Genetics for Monitoring Prescription Practices of Commonly Used Drugs in Populations

Daniel I. Chasman*

High-throughput genotyping, the rapid determination of genetic information on an individual basis, is unquestionably one of the most important recent technological developments for medical research and diagnosis and holds the promise of leveraging the human genome sequence for dramatic improvements in healthcare. In research, one gain from high-throughput genotyping is the ongoing dissection of clinical traits that are both prognostic for disease and the targets for therapy, e.g., LDL cholesterol (LDL-C)\(^2\) (1). In summary, these studies have found that a large number of common genetic polymorphisms appear to contribute to heritable clinical traits such as LDL-C concentration, with each polymorphism explaining a small fraction of the variance, typically <1%. In addition, the multitude of genetic associations highlights the diversity of biological pathways that contribute to each clinical trait. Among the largest common genetic effects, the E2 and E4 alleles of the APOE (apolipoprotein E) gene are associated with a shift of approximately −0.4 mmol/L and 0.1 mmol/L, respectively, in LDL-C concentration, compared with the E3 allele (2). With minor-allele frequencies of approximately 7%–9% (E2) (3) and 14%–15% (E4) (4) in populations of European ancestry, the APOE variants explain a few percent of the variance on a population basis.

Even effects as large as those observed for the APOE alleles, however, present challenges for translating the newly discovered genetic associations to the clinic. On an individual basis, the incremental prognostic information provided by single common genetic variants is typically small, often smaller than the information gained by examining readily available clinical correlations. This observation has been especially true with respect to predicting future disease, for which easily ascertained clinical characteristics (e.g., age, diet, exercise, body mass index, smoking status, or family medical history) have been more prognostically useful than genotype (5). Some gains have been made by aggregating combinations of genetic variants into predictive scores, but these approaches have been useful mostly for explaining the extremes of clinical characteristics (1). Thus, a more general application for translating genotype information into the clinical setting may arise in the context of populations, for which even small differences may be compounded into large societal benefits.

In this issue of Clinical Chemistry (4), Davies et al. propose one such population-based application, which is aimed at tracking prescribing practices of commonly used drugs that alter (usually decrease) clinical risk factors that are influenced in part by genetic variation. The authors note some unique properties of genetic variation: (a) It is essentially allocated at random at conception; (b) it is typically not ascertained before and thus not involved in the decision to begin therapy, and is therefore free of bias; (c) it is essentially immutable over the course of a lifetime; and (d) its effects on a clinical characteristic of interest are stable over time, or at least vary predictably. If a drug were to lower a clinical risk factor that is influenced by a genetic variant, then examining the genotype frequencies in treated and untreated individuals in the population might be informative about the threshold for which the drug was prescribed. Specifically, the authors construct a genotype ratio treatment index (GRTI), a quotient of the proportions of treated and untreated individuals for 2 genotypes of a genetic variant that is associated with a clinical risk factor. With a few additional assumptions, computing the GRTI for a genotyped population may be used to “backcalculate” the threshold at which the drug was prescribed, in some average sense.

The authors apply the GRTI to genetic variation in the APOE gene for the situation of the statin-prescribing threshold of LDL-C. Comparing the E3/E2 and the E3/E4 genotypes to the E3/E3 genotype, the authors compute the GRTI for statin treatment for a population of British women and for subgroups within this population. The authors infer that statin was prescribed at a threshold of 5.3 mmol/L LDL-C (205 mg/dL) in the full sample. They also infer no significant differences between northern England and Scotland in prescribing practices and no differences by social class considered as a binary variable. Consistent with expectations,
GRTI-inferred prescribing thresholds of LDL-C were significantly lower among women with coronary heart disease, compared with those who were disease free [4.39 mmol/L vs 5.65 mmol/L (170 mg/dL vs 218 mg/dL)], as well as for women who ever smoked compared with those who never smoked [5.10 mmol/L vs 5.47 mmol/L (197 mg/dL vs 211 mg/dL)].

The authors acknowledge that their exploration of the GRTI for statin use represents a proof of principle requiring further development, yet the underlying methodologic assumptions are sufficiently constricting that the proposal may have limited utility. One class of criticism is related to the small size of the effects of the common genetic variants. In estimating treatment threshold from the GRTI, the small genetic effects manifest as large confidence intervals, which require large populations for precision, much larger than may be available today for investigating prescribing practices. In response, the authors suggest that every individual in a population will be genotyped in the future, a conjecture that remains highly speculative. It may be equally likely to expect that LDL-C measurement will be similarly widespread in the future, a development that would obviate the genetic test. To boost the genetic signal, the authors propose using the aggregated effects of multiple genetic variants, for example the 95 loci recently reported to be associated with lipid fractions (1); however, such multifactorial biological pathways represented in a complex genetic score raise very serious complications related to potential confounding effects and/or interactions with the environment. The authors propose models that would anticipate these nongenetic factors. These models abandon the simplicity of genetic testing, however, and there may be additional difficulties in accurately ascertaining these clinical characteristics retrospectively to the initiation of statin treatment. For example, the impact of one of the clinical factors, age, may even introduce a survival bias on genotype frequencies that is difficult to model, and the authors’ analysis does not explicitly address the possibility that the clinical characteristics alone might be more precise indicators of prescription threshold than genotype information alone. Finally, the possible existence of multiple prescribing thresholds will further erode the precision of inferring prescription patterns and the interpretation of an “average” estimate, such as that provided by the GRTI. This predicament is the case for statin therapy, for which the presence of a family history of cardiovascular disease and smoking may recommend statin therapy at lower thresholds of LDL-C. Multiple thresholds may also arise from idiosyncratic deviations from prescription guidelines, practices that are tolerated for statins because of their very low incidence of adverse effects.

Nevertheless, it may be useful to contemplate the potential benefits of the proposal aside from the technical issues, especially as genotyping a single or a few genetic variants becomes increasingly economical. One can imagine that surveillance of prescribing practices could influence the efficacy of disease prevention (6), cardiovascular disease in this case. Similarly, the cost–benefit consequences of drug-prescribing practices at the population level might be understood through monitoring drug use (7), for example in rural settings where healthcare may not be centralized. Presumably, such examples of applications are what the authors have in mind, although, regrettably, they do not explicitly discuss the ramifications of the GRTI beyond the inference of prescribing thresholds.

In any of the preceding scenarios, and probably others, the ultimate issue is whether the genotype is more accessible and informative about prescription practices than clinical data recorded in conjunction with the initiation of therapy. Unless statins or other widely prescribed drugs come to be administered in the absence of any accompanying consultation at all, it seems unlikely that genotype will supersede information available in medical records for retrospectively investigating the circumstances that trigger the initiation of therapy. Even a sampling of pre-statin LDL-C measurements among statin users in a population may give a more precise estimate of prescribing practices than population-wide genotype information. Moreover, the same LDL-C measurements could be used to evaluate the outcome of therapy directly, which is not currently possible with the APOE or any other genetic variation. In imagining the future of healthcare, access to medical-record data may ultimately be more useful, both for reviewing an individual’s course of treatment and for understanding the population trends related to the clinical traits that are eligible for GRTI, than genotyping of a few common variants whose utility may be limited to imprecise estimates of the population trends alone.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: None declared.
Stock Ownership: None declared.
Honoraria: None declared.

Clinical Chemistry 57:3 (2011) 367
Research Funding: Funding from AstraZeneca related to genetics of statin response.

Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

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