	***SLCO1B1*** (+/- *CYP2C19*)	• PGx results accessible through laboratory database and faxed to pharmacist and prescriber • Pharmacists reviewed results with patients and prescribers	Test interpretation included CPIC guidelines	—
Duke University 3[37,38]	Intervention study (United States) Patients at two cardiology clinics[30] • Taking simvastatin and/or clopidogrel • No prior PGx testing or MTM in prior 3 years	*CYP2C9*, *CYP2C19*, *CYP2D6*, ***SLCO1B1***, *VKORC1*	• Pretest and posttest MTM sessions with pharmacist for patients • MTM also included recommendations for lifestyle modification and OTC medications • Patients and referring cardiologists received PGx results	Pharmacist discussed recommendations on the basis of the FDA and/or CPIC guidelines with cardiologist before sharing action plan with patients	—

(*Continues*)

Table 1 (Continued)

Study/institution	Design (country)	Population (*n*)	Genotype(s) reported	Experimental intervention	Decision support	Control group (*n*)
Duke University 4[34–36]	Nonrandomized trial (United States)	Primary care patients at two internal medicine practices (**63**)	*CYP2C9*, *CYP2C19*, *CYP2D6*, *HLA-B*1502*, ***SLCO1B1***, *VKORC1*	• Site 1: Pharmacist on call: physician consulted pharmacist about PGx testing; pharmacists screened patients and notified physicians about eligibility • Site 2: Pharmacist in house: pharmacist screened patients and alerted physicians to availability of PGx testing for relevant medications	All participating physicians first attended a 1-hour CME session about PGx	—
Duke University 5[42,43]	Randomized control trial (United States)	Patients not currently taking statins because of a history of an adverse effect, ineligible if prior rhabdomyolysis or CK >10x ULN (**167**)	***SLCO1B1***	• Genotyping at a research visit • Patients and their physicians received PGx results by email	Physician reports: • *SLCO1B1* results • Risk of rhabdomyolysis • General expectations of LDL-C reduction from different statin types and doses Patient reports: • *SLCO1B1* results • Reassurance about which statins should be tolerable and lower CVD risk	Physician reports: • General information about LDL-C reductions from different statins Patient reports: • General information about statins and CVD risk
First Moscow State Medical University[41]	Intervention study (Russia)	Patients with hyperlipidemia already receiving statin therapy (35)	***SLCO1B1***	Patients received results	Not specified	—
INdiana GENomics Implementation: an Opportunity for the UnderServed (INGENIOUS)[b13,50,51]	Randomized control trial (United States)	Safety-net hospital system of 10 clinics with common EHR (**2,000 planned**) • Aged ≥18 years • New prescription for 1 of 28 index medications	*CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP4F2*, *DPYD*, *G6PD*, *IFNL3*, *ITPA*, ***SLCO1B1***, *TPMT*, *VKORC1*	• Enrolling prescriber receives PGx reports • PGx results uploaded to EHR and viewable by all providers	• Reports include alternative prescribing recommendations for index medication on the basis of CPIC guidelines • Subsequent prescription prompts an alert notifying provider a genotype report is available and gives dosing recommendations • Providers may consult PGx service that documents recommendations in EHR	Patient does not undergo genotyping (**4,000 planned**)

(*Continues*)

Table 1 (Continued)

Study/institution	Design (country)	Population (*n*)	Genotype(s) reported	Experimental intervention	Decision support	Control group (*n*)
La Paz University Hospital[10]	Intervention study (Spain)	Patients receiving specialty care at a tertiary care teaching hospital (**600**)	*ABCB1*, *ABCC2*, *ABCG2*, *APOE*, *COMT*, *CFTR*, *CYP2C19*, *CYP2C8*, *CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP4F2*, *DPYD*, *ERCC1*, *EPHX1*, *FCGR2A*, *HTR2A*, *IL10*, *IL23R*, *KCNJ6*, *MTHFR*, *POR*, *SLC15A2*, *SLC22A1*, *SLC22A2*, *SLC22A6*, ***SLCO1B1***, *TLR2*, *TLR9*, *TNF*, *TP53*, *TPMT*, *UGT1A1*, *UGT2B7*, *VKORC1*, *XPC*, *XRCC1*	Providers request testing from PGx unit, which generates report according to prespecified drug–gene protocol or after PGx consultation	Recommendation from PGx unit, on the basis of CPIC and DPWG reviews	—
Marshfield Clinic[c12,52]	Intervention study (United States)	Adults aged ≥50 years with healthcare system primary care physician and no prior use of simvastatin, warfarin, or clopidogrel (**750 planned**)	*CYP2C9*, *CYP2C19*, ***SLCO1B1***, *VKORC1*	• Providers receive PGx results • Patients have access to website with information about their PGx results	Active CDS alerts with CPIC dosing recommendation triggered by prescription in EHR	—
MedSeq Project[66,67]	Randomized control trial (United States)	Generally healthy adult primary care patients (**100**)	Genome sequencing, including monogenic disease variants, carrier status, eight polygenic risks, and five PGx results: *ABCB1*, *C11orf65*, *CYP2C9/VKORC1*, *CYP2C19*, ***SLCO1B1***	Patients discussed interpreted genome report and family history pedigree with physician	Report included statement about simvastatin-associated myopathy risk	Patients discussed family history pedigree alone with physician
OSU–Coriell Personalized Medicine Collaborative[a] [11,49,58,59,62,64,65]	Intervention study (United States)	Participants with heart failure and hypertension enrolled in RCT of genomic counseling for polygenic risk estimates and *CYP2C19* (**208**)	Polygenic risk estimates for eight diseases plus PGx results for *CYP2C9*, *VKORC1*, *CYP4F2*, *CYP2C19*, ***SLCO1B1***	• Patients received genetic reports by mail and by patient Web portal • Reports also uploaded to EHR • Half of patients were randomly allocated to in-person genomic counseling; half could access a genetic counselor by telephone if requested	Reports to patients and in EHR included CPIC recommendations	—

(*Continues*)

Table 1 (Continued)

