Clinical Chemistry 59:4
592–594 (2013)

Pharm-Econogenomics: A New Appraisal

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Pharmacogenomics is poised to radically alter the way drugs are designed, developed, and prescribed. Given that much of the variation in drug response can be attributed to genetic differences, tailoring drugs to an individual's unique genetic signature provides the opportunity to reduce adverse drug events, improve drug efficacy, optimize trial design, and prevent costly drug recalls *(1)*. Developing pharmacogenomic strategies to address these issues is critical, given that lack of efficacy and adverse drug events cost the US well over $100 billion annually and that the overall cost for developing a single drug now exceeds $1 billion *(2–4)*.

Although genomewide association studies have identified, in general, common sequence variants with increased risks in susceptibility of only 10%–20%, the odds ratios for major side effects or drug responsiveness have been exceptionally large, such as 3- to 20-fold (an increase in risk of 300% to 2000%). This large difference is likely attributable to the fact that humans have been exposed, in