Editorial Commentary

Pharmacogenetic screening in a knowledge-based economy: shouldn't more be better?

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Much human capital has been devoted to describing the ontological journey associated with the technology revolution. We are now in the midst of the digital era within a knowledge-based economy, where information accessibility and synthesis drives market-innovation (1). Our knowledge-based economy has facilitated the democratization of healthcare, where data and information can be used to empower individuals to help make medical decisions and improve self-management. It would stand to reason then, as it pertains to health information, 'more' should be 'better'.

It is with this context that a study published in the *Journal of the American Medical Association* by Vassy and colleagues entitled, "*The effect of pharmacogenetic testing for statin myopathy risk vs. usual care on blood cholesterol*", deserves interest (2). This randomized clinical non-inferiority trial comprising eight primary care practices and 408 patients from the Veterans Affairs Boston Healthcare system, sought to determine the impact of disclosing SLCO1B1 pharmacogenetic test results on guideline care statin-naïve patients with elevated cardiovascular risk between December 2015 and July 2019. One-year changes in low-density lipoprotein (LDL) Cholesterol levels served as the study's primary outcome, while concordance with American College of Cardiology-American Heart Association and Clinical Pharmcogenetics Implementation Consortium (CPIC) guidelines for statin therapy and effectiveness served as secondary outcomes.

In total 120 participants (29% of the entire clinical trial sample) had a SLCO1B1 genotype indicating increased simvastatin myopathy risk. The study demonstrated no significant differences in the offering of statin therapy between the intervention group and controls (33.7% *vs.* 32.1%, intervention *vs.* controls, respectively). Patients whose physicians had knowledge of the SLCO1B1 results at baseline had noninferior reductions in LDL-C at 12 months [−1.1 *vs.* −2.2 mg/dL reduction in the intervention *vs.* control group respectively, (P<0.001) for noninferiority margin of 10 mg/dL]. Similarly, guideline concordant statin prescribing was non-inferior among the intervention group as compared with the control, and all patients in both groups were concordant with CPIC guidelines for safe statin prescribing. Among those with the SLCO1B1 transporter function genotype, only one control patient (and no intervention patient) was prescribed Simvastatin. The incidence of statin-induced myopathy was similarly rare in both groups. The authors conclude that non-inferiority in LDL cholesterol and concordance with guideline-driven statin care should provide stakeholders contemplating the clinical use of available pharmacogenetic results reassurance that such information does not yield excess harm in medical management outcomes.

Notwithstanding evidence supporting the public's desire for wider accessibility of genomic information, concerns have been raised. For example, in a recent nationwide poll conducted by the Associated Press-NORC Center for Public Affairs Research in 2018 involving 1,109 adults at the University of Chicago, the majority of those surveyed

acknowledged either having already undergone, or, are interested in receiving genetic testing information as part of routine screening or surveillance. Yet, responses varied as to which stakeholders should and should not have access to such information. Nearly half of the respondents were extremely concerned or very concerned that for-profit DNA testing companies, medical researchers, and/or medical doctors might undermine the privacy and confidentiality of such data and share such genetic information without consent, to other stakeholders who may not necessarily comprise the immediate circle of care (3). In short, the concerns over data-security and confidentiality have attenuated enthusiasm around pharmacogenetic testing.

Another issue of public concern relates to the lack of evaluation and outcomes associated with pharmacogenetic testing. For example, the US Food and Drug Administration (FDA) has taken a cautious approach to pharmacogenetic surveillance and have issued warnings to laboratories to stop marketing certain pharmacogenetic tests that have not yet been reviewed for safety and effectiveness, due to potential unintended negative consequences on shared medical decision-making. In such circumstances, misleading or erroneous test results could lead to incorrect treatment decisions with errors of omission or commission, leading to adverse health outcome consequences as a result (4,5).

In short, as it pertains to pharmacogenetic screening some have contended that 'more' may not be 'better'. How then do we reconcile such perspectives against those drawn from the aforementioned clinical trial by Vassy and colleagues?