Study/institution	Design (country)	Population (*n*)	Genotype(s) reported	Experimental intervention	Decision support	Control group (*n*)
PRIMER[60]	Intervention study (United States)	Patients of 27 providers with likelihood of exposure to a relevant medication (**705**)	*COMT*, *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP1A2*, *CYP3A4*, *CYP3A5*, *F2*, *F5*, *MTHFR*, *OPRM1*, ***SLCO1B1***, *SLC6A4*, *VKORC1*	Providers ordered PGx panel testing and received report	Report with drug–drug and drug–gene interactions categorized as contraindicated, major, moderate, or minor, some with explanatory annotations	—
RIGHT Protocol[c8,11,12,53–56]	Intervention study (United States)	Health system patients, including biobank participants, likely to initiate statin treatment within 3 years (**3,788**)	*CYP2C9*, *CYP2C19*, *CYP2D6*, *HLA-B*1502*, *HLA-B*5701*, ***SLCO1B1***, *TPMT*, *VKORC1*	Preemptive genotyping, with results available to provider in EHR and to patients through patient portal	Active CDS • Alerts triggered when simvastatin ordered on high-risk patients • Alerts sent to provider and added to problem list Passive CDS • Internal online medical information system, AskMayoExpert	—
Yale University[57]	Intervention study (United States)	Series of consecutive high-risk cardiovascular patients (**32**)	*CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *F2*, *F5*, *MTHFR*, ***SLCO1B1***, *VKORC1*	Results reported to clinicians	Not specified	—

Bold text highlights study sample sizes and presence of SLCO1B1 in panel tests.
CDS, clinical decision support; CK, creatine kinase; CME, continuing medical education; CPIC, Clinical Pharmacogenetics Implementation Consortium; CVD, cardiovascular disease; DPWG, Dutch Pharmacogenetics Working Group; EHR, electronic health record; FDA, US Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; MTM, medication therapy management; OSU, The Ohio State University; OTC, over-the-counter; PGx, pharmacogenetics; RCT, randomized controlled trial; ULN, upper limit of normal.
[a]Part of the Pharmacogenomics Research Network Translational Pharmacogenetics Program.[11]
[b]Part of the Implementing Genomics in Practice (IGNITE) Consortium.[13]
[c]Part of the Electronic Medical Records and Genomics (eMERGE)–PGx Consortium.[12]

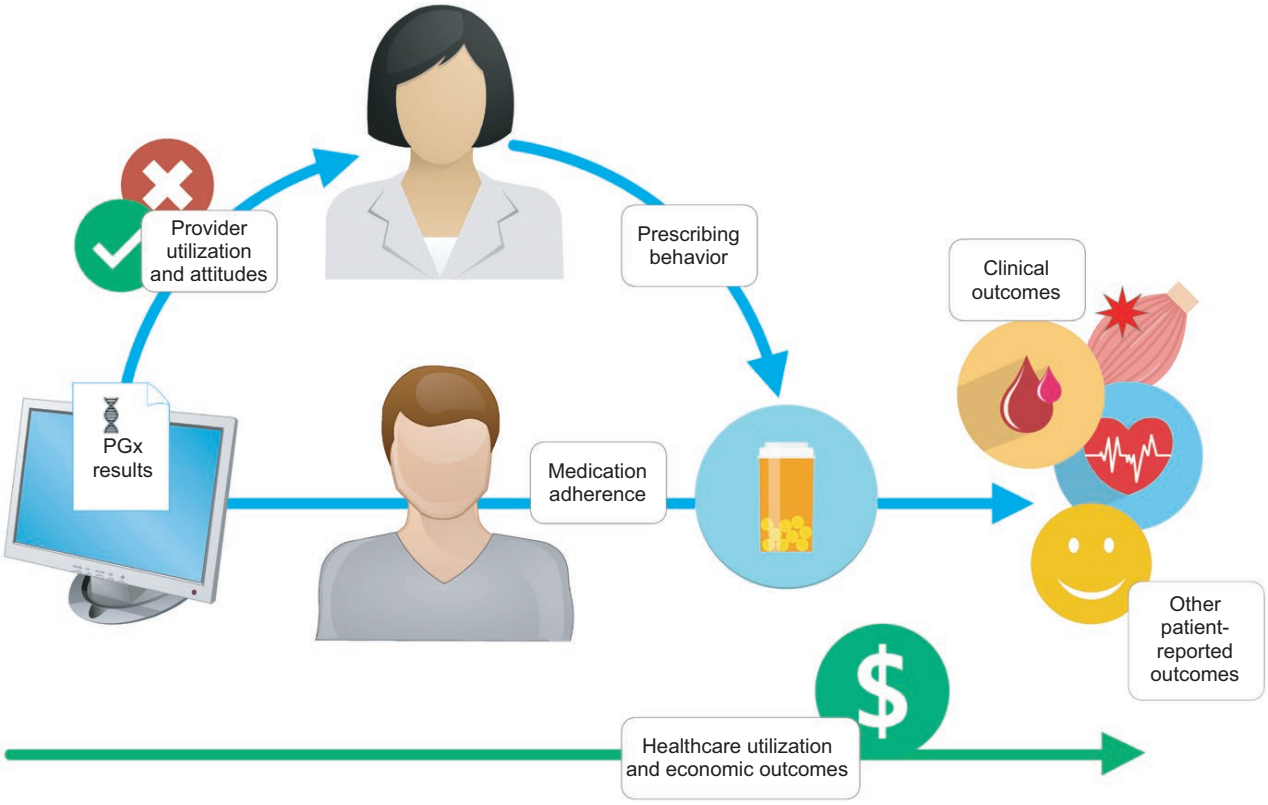

Figure 2 Conceptual model of patient and healthcare outcomes after delivery of *SLCO1B1* PGx test results. PGx, pharmacogenetics.

Figure 2, which guided the creation of the six outcome categories in **Table 2** and our presentation of the results later. In this conceptual model, *SLCO1B1* results might act on provider and patient attitudes and behaviors to effect a change in clinical, economic, and other outcomes (**Figure 2**). We categorized all reported outcomes as either *utility outcomes* (including clinical outcomes and healthcare use and economic outcomes) or *process outcomes* that might mediate the relationship between *SLCO1B1* testing (including provider use and attitudes, prescribing behavior and prescriptions, medication adherence, and other patient-reported outcomes).

