Impact of SLC01B1 Pharmacogenetic Testing on Patient and Healthcare Outcomes: A Systematic Review

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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 (SLCO1B1) and statin-associated muscle symptoms (SAMSs) as a model, we conducted a systematic review of patient outcomes after delivery of SLCO1B1 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 SLCO1B1 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 SLCO1B1 testing among previously statin intolerant patients. Evidence from large implementation projects suggests that SLCO1B1 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 SLCO1B1 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.1-4 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.5 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 dose6-8 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 weakness21,22 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.27 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,32,33 but none has reviewed the prospective outcomes of integrating SLCO1B1 genotype

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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, all but one of which were conducted by investigators at Duke University. 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. 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. 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, 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.

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; INdiana GENomics Implementation: an Opportunity for the UnderServed (INGENIOUS); the Marshfield Clinic; and the RIGHT protocol) and one from La Paz University Hospital in Spain. 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 and one pilot RCT of genome sequencing.

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 Figure 1.
### Table 1 Characteristics of eligible studies

<table>
<thead>
<tr>
<th>Study/institution</th>
<th>Design (country)</th>
<th>Population (n)</th>
<th>Genotype(s) reported</th>
<th>Experimental intervention</th>
<th>Decision support</th>
<th>Control group (n)</th>
</tr>
</thead>
</table>
| 1,200 Patients Project 1,4-49 | 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, KIR6, LDR, 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, CYP2D6, CYP3A4/CYP3A5, F2, F5, HTR2A, HTR2C, MTHFR, OPR1, SLC6A2, SLC6A4, SLC6A8, 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 | 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 | 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 | 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 | — | — |

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| Duke University 4[34-36]                          | Nonrandomized trial     | 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| Patients not currently taking statins because of a history of an adverse effect, ineligible if prior rhabdomyolysis or CK >10x ULN (187) | SLC01B1                                                                              | • Genotyping at a research visit  
• Patients and their physicians received PGx results by email  
|                                                  |                         |                                                                                 |                                                                                       |                                                                                       |                                                                                       |                  |
| First Moscow State Medical University[41]         | Intervention study      | Patients with hyperlipidemia already receiving statin therapy (35)             | SLC01B1                                                                              |                                                                                       | Patient does not undergo genotyping (4,000 planned)                                  | —                |
| INdiana GENomics Implementation: an Opportunity for the UnderServed (INGENIOUS)[6,13,50,51] | Randomized control trial | Safety-net hospital system of 10 clinics with common EHR (2,000 planned)       | CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP4F2, DPYD, G6PD, IFNL3, ITPA, SLC01B1, 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. |                  |
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<tbody>
<tr>
<td>La Paz University Hospital&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Intervention study (Spain)</td>
<td>Patients receiving specialty care at a tertiary care teaching hospital (&lt;strong&gt;600&lt;/strong&gt;)</td>
<td>ABCB1, ABC2, ABCG2, APOE, CDMT, CFTR, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, DPYD, ERCC1, EPHA1, FGFR2A, HTR2A, IL10, IL23R, KCNJ6, MTHFR, POR, SLC15A2, SLC22A1, SLC22A2, SLC22A6, SLC01B1, TLR2, TLR9, TNF, TP53, TPM7, UGT1A1, UGT2B7, VKORC1, XPC, XRCC1</td>
<td>Providers request testing from PGx unit, which generates report according to prespecified drug–gene protocol or after PGx consultation</td>
<td>Recommendation from PGx unit, on the basis of CPIC and DPWG reviews</td>
<td>—</td>
</tr>
<tr>
<td>Marshfield Clinic&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Intervention study (United States)</td>
<td>Adults aged ≥50 years with healthcare system primary care physician and no prior use of simvastatin, warfarin, or clopidogrel (&lt;strong&gt;750 planned&lt;/strong&gt;)</td>
<td>CYP2C9, CYP2C19, SLC01B1, VKORC1</td>
<td>• Providers receive PGx results &lt;br&gt;• Patients have access to website with information about their PGx results</td>
<td>Active CDS alerts with CPIC dosing recommendation triggered by prescription in EHR</td>
<td>—</td>
</tr>
<tr>
<td>MedSeq Project&lt;sup&gt;66,67&lt;/sup&gt;</td>
<td>Randomized control trial (United States)</td>
<td>Generally healthy adult primary care patients (&lt;strong&gt;100&lt;/strong&gt;)</td>
<td>Genome sequencing, including monogenic disease variants, carrier status, eight polygenic risks, and five PGx results: ABCB1, C11orf65, CYP2C9/VKORC1, CYP2C19, SLC01B1</td>
<td>Patients discussed interpreted genome report and family history pedigree with physician</td>
<td>Report included statement about simvastatin-associated myopathy risk</td>
<td>Patients discussed family history pedigree alone with physician</td>
</tr>
<tr>
<td>OSU–Coriell Personalized Medicine Collaborative&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Intervention study (United States)</td>
<td>Participants with heart failure and hypertension enrolled in RCT of genomic counseling for polygenic risk estimates and CYP2C19 (&lt;strong&gt;208&lt;/strong&gt;)</td>
<td>Polygenic risk estimates for eight diseases plus PGx results for CYP2C9, VKORC1, CYP4F2, CYP2C19, SLC01B1</td>
<td>• Patients received genetic reports by mail and by patient Web portal &lt;br&gt;• Reports also uploaded to EHR &lt;br&gt;• Half of patients were randomly allocated to in-person genomic counseling; half could access a genetic counselor by telephone if requested</td>
<td>Reports to patients and in EHR included CPIC recommendations</td>
<td>—</td>
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</table>