Several issues must be considered:

First, both perspectives may be true. For example, it is theoretically possible that a positive pharmacogenetic SLCO1B1 screening test for some patients may have inadvertently increased their hesitancy to all statins regardless of type, for fear of a genetic predisposition to statin induced myopathies in general. Yet, that same positive SLCO1B1 pharmacogenetic test may have provided reassurances to others, given that they would have likely been prescribed non-simvastatin class-specific alternates and followed more closely because of their positive test result. The net effect on patient outcomes may have been similarities in overall LDL cholesterols between the intervention group and controls, given that LDL cholesterol levels were aggregated over the entire sample. Second, it is possible that the conclusions drawn by Vassy and colleagues may not necessarily be generalizable to other pharmacogenetic screening tests. For example, Vassy examined a pharmacogenetic marker that screened for simvastatin associated myopathy. Simvastatin is only one of several available statins. In their trial, it is almost certain that substitute statins were prescribed explicitly because patients screened positive for the *SLCO1B1* gene. Third, there are widely available biomarkers, such as Creatine Kinase (CK), which can be used to monitor patients for rhabdomyolysis, regardless of whether patients screened positive or negative for SLCO1B1. Fourth, despite the potential life-threatening complication, statin-induced myopathy is still a rare event; the cardioprotective benefits associated with statins may still favour aggressive LDL cholesterol targets using alternative higher-intensity and/or higher dose statins (with or without the addition of Ezetimibe) even where positivity for SLCO1B1 exists. Fifth, Vassy and colleagues drew conclusions based on outcomes of LDL cholesterol levels and concordance with treatment guidelines. However, in reality, many factors unrelated to the feedback of pharmacogenetic testing may have accounted for the similarity in outcomes between the two groups. For example, baseline prescribing behaviours were never accounted for in the study. Moreover, patient adherence to statins and/or healthy lifestyle behaviours may have been the dominating factor that accounted for LDL cholesterol levels more so than the feedback of pharmacogenetic information.

In sum, while non-inferior outcomes in the attainment of LDL cholesterol levels were observed among physicians randomized to receiving patient's SLCO1B1 genetic markers, the authors' conclusions of reassurance and "no-harm" may neither negate concerns over data privacy and medical decision-making, nor be applicable to other pharmacogenetic screening tests that have yet to be examined.

Even if their results were generalizable to other pharmacogenetic screening, one could argue that the most significant limitation associated with the study by Vassy and colleagues related to their lack of process evaluation. Specifically, no information was provided on how pharmacogenetic test results were communicated to patients and how such communication impacted on shared medical decision-making between patients and providers. In their study, only 15% of physicians randomized to the intervention group documented any communication of SLCO1B1 test results to their patients. Among those who did document some communication to patients, details of such discussions were not provided. Moreover, the study provided no insights into how such communication

may have impacted on patient statin-taking hesitancy and/or fears. Such study limitations underscore missed-opportunities in pharmacogenetic testing research.

Such limitations are not unique to Vassy's study. Available evidence has demonstrated that physicians often lack knowledge, expertise, skill, or time to adequately engage in comprehensive discussions pertaining to genetic screening and medical decision-making (6). Such communication gaps may be attributable to physicians' lack of confidence in forecasting treatment implications and potential legal, ethical, and social ramifications associated with genetic screening results themselves, in the face of medical uncertainty (6-9). While interactive web-based decision aids have been shown to improve physician knowledge, confidence, and communication skills related to genetic testing, the impact of such tools on shared decision-making behaviour within real-world clinical settings have been met with disappointing results (10). Addressing such communication gaps may necessitate broader support systems for both physicians and patients.

Unquestionably, Vassy and colleagues provide an important contribution to the medical literature. However, if their study is to inform future pharmacogenetic evaluations, outcomes must focus more on the process of communication and how such information impacts on shared medical decision-making between physicians and their patients. The understanding of the communication process, and their resultant risks, benefits, opportunities and challenges will ultimately allow the medical community to optimize the use of technology in a knowledge-based economy. Once accomplished, "more will be better"—pharmacogenetic screening being no exception.

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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