Utility outcomes. *Clinical outcomes*: Only two studies to date have quantitatively reported clinical outcomes after *SLCO1B1* testing. The Duke nonrandomized pilot trial among previously statin-intolerant patients reported a nonsignificantly greater reduction in LDL-C in the intervention group (−12 ± 45 mg/dl) compared with concurrent controls (6 ± 38 mg/dl; $P = 0.06$) after 1 year.[39] In the subsequent RCT, LDL-C values were significantly lower in the intervention group compared with the control group at 3 months (132 ± 42 vs. 144 ± 43 mg/dl; $P = 0.04$) but not at 8 months (129 ± 38 vs. 141 ± 44 mg/dl; $P = 0.07$).[43] Improvements observed in total cholesterol, but not high-density lipoprotein cholesterol or triglycerides, were consistent with these LDL-C changes. In a follow-up analysis, when patients in the usual-care arm received their *SLCO1B1* results at the end of the study, they had a greater decrease in LDL-C values compared with intervention patients during the same poststudy period, such that the two arms ultimately achieved similar LDL-C reductions from baseline. This RCT found no significant differences in medication adverse effects between the intervention arms, as measured by pain and quality-of-life instruments.[43] Other studies of pharmacogenetic testing have made general qualitative statements that no participants experienced medication adverse effects during the observation periods.[41,57,60,66] No study has reported creatinine kinase values, SAMSs, or cardiovascular events after *SLCO1B1* testing.

Healthcare use and economic outcomes: Some studies have tracked the costs and resources required to conduct their pharmacogenetics projects or those incurred as a result of that implementation.[10,38,50,66] The clinical pharmacogenetic service in Spain cost the national health system €202,140 over 3 years, with the cost of each consultation averaging €216.[10] Preliminary results from the INGENIOUS RCT of pharmacogenetic panel testing show that genotyping the first 106 participants generated 25 actionable genotypes and prompted 10 consult requests (9%) by physicians.[50] Two studies have reported patient willingness to pay for multigene pharmacogenetic testing that included *SLCO1B1*. In one study, participants in The Ohio State University–Coriell Personalized Medicine Collaborative RCT of genomic counseling, 28% of whom had an actionable *SLCO1B1* result, reported a mean (SD) willingness to pay of $56 ($81) for a clinical pharmacogenetics service.[59] In the second study, the RIGHT Protocol at the Mayo Clinic, a survey of 869 participants who had undergone panel

Table 2 Utility and process outcomes after *SLCO1B1* genotyping in eligible studies

	Utility outcomes		Process outcomes				
Study/institution	Clinical outcomes	Healthcare use and economic outcomes	Provider use and attitudes	Prescribing behavior and prescriptions	Medication adherence	Other patient-reported outcomes	Key findings
1200 Patients Project[a11,44–49]			X	X			• Among 868 patients over 3 years, CDS influenced simvastatin discontinuation in 8 cases
AltheaDx[61,63]				X			• 54 (48%) of 112 patients had one or more medication change
Duke University 1[39]	X			X	X		• 47% vs. 15% of intervention vs. control patients taking statin after 4 months ($P < 0.001$) • **1-year LDL-C reduction −12 ± 45 mg/dl in invention group vs. 6 ± 38 mg/dl in controls (*P* = 0.06)**
Duke University 2[40]			X	X	X	X	• No prescription changes observed
Duke University 3[37,38]		X		X	X	X	• **Pharmacist medication management and PGx visit lasted a mean of 16 (range, 8–29) minutes** • Three PGx-based medication changes were made among 28 patients
Duke University 4[34–36]		X	X	X	X	X	• **Providers consulted pharmacist for 15 cases, averaging 5.7 minutes per consult** • 1/63 patients tested had simvastatin dose halved because of *SLCO1B1*5* result
Duke University 5[42,43]	X			X	X		• **LDL-C lower in the intervention group vs. controls at 3 months (132 ± 42 vs. 144 ± 43 mg/dL; *P* = 0.04) but not 8 months (129 ± 38 vs. 141 ± 44 mg/dl; *P* = 0.07)** • **No between-group differences in pain or quality of life**
First Moscow State Medical University[41]	X				X		• **No medication adverse effects reported**
INdiana GENomics Implementation: an Opportunity for the UnderServed (INGENIOUS)[b13,50,51]		X					• **Genotyping prompted PGx consults for 10 (9%) of 106 patients**
La Paz University Hospital[10]		X	X			X	• **Clinical PGx service cost €202,140 over 3 years, with each consult averaging €216**
Marshfield Clinic[c 12,52]			X	X			• Simvastatin prescriptions have triggered five CDS alerts over 3 years, prompting one medication change

(*Continues*)

Table 2 (Continued)

Study/institution	Utility outcomes		Process outcomes				Key findings
	Clinical out-comes	Healthcare use and economic outcomes	Provider use and attitudes	Prescribing behavior and prescriptions	Medication adherence	Other patient-reported outcomes	
MedSeq Project[66,67]	X	X		X	X	X	• **No between-group differences in 6-month healthcare costs (mean, $1,490 vs. %1,142).** • **No medication adverse effects reported**
OSU–Coriell Personalized Medicine Collaborative[a11,49,58,59,62,64,65]		X				X	• **Mean patient willingness to pay for clinical PGx service was $56 ($81)**
PRIMER[60]	X	X	X				• **42% of patients not willing to pay out-of-pocket costs for PGx tests; 58% of remainder reported willingness to pay of $100**
RIGHT Protocol[c 8,11,12,53–56]			X			X	• **No medication adverse effects reported**
Yale University[57]	X			X			• **No medication adverse effects reported**

Outcomes are categorized as utility outcomes from *SLCO1B1* testing or the process outcomes that might mediate the relationship between *SLCO1B1* testing and utility outcomes. Clinical outcomes include biomarker changes, morbidity, and mortality, whereas healthcare use and economic outcomes include willingness to pay and the healthcare costs or other resources required to implement the intervention or resulting from its implementation. Provider use and attitudes include frequency of test ordering by providers, their use of the information, and their attitudes about its value. Prescribing behavior includes medication prescriptions, whereas medication adherence measures patient use of prescribed medications. Other patient-reported outcomes include patient recall of test results, concern or distress about results, and patient perceived utility of the information. Bolded text in the "Key findings" column refers to utility outcomes (either clinical or healthcare use/economic outcomes).
CDS, clinical decision support; LDL-C, low-density lipoprotein cholesterol; OSU, The Ohio State University; PGx, pharmacogenetics.
[a]Part of the Pharmacogenomics Research Network Translational Pharmacogenetics Program.[11]
[b]Part of the Implementing Genomics in Practice (IGNITE) Consortium.[13]
[c]Part of the Electronic Medical Records and Genomics (eMERGE)–PGx Consortium.[12]

pharmacogenotyping found that 42% were not willing to incur out-of-pocket costs for pharmacogenetic tests; 58% of the rest reported a maximum willingness to pay of $100.[54] No study has reported downstream healthcare costs after receipt of *SLCO1B1* results specifically, although the MedSeq Project pilot RCT found no differences in 6-month healthcare costs between participants receiving genome sequencing, including *SLCO1B1* genotyping, vs. no genome sequencing (mean, $1490 vs. $1142, excluding the costs of sequencing and interpretation).[66]