Table 1 (Continued)
<table>
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<th>Control group (n)</th>
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</thead>
<tbody>
<tr>
<td><strong>PRIMER</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Intervention study (United States)</td>
<td>Patients of 27 providers with likelihood of exposure to a relevant medication (&lt;sup&gt;705&lt;/sup&gt;)</td>
<td>COMT, CYP2D6, CYP2C19, CYP2C9, CYP1A2, CYP3A4, CYP3A5, F2, F5, MTHFR, OPRM1, <strong>SLCO1B1</strong>, SLC6A4, VKORC1</td>
<td>Providers ordered PGx panel testing and received report</td>
<td>Report with drug–drug and drug–gene interactions categorized as contraindicated, major, moderate, or minor, some with explanatory annotations</td>
<td>—</td>
</tr>
<tr>
<td><strong>RIGHT Protocol</strong>&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>Intervention study (United States)</td>
<td>Health system patients, including biobank participants, likely to initiate statin treatment within 3 years (&lt;sup&gt;3,788&lt;/sup&gt;)</td>
<td>CYP2C9, CYP2C19, CYP2D6, HLA-B<em>1502, HLA-B</em>5701, <strong>SLCO1B1</strong>, TPMT, VKORC1</td>
<td>Preemptive genotyping, with results available to provider in EHR and to patients through patient portal</td>
<td>Active CDS</td>
<td>—</td>
</tr>
<tr>
<td><strong>Yale University</strong>&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Intervention study (United States)</td>
<td>Series of consecutive high-risk cardiovascular patients (&lt;sup&gt;32&lt;/sup&gt;)</td>
<td>CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, F2, F5, MTHFR, <strong>SLCO1B1</strong>, VKORC1</td>
<td>Results reported to clinicians</td>
<td>Not specified</td>
<td>—</td>
</tr>
</tbody>
</table>

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.