Process outcomes. *Provider use and attitudes*: Studies in which results were delivered to prescribers enabled an examination of how frequently they interfaced with the information and their attitudes about its value. Studies in which providers initiated *SLCO1B1* testing generally reported low testing uptake.[10,34–36] Studies delivering *SLCO1B1* results to providers through the EHR without provider initiation have reported providers' EHR transactional data. For example, the 1,200 Patients Project of more than a dozen drug–gene pairs reported that 69% of 2,279 patient visits over 3 years were associated with a provider log-in to the pharmacogenetics CDS system within 72 hours.[48] Approximately one third of patients' active medications had associated pharmacogenetic alerts (0.5% red, 13% yellow, and 21% green)[48]; a 10-month analysis in the first 608 patients reported that providers clicked on 100%, 72%, and 20% of red, yellow, and green alerts, respectively.[47] However, *SLCO1B1* transactions were not specifically reported. During the first 14 months that *SLCO1B1* CDS was in production in the RIGHT Protocol, there were 0.7 interruptive alerts per month for simvastatin orders attempted for rs4149056 TC or *CC* patients among 3,788 patients seen by 1,247 unique providers.[55] Studies surveying providers about their experiences have reported overall positive attitudes about pharmacogenetics, including its clinical relevance and impact on management,[10,47,60] although no study reported provider attitudes about *SLCO1B1* testing specifically.

Prescribing behavior and prescriptions: Most studies have reported or are actively collecting data on the impact of *SLCO1B1* results on medication prescriptions, measured from either the EHR or the provider or patient report. Some studies of pharmacogenetic panel testing have reported only composite medication changes,[10,60,61,63] whereas small pilot studies have reported specific cases where *SLCO1B1* results guided therapy.[34,35,38,40,57,66] Large studies with *SLCO1B1* CDS alerts have reported counts of medication changes attributed to pharmacogenetic results. The 1,200 Patients Project reported that 25% of 2,279 visits over 3 years had medication changes; simvastatin was the drug with the highest percentage of

changes influenced by CDS (69%), although this represented only eight simvastatin discontinuations in *SLCO1B1* C carriers among 868 patients.[48] In the first 3 years of the Marshfield Clinic project, there have been five CDS alert recommendations triggered by simvastatin prescriptions, only one of which was followed, prompting the provider to prescribe atorvastatin instead (personal communication, Terrie Kitchner, December 6, 2017). Similarly, pharmacists in a Duke pilot study did not recommend any simvastatin prescription changes to the providers caring for six patients with carrier or homozygous *SLCO1B1**5 results.[40] Two controlled studies have examined prescribing behavior. In the Duke nonrandomized pilot trial, 55% of patients with a history of statin nonadherence had statin prescriptions 4 months after receiving *SLCO1B1* results, compared with 20% of concurrent controls with statin prescriptions after 1 year ($P < 0.001$).[39] In the subsequent RCT, more participants receiving *SLCO1B1* results were receiving statin therapy at 3 months compared with usual care (55% vs. 38%; $P = 0.04$), but this difference was not statistically significant after 8 months (54% vs. 37%; $P = 0.07$).[43]

Medication adherence: Although prescriptions largely reflect provider behavior, medication adherence is a patient behavior. Small pilot studies have either found no impact of *SLCO1B1* testing on statin adherence or did not collect data to enable before–after or between-group comparisons.[34,35,38,41] The Duke nonrandomized pilot study among patients with prior statin discontinuation found that 47% of intervention patients reported taking a statin after 4 months compared with 15% of concurrent controls after 1 year ($P < 0.001$).[39] The subsequent RCT, however, found no differences in adherence or the medication possession ratio after 3 or 8 months between the subsets of patients in both arms reinitiated on statin therapy.[43] The authors reported that intervention patients perceived higher necessity of their medications than control patients at 3 months, but not at 8 months,[43] consistent with observations from the pilot study.[39]

Other patient-reported outcomes: Uncontrolled studies have reported that some patients had difficulty recalling their specific *SLCO1B1* results[35,38] and had variable understanding of them.[10,40,59] Nonetheless, patients generally perceived the information as useful to their providers.[35,38,54,59] Pilot studies have also reported that patients generally had no concerns or distress after receiving pharmacogenetic results.[35,40,66]

DISCUSSION

Ten years after the publication of the association between *SLCO1B1* and SAMSs,[26] we found few high-quality studies reporting patient outcomes after the delivery of *SLCO1B1* results. Most notably, a pilot trial and subsequent small RCT among previously statin-intolerant patients observed at least short-term improvements in LDL-C after *SLCO1B1* testing. Although these findings require replication, the 10-mg/dl reduction in LDL-C the investigators observed, if sustained, would result in a 5% lower 5-year risk of a major CVD event.[68] Apart from this, although the proposed benefit of *SLCO1B1* testing is the avoidance of SAMSs, it is worth noting that no study has empirically demonstrated this outcome or the impact of *SLCO1B1* testing on CVD events. Evidence from small pilot studies and large healthcare system implementation projects does suggest that *SLCO1B1* results may change providers' prescribing patterns for some, but not all, high-risk patients receiving simvastatin; however, to date, the number of potential opportunities to observe prescription changes in large healthcare systems with *SLCO1B1* CDS in the EHR has been small. Receipt of *SLCO1B1* test results seems generally well tolerated by providers and patients. No study has specifically tracked the economic impact of *SLCO1B1* testing and its downstream outcomes.

The clinical validity of the *SLCO1B1*-SAMS association has been well established (i.e., the observed association between rs4149056 in *SLCO1B1* and statin-associated myotoxicity of varying severity has been replicated in numerous studies, particularly for simvastatin).[30] The PharmGKB knowledge resource rates the genotype–phenotype association between *SLCO1B1* and simvastatin myopathy as having the highest level of evidence (level 1A).[69] On the other hand, the clinical utility of *SLCO1B1* testing, or its ability to inform a change in clinical management that demonstrably improves patient outcomes, is less certain. A 2013 review by Stewart found no studies comparing clinical outcomes between patients whose statin prescriptions were guided or not guided by *SLCO1B1* results,[32] and Sorich and colleagues found no studies of the cost-effectiveness of *SLCO1B1* genotyping.[70] A more recent review examined 89 studies purporting to address either the clinical validity or clinical utility of pharmacogenetic testing for statin use and found almost all claims of clinical utility to be lacking when examined against benchmarks such as number needed to genotype, the effect and risks of the intervention, and costs per quality-adjusted life year.[33] Many of the studies we identified in the present review are collecting data on prescription changes, a measure of the actionability of pharmacogenetic results. Still, the absence of prospective outcomes data for pharmacogenetic testing will continue to make health insurers reluctant to cover the costs of testing[71] and many clinicians reluctant to incorporate pharmacogenetics into their practices.[72]

Our review of patient outcomes after *SLCO1B1* testing prompts the following recommendations for future research. First, although RCT evidence may not be necessary to justify every clinical application of pharmacogenetic testing,[11,73,74] prospectively collected outcomes data might be, ideally from studies with suitable control groups. Investigators are encouraged to identify and collect data from concurrent matched controls for the participants in ongoing and planned pharmacogenetic projects, to enable a less biased determination of the impact of testing. Second, these outcomes should include those of interest to patients, providers, and payers, including clinical outcomes, quality of life, and costs. Third, even with the multigene pharmacogenetic panels that some implementation projects are using, it is important to report outcomes specific to individual pharmacogenetic tests, such as *SLCO1B1* for statins and *cytochrome P450 family 2 subfamily C member 19* (*CYP2C19*) for clopidogrel.[75] Few studies using panels in our review reported outcomes pertaining to *SLCO1B1* results specifically. Although panels enable efficiencies of scale in genotyping, additional costs, such as the development and implementation of CDS for each drug–gene pair, are not trivial.[76] Locus-specific outcomes data will enable a determination of the returns on those investments. Fourth, as more outcomes data accrue, the effect of context on those outcomes should be examined, including the

degree of patient and provider engagement in the process, the type of CDS used in results delivery, and the characteristics of patients most likely to benefit. To date, the strongest evidence supporting the use of *SLCO1B1* testing derives from an RCT among previously statin-intolerant patients.[43] This finding is consistent with the French National Network of Pharmacogenetics recommendation that *SLCO1B1* testing is potentially useful for patients experiencing SAMSs after statin initiation or with at least one SAMS risk factor; it does not recommend routine preemptive *SLCO1B1* testing before general simvastatin initiation.[77] Further research should examine the clinical utility of *SLCO1B1* testing among statin-naïve patients and among patients already tolerating statin therapy.

With the previously described recommendations, ongoing projects using *SLCO1B1* genotyping in research or clinical care in the United States and internationally have a tremendous opportunity to contribute to the lack of evidence for its clinical utility. We identified 10 institutions with ongoing studies whose designs and planned outcomes would have been eligible for this review.[11,12,14,78–81] Most of these represent multi-institutional efforts, such as the Electronic Medical Records and Genomics (eMERGE)–PGx Consortium,[12] the Pharmacogenomics Research Network Translational Pharmacogenetics Program (TPP),[11] the Implementing Genomics in Practice (IGNITE) Consortium,[13] and the seven-country Ubiquitous Pharmacogenomics (U-PGx) Consortium.[14] These projects are collecting a range of prescription, clinical, and economic outcomes, and their large scale will enable more precise estimates of the clinical utility of pharmacogenetic testing. For example, although preliminary reports suggest that individual healthcare systems may observe few instances where *SLCO1B1* results change medication prescriptions, a recent update from the TPP reported that 14,508 *SLCO1B1* results have been reported in the EHR of five participating institutions, of which 3,513 (24%) were actionable.[11] In addition to these large projects of pharmacogenetics panels, we are conducting the Integrating Pharmacogenetics in Clinical Care Study, an RCT specifically examining the impact of *SLCO1B1* genotyping on LDL-C and concordance with statin therapy guidelines among statin-naïve patients (ClinicalTrials.gov Identifier: NCT02871934).

This review has a few limitations to note. The paucity of published clinical utility outcomes and the heterogeneity in other outcomes reported after *SLCO1B1* testing precluded meta-analysis or between-study comparisons. We examined outcomes data from only a single specific gene–drug pair as an in-depth case study, paradigmatic of the state of the evidence for most other pharmacogenetic tests. It is unknown how the use of multigene pharmacogenetic panels would change the impact of *SLCO1B1* information alone, because multiple genetic test results can interact in unpredictable ways on patient outcomes.[82] Although *SLCO1B1* testing might be increasingly common in medical practice outside academic centers, we were only able to examine outcomes published in the biomedical literature.

In conclusion, despite advances bringing pharmacogenetic testing to clinical care, we found few patient outcomes reported after the delivery of *SLCO1B1* results, a well-validated pharmacogenetic locus. Outcomes data are needed to accelerate the pace of this clinical translation.

METHODS

Protocol and registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines were followed for this systematic review (see PRISMA checklist, **Table S2**). We performed initial scoping searches of PubMed and Embase on June 22, 2017, before registering the review protocol on the PROSPERO register of systematic reviews on August 28, 2017 (CRD42017074795). After our initial searches and record review, we updated our searches on December 19, 2017, to identify new records.

Search strategy

We searched the PubMed and Embase databases for published reviews, meta-analyses, and primary studies published in or after 2005 using combinations of the following search strategy concepts: pharmacogenetics/pharmacogenomics, precision medicine, *SLCO1B1*, statins, and cardiovascular disease. The full search strategies are included in the **Supporting Information S1**.

Scope and eligibility criteria

The primary aim of the systematic review was to review the evidence for the clinical utility of *SLCO1B1* testing, as determined by patient outcomes observed after *SLCO1B1* genotyping. We included intervention studies in which (i) participants were directly or indirectly (e.g., via their providers) given their *SLCO1B1* genotype results as a part of a research study or clinical care and (ii) subsequent outcomes were prospectively collected and reported. Our scoping search enabled us to determine the appropriate breadth of eligibility criteria for both study designs and outcomes. Identifying few eligible randomized trials, we chose to additionally include pilot studies, implementation projects, and nonrandomized trials. We excluded case reports. We excluded studies reporting the association between *SLCO1B1* genotype and statin effects (i.e., the clinical validity of the *SLCO1B1* genotyping), as this has been reviewed in detail elsewhere, particularly by the Clinical Pharmacogenetics Implementation Consortium.[30,32,33] We excluded retrospective observations among cohorts who had undergone direct-to-consumer pharmacogenetic testing.[83] We excluded records reporting only the frequency of *SLCO1B1* genotypes among participants or in which *SLCO1B1* genotype results were used to estimate hypothetical recommendations for medication changes. [5] We included records in any language. After our scoping search identified few studies with eligible designs that reported clinical outcomes, such as biomarker changes, morbidity, or mortality, we defined an eligible outcome broadly as any provider- or patient-reported outcome, EHR-derived outcome, or other study outcome measured *after* an intervention that involved the reporting of *SLCO1B1* results to providers and/or patients. Our approach to categorizing these clinical utility and process outcomes was described previously in the Results. Any record describing an ongoing study whose design and planned outcomes would be eligible for inclusion was noted so that authors could be contacted for more information.