<sup>a</sup>Part of the Pharmacogenomics Research Network Translational Pharmacogenetics Program.<sup>11</sup>

<sup>b</sup>Part of the Implementing Genomics in Practice (IGNITE) Consortium.<sup>13</sup>

<sup>c</sup>Part of the Electronic Medical Records and Genomics (eMERGE)–PGx Consortium.<sup>12</sup>
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 ($-12 \pm 45$ mg/dl) compared with concurrent controls ($6 \pm 38$ mg/dl; $P = 0.06$) after 1 year. 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; $P = 0.07$). 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. Other studies of pharmacogenetic testing have made general qualitative statements that no participants experienced medication adverse effects during the observation periods. 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. The clinical pharmacogenetic service in Spain cost the national health system €202,140 over 3 years, with the cost of each consultation averaging €216. 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. 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. 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

<table>
<thead>
<tr>
<th>Study/institution</th>
<th>Utility outcomes</th>
<th>Process outcomes</th>
<th>Other patient-reported outcomes</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1200 Patients Project</strong>&lt;sup&gt;41,44–49&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
<td>- Among 868 patients over 3 years, CDS influenced simvastatin discontinuation in 8 cases</td>
</tr>
<tr>
<td><strong>AltheaDx</strong>&lt;sup&gt;61,63&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>- 54 (48%) of 112 patients had one or more medication change</td>
</tr>
<tr>
<td><strong>Duke University 1</strong>&lt;sup&gt;39&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>- 47% vs. 15% of intervention vs. control patients taking statin after 4 months (&lt;i&gt;P&lt;/i&gt; = 0.001) - 1-year LDL-C reduction −12 ± 45 mg/dl in invention group vs. 6 ± 38 mg/dl in controls (&lt;i&gt;P&lt;/i&gt; = 0.06)</td>
</tr>
<tr>
<td><strong>Duke University 2</strong>&lt;sup&gt;50&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>- No prescription changes observed</td>
</tr>
<tr>
<td><strong>Duke University 3</strong>&lt;sup&gt;37,38&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>- 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</td>
</tr>
<tr>
<td><strong>Duke University 4</strong>&lt;sup&gt;34–36&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>- Providers consulted pharmacist for 15 cases, averaging 5.7 minutes per consult - 1/63 patients tested had simvastatin dose halved because of <em>SLCO1B1</em>&lt;sup&gt;∗&lt;/sup&gt;5 result</td>
</tr>
<tr>
<td><strong>Duke University 5</strong>&lt;sup&gt;42,43&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>- LDL-C lower in the intervention group vs. controls at 3 months (132 ± 42 vs. 144 ± 43 mg/dl; &lt;i&gt;P&lt;/i&gt; = 0.04) but not 8 months (129 ± 38 vs. 141 ± 44 mg/dl; &lt;i&gt;P&lt;/i&gt; = 0.07) - No between-group differences in pain or quality of life</td>
</tr>
<tr>
<td><strong>First Moscow State Medical University</strong>&lt;sup&gt;41&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>- No medication adverse effects reported</td>
</tr>
<tr>
<td><strong>INdiana GENomics Implementation: an Opportunity for the UnderServed (INGENIOUS)</strong>&lt;sup&gt;61,50,51&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>- Genotyping prompted PGx consultations for 10 (9%) of 106 patients</td>
</tr>
<tr>
<td><strong>La Paz University Hospital</strong>&lt;sup&gt;10&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>- Clinical PGx service cost €202,140 over 3 years, with each consult averaging €216</td>
</tr>
<tr>
<td><strong>Marshfield Clinic</strong>&lt;sup&gt;12,52&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>- Simvastatin prescriptions have triggered five CDS alerts over 3 years, prompting one medication change</td>
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(Continues)
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. 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, $1,490 vs. $1,142, excluding the costs of sequencing and interpretation).