Review process

The titles and abstracts of all search records were screened for potential eligibility by two independent reviewers; discrepancies were resolved by discussion and consensus among the study team. Potentially eligible records progressed to full record review for determination of eligibility. The references of review articles and eligible studies were manually searched for additional eligible studies.

Data abstraction

A Microsoft Excel database was used to abstract the following from each eligible study: country; study design; patient population and number; the genotyping intervention, including any genotypes other than *SLCO1B1* reported and any associated decision support; any

control group; any quantitative or qualitative outcome reported, including the method of collection and results; and the current status of the study. We categorized any intervention study with a control group as a nonrandomized trial if historical or concurrent controls were used or as an RCT if participants were randomly allocated to the study arms.[84] All other eligible studies were categorized as intervention studies, which included pharmacogenetics interventions delivered through pilot studies or operational clinical innovation programs.

Author communication

For each ongoing study with a potentially eligible study design (typically identified through a manuscript describing the study design and rationale), we emailed the corresponding author(s) a link to a brief survey requesting any published or unpublished results from the study referenced in the records we identified (**Supporting Information S1**). Each author was sent up to three requests, each separated by at least 7 days. We also performed targeted author searches to identify any additional records from these ongoing studies.

Assessing study quality and risk of bias

Bias and study quality were systemically assessed using the Newcastle–Ottawa Scale for the quality of intervention studies and nonrandomized studies, with greater scores indicative of higher study quality.[85] For the RCTs, the Jadad scale[86] was used for the study quality assessment.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Supporting Information S1. PubMed search strategy, Embase search strategy, Corresponding author survey.
Table S1. Quality and risk of bias of eligible studies.
Table S2. PRISMA checklist for systematic reviews

FUNDING

J.L.V. is supported by Career Development Award IK2 CX001262 from the US Department of Veterans Affairs (VA) Clinical Sciences Research and Development Service. This work does not reflect the views of the VA or the US government, which had no role in the research.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

1. Manolio, T.A. *et al.* Implementing genomic medicine in the clinic: the future is here. *Genet. Med.* **15**, 258 (2013).
2. Relling, M.V. & Evans, W.E. Pharmacogenomics in the clinic. *Nature* **526**, 343–350 (2015).
3. US Food and Drug Administration. Table of pharmacogenomic biomarkers in drug labels. <https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm> (2018). Accessed 1 March 2018.
4. Snyder, S.R., Mitropoulou, C., Patrinos, G.P. & Williams, M.S. Economic evaluation of pharmacogenomics: a value-based approach to pragmatic decision making in the face of complexity. *Public Health Genomics* **17**, 256–264 (2014).
5. Van Driest, S.L. *et al.* Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. *Clin. Pharmacol. Ther.* **95**, 423–431 (2014).
6. Bell, G.C. *et al.* Development and use of active clinical decision support for preemptive pharmacogenomics. *J. Am. Med. Inform. Assoc.* **21**, e93–e99 (2013).
7. Goldspiel, B.R. *et al.* Integrating pharmacogenetic information and clinical decision support into the electronic health record. *J. Am. Med. Inform. Assoc.* **21**, 522–528 (2014).
8. Dunnenberger, H.M. *et al.* Preemptive clinical pharmacogenetics implementation: current programs in five US medical centers. *Annu. Rev. Pharmacol. Toxicol.* **55**, 89–106 (2015).
9. Hinderer, M. *et al.* Integrating clinical decision support systems for pharmacogenomic testing into clinical routine: a scoping review of designs of user-system interactions in recent system development. *BMC Med. Inform. Decis. Mak.* **17**, 81 (2017).
10. Borobia, A.M. *et al.* Clinical implementation of pharmacogenetic testing in a Hospital of the Spanish National Health System: strategy and experience over 3 years. *Clin. Transl. Sci.* **11**, 189–199 (2018).
11. Luzum, J.A. *et al.* The pharmacogenomics research network translational pharmacogenetics program: outcomes and metrics of pharmacogenetic implementations across diverse healthcare systems. *Clin. Pharmacol. Ther.* **102**, 502–510 (2017a).
12. Rasmussen-Torvik, L.J. *et al.* Design and anticipated outcomes of the eMERGE-PGx project: a multicenter pilot for preemptive pharmacogenomics in electronic health record systems. *Clin. Pharmacol. Ther.* **96**, 482–489 (2014).
13. Weitzel, K.W. *et al.* The IGNITE network: a model for genomic medicine implementation and research. *BMC Med. Genomics* **9**, 1 (2016).
14. van der Wouden, C.H.C.-T. *et al.* Implementing pharmacogenomics in Europe: design and implementation strategy of the ubiquitous pharmacogenomics consortium. *Clin. Pharmacol. Ther.* **101**, 341–358 (2017).
15. Rogers, E.M. *Diffusion of Innovations*. 5th edn. (The Free Press, New York, 2003).
16. Mrazek, D.A. & Lerman, C. Facilitating clinical implementation of pharmacogenomics. *JAMA* **306**, 304–305 (2011).
17. Feero, W.G., Manolio, T.A. & Khoury, M.J. Translational research is a key to nongeneticist physicians' genomics education. *Genet. Med.* **16**, 871–873 (2014).
18. Patel, H.N., Ursan, I.D., Zueger, P.M., Cavallari, L.H. & Pickard, A.S. Stakeholder views on pharmacogenomic testing. *Pharmacotherapy* **34**, 151–165 (2014).
19. Hess, G.P., Fonseca, E., Scott, R. & Fagerness, J. Pharmacogenomic and pharmacogenetic-guided therapy as a tool in precision medicine: current state and factors impacting acceptance by stakeholders. *Genet. Res.* **97**, e13 (2015).
20. National Center for Health Statistics. Health, United States, 2013: with special feature on prescription drugs. <http://www.cdc.gov/nchs/data/hus/hus13.pdf - listfigures> (2014). Accessed 2 February 2018.
21. Zhang, H. *et al.* Discontinuation of statins in routine care settings: a cohort study. *Ann. Intern. Med.* **158**, 526–534 (2013).
22. Buettner, C., Davis, R.B., Leveille, S.G., Mittleman, M.A. & Mukamal, K.J. Prevalence of musculoskeletal pain and statin use. *J. Gen. Intern. Med.* **23**, 1182–1186 (2008).
23. Silva, M.A., Swanson, A.C., Gandhi, P.J. & Tataronis, G.R. Statin-related adverse events: a meta-analysis. *Clin. Ther.* **28**, 26–35 (2006).
24. Law, M. & Rudnicka, A.R. Statin safety: a systematic review. *Am. J. Cardiol.* **97**, 52C–60C (2006).
25. Armitage, J. The safety of statins in clinical practice. *Lancet* **370**, 1781–1790 (2007).
26. Link, E.P. *et al.* SLCO1B1 variants and statin-induced myopathy: a genomewide study. *N. Engl. J. Med.* **359**, 789–799 (2008).
27. 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**, 210–216 (2011).
28. Puccetti, L., Ciani, F. & Auteri, A. Genetic involvement in statins induced myopathy: preliminary data from an observational case-control study. *Atherosclerosis* **211**, 28–29 (2010).
29. Brunham, L.R. *et al.* Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. *Pharmacogenomics J.* **12**, 233–237 (2012).
30. Ramsey, L.B.J. *et al.* The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced

myopathy: 2014 update. *Clin. Pharmacol. Ther.* **96**, 423–428 (2014).
31. Wilke, R.A. *et al.* The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. *Clin. Pharmacol. Ther.* **92**, 112–117 (2012).
32. Stewart, A. SLCO1B1 polymorphisms and statin-induced myopathy. *PLoS Curr.* **5** (2013).
33. Jansen, M.E. *et al.* Review of the reported measures of clinical validity and clinical utility as arguments for the implementation of pharmacogenetic testing: a case study of statin-induced muscle toxicity. *Front. Pharmacol.* **8**, 555 (2017).
34. Haga, S.B., Mills, R., Moaddeb, J., Allen LaPointe, N., Cho, A. & Ginsburg, G.S. Primary care providers' use of pharmacist support for delivery of pharmacogenetic testing. *Pharmacogenomics* **18**, 359–367 (2017).
35. Haga, S.B., Mills, R., Moaddeb, J., Lapointe, N.A., Cho, A. & Ginsburg, G.S. Patient experiences with pharmacogenetic testing in a primary care setting. *Pharmacogenomics* **17**, 1629–1636 (2016).
36. Haga, S.B. *et al.* Pilot study of pharmacist-assisted delivery of pharmacogenetic testing in a primary care setting. *Pharmacogenomics* **15**, 1677–1686 (2014).
37. Haga, S.B. *et al.* Pilot study: incorporation of pharmacogenetic testing in medication therapy management services. *Pharmacogenomics* **15**, 1729–1737 (2014).
38. Haga, S.B. *et al.* Incorporation of pharmacogenetic testing into medication therapy management. *Pharmacogenomics* **16**, 1931–1941 (2015).
39. Li, J.H.J. *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**, 147–162 (2014).
40. Moaddeb, J., Mills, R. & Haga, S.B. Community pharmacists' experience with pharmacogenetic testing. *J. Am. Pharm. Assoc. (2003)* **55**, 587–594 (2015).
41. Rumyantsev, N.A., Kukes, V.G., Kazakov, R.E., Rumyantsev, A.A. & Sychev, D.A. Use of pharmacogenetic testing to prevent adverse drug reactions during statin therapy. *Ter. Arkh.* **89**, 82–87 (2017).
42. Singh, K. *et al.* Rationale and design of the SLCO1B1 genotype guided statin therapy trial. *Pharmacogenomics* **17**, 1873–1880 (2016).
43. Voora, D. Genetically Guided Statin Therapy. Report AFRL-SA-WP-TR-2017-0005 (Wright-Patterson Air Force Base, OH, 2017).
44. Hussain, S. *et al.* Disease–drug database for pharmacogenomic-based prescribing. *Clin. Pharmacol. Ther.* **100**, 179–190 (2016).
45. Lee, Y.M., McKillip, R.P., Borden, B.A., Klammer, C.E., Ratain, M.J. & O'Donnell, P.H. Assessment of patient perceptions of genomic testing to inform pharmacogenomic implementation. *Pharmacogenet. Genomics* **27**, 179–189 (2017).
46. O'Donnell, P.H. *et al.* The 1200 Patients Project: creating a new medical model system for clinical implementation of pharmacogenomics. *Clin. Pharmacol. Ther.* **92**, 446–449 (2012).
47. O'Donnell, P.H. *et al.* Adoption of a clinical pharmacogenomics implementation program during outpatient care: initial results of the University of Chicago "1,200 Patients Project." *Am. J. Med. Genet. C Semin. Med. Genet.* **166**, 68–75 (2014).
48. O'Donnell, P.H. *et al.* Pharmacogenomics-based point-of-care clinical decision support significantly alters drug prescribing. *Clin. Pharmacol. Ther.* **102**, 859–869 (2017).
49. Shuldiner, A. *et al.* The pharmacogenomics research network translational pharmacogenetics program: overcoming challenges of real-world implementation. *Clin. Pharmacol. Ther.* **94**, 207–210 (2013).
50. Eadon, M. *et al.* Implementation of a pharmacogenomics consult service to support the INGENIOUS trial. *Clin. Pharmacol. Ther.* **100**, 63–66 (2016).
51. Sperber, N.R. *et al.* Challenges and strategies for implementing genomic services in diverse settings: experiences from the Implementing GeNomics In pracTicE (IGNITE) network. *BMC Med. Genomics* **10**, 35 (2017).
52. Vitek, C.R.R. *et al.* Healthcare provider education to support integration of pharmacogenomics in practice: the eMERGE Network experience. *Pharmacogenomics* **18**, 1013–1025 (2017).
53. Bielinski, S.J. *et al.* Preemptive genotyping for personalized medicine: design of the right drug, right dose, right time-using genomic data to individualize treatment protocol. *Mayo Clin. Proc.* **89**, 25–33 (2014).
54. Bielinski, S.J. *et al.* Are patients willing to incur out-of-pocket costs for pharmacogenomic testing? *Pharmacogenomics J.* **17**, 1–3 (2017).
55. Caraballo, P.J. *et al.* Multidisciplinary model to implement pharmacogenomics at the point of care. *Genet. Med.* **19**, 421–429 (2016).
56. Ji, Y. *et al.* Preemptive pharmacogenomic testing for precision medicine: a comprehensive analysis of five actionable pharmacogenomic genes using next-generation DNA sequencing and a customized CYP2D6 genotyping cascade. *J. Mol. Diagn.* **18**, 438–445 (2016).
57. Allen, A.J., Wetmore, J.M., Maturi Allen, M.F. & Talreja, D.R. Evaluation of genetic profiles in medication adjustments. *Cardiology* **134** (suppl. 1), 247 (2016).
58. Gharani, N. *et al.* The Coriell personalized medicine collaborative pharmacogenomics appraisal, evidence scoring and interpretation system. *Genome Med.* **5**, 93 (2013).
59. Mukherjee, C., Sweet, K.M., Luzum, J.A., Abdel-Rasoul, M., Christman, M.F. & Kitzmiller, J.P. Clinical pharmacogenomics: patient perspectives of pharmacogenomic testing and the incidence of actionable test results in a chronic disease cohort. *Per. Med.* **14**, 383–388 (2017).
60. Reynolds, K.K., Pierce, D.L., Weitendorf, F. & Linder, M.W. Avoidable drug-gene conflicts and polypharmacy interactions in patients participating in a personalized medicine program. *Per. Med.* **14**, 221–233 (2017).
61. Saldivar, J.S. *et al.* Initial assessment of the benefits of implementing pharmacogenetics into the medical management of patients in a long-term care facility. *Pharmacogenomics Pers. Med.* **9**, 1–6 (2016).
62. Sturm, A.C., Sweet, K. & Manickam, K. Implementation of a clinical research pharmacogenomics program at an academic medical center: role of the genetics healthcare professional. *Pharmacogenomics* **14**, 703–706 (2013).
63. Sugarman, E.A., Cullors, A., Centeno, J. & Taylor, D. Contribution of pharmacogenetic testing to modeled medication change recommendations in a long-term care population with polypharmacy. *Drugs Aging* **33**, 929–936 (2016).
64. Sweet, K. *et al.* Design and implementation of a randomized controlled trial of genomic counseling for patients with chronic disease. *J. Pers. Med.* **4**, 1–19 (2014).
65. Sweet, K. *et al.* Outcomes of a randomized controlled trial of genomic counseling for patients receiving personalized and actionable complex disease reports. *J. Genet. Couns.* 26, 980–998 (2017).
66. Vassy, J.L. *et al.* The impact of whole-genome sequencing on the primary care and outcomes of healthy adult patients: a pilot randomized trial. *Ann. Intern. Med.* **167**, 159–169 (2017).
67. Vassy, J.L. *et al.* The MedSeq Project: a randomized trial of integrating whole genome sequencing into clinical medicine. *Trials* **15**, 85 (2014).
68. Baigent, C. *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* **366**, 1267–1278 (2005).
69. Whirl-Carrillo, M. *et al.* Pharmacogenomics knowledge for personalized medicine. *Clin. Pharmacol. Ther.* **92**, 414–417 (2012).
70. Sorich, M.J., Coory, M. & Pekarsky, B.A. Indirect estimation of the comparative treatment effect in pharmacogenomic subgroups. *PLoS ONE* **8**, e72256 (2013).
71. Pezalla, E.J. Payer view of personalized medicine. *Am. J. Health Syst. Pharm.* **73**, 2007–2012 (2016).
72. Feero, W.G. Clinical application of whole-genome sequencing: proceed with care. *JAMA* **311**, 1017–1019 (2014).
73. Khoury, M.J. Dealing with the evidence dilemma in genomics and personalized medicine. *Clin. Pharmacol. Ther.* **87**, 635–638 (2010).