**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. 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. Approximately one third of patients’ active medications had associated pharmacogenetic alerts (0.5% red, 13% yellow, and 21% green); 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. 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. Studies surveying providers about their experiences have reported overall positive attitudes about pharmacogenetics, including its clinical relevance and impact on management, 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, whereas small pilot studies have reported specific cases where \( SLCO1B1 \) results guided therapy. 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

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**Table 2 (Continued)**

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<tr>
<th>Study/institution</th>
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<tbody>
<tr>
<td>MedSeq Project(^{66,67})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>OSU–Coriell Personalized Medicine Collaborative(^{41,49,58,59,62,64,65})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>• Mean patient willingness to pay for clinical PGx service was $56 ($81).</td>
</tr>
<tr>
<td>PRIMER(^{50})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>• 42% of patients not willing to pay out-of-pocket costs for PGx tests; 58% of remainder reported willingness to pay of $100</td>
</tr>
<tr>
<td>RIGHT Protocol(^{8,11,12,53–56})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>• No medication adverse effects reported</td>
</tr>
<tr>
<td>Yale University(^{57})</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>• No medication adverse effects reported</td>
</tr>
</tbody>
</table>

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.\(^{12}\)
changes influenced by CDS (69%), although this represented only eight simvastatin discontinuations in SLC01B1 C carriers among 868 patients.38 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 SLC01B1*5 results.39 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 SLC01B1 results, compared with 20% of concurrent controls with statin prescriptions after 1 year (P < 0.001).39 In the subsequent RCT, more participants receiving SLC01B1 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).45

Medication adherence: Although prescriptions largely reflect provider behavior, medication adherence is a patient behavior. Small pilot studies have either found no impact of SLC01B1 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.45 The authors reported that intervention patients perceived higher necessity of their medications than control patients at 3 months, but not at 8 months,45 consistent with observations from the pilot study.39

Other patient-reported outcomes: Uncontrolled studies have reported that some patients had difficulty recalling their specific SLC01B1 results35,38 and had variable understanding of them.10,40,56 Nonetheless, patients generally perceived the information as useful to their providers.35,38,54,55 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 SLC01B1 and SAMs,26 we found few high-quality studies reporting patient outcomes after the delivery of SLC01B1 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 SLC01B1 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.65 Apart from this, although the proposed benefit of SLC01B1 testing is the avoidance of SAMs, it is worth noting that no study has empirically demonstrated this outcome or the impact of SLC01B1 testing on CVD events. Evidence from small pilot studies and large healthcare system implementation projects does suggest that SLC01B1 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 SLC01B1 CDS in the EHR has been small. Receipt of SLC01B1 test results seems generally well tolerated by providers and patients. No study has specifically tracked the economic impact of SLC01B1 testing and its downstream outcomes.

The clinical validity of the SLC01B1-SAMS association has been well established (i.e., the observed association between rs4149056 in SLC01B1 and statin-associated myotoxicity of varying severity has been replicated in numerous studies, particularly for simvastatin).30 The PharmGKB knowledge rate rates the genotype–phenotype association between SLC01B1 and simvastatin myopathy as having the highest level of evidence (level 1A).69 On the other hand, the clinical utility of SLC01B1 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 SLC01B1 results,33 and Sorich and colleagues found no studies of the cost-effectiveness of SLC01B1 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.71 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 testing72 and many clinicians reluctant to incorporate pharmacogenetics into their practices.72

Our review of patient outcomes after SLC01B1 testing prompts the following recommendations for future research. First, although RCT evidence may not be necessary to justify every clinical application of pharmacogenetic testing,71,73,74 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 SLC01B1 for statins and cytochrome P450 family 2 subfamily C member 19 (CYP2C19) for clopidogrel.73 Few studies using panels in our review reported outcomes pertaining to SLC01B1 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. 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. Further research should examine the clinical utility of SLCO1B1 testing among statin-naive 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. Most of these represent multi-institutional efforts, such as the Electronic Medical Records and Genomics (eMERGE)–PGx Consortium, the Pharmacogenomics Research Network Translational Pharmacogenetics Program (TPP), the Implementing Genomics in Practice (IGNITE) Consortium, and the seven-country Ubiquitous Pharmacogenomics (U-PGx) Consortium. 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. 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. 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.
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. 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. For the RCTs, the Jadad scale 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

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CONFLICT OF INTEREST
The authors declared no competing interests for this work.

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