74. Pirmohamed, M. *et al.* A randomized trial of genotype-guided dosing of warfarin. *N. Engl. J. Med.* **369**, 2294–2303 (2013).
75. Scott, S.A. *et al.* Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin. Pharmacol. Ther.* **94**, 317–323 (2013).
76. Mathias, P.C., Tarczy-Hornoch, P. & Shirts, B.H. Modeling the costs of clinical decision support for genomic precision medicine. *AMIA Jt. Summits Transl. Sci. Proc.* **2016**, 60–64 (2016).
77. Lamoureux, F. & Duflot, T. Pharmacogenetics in cardiovascular diseases: state of the art and implementation-recommendations of the French National Network of Pharmacogenetics (RNPGx). *Therapie* **72**, 257–267 (2017).
78. Borobia, A.M. *et al.* Ipharmgx project: national collaborative study to evaluate effectiveness and efficiency of pharmacogenetics implementation in the clinical practice. *Basic Clin. Pharmacol. Toxicol.* **119** (suppl. 1), 32 (2016).
79. Gottesman, O.S. *et al.* The CLIPMERGE PGx program: clinical implementation of personalized medicine through electronic health records and genomics-pharmacogenomics. *Clin. Pharmacol. Ther.* **94**, 214–217 (2013).
80. Sissung, T.M. *et al.* Pharmacogenomics implementation at the National Institutes of Health Clinical Center. *J. Clin. Pharmacol.* **57**, S67–S77 (2017).
81. Weitzel, K.W. *et al.* Clinical pharmacogenetics implementation: approaches, successes, and challenges. *Am. J. Med. Genet. C Semin. Med. Genet.* 56–67 (2014).
82. Christensen, K.D. *et al.* Disclosing pleiotropic effects during genetic risk assessment for Alzheimer disease: a randomized trial. *Ann. Intern. Med.* **164**, 155–163 (2016).
83. Chua, E.W. & Kennedy, M.A. Current state and future prospects of direct-to-consumer pharmacogenetics. *Front Pharmacol* **3**, 152 (2012).
84. Friedman, L.M., Furberg, C.D. & DeMets, D.L. Basic study design. In *Fundametnals of Clinical Trials 4th edn.*, 67–96 (Springer, New York, 2010).
85. Wells, G. *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. <http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp> (2014). Accessed 18 April 2018.
86. Jadad, A.R. *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control. Clin. Trials* **17**, 1–12 (1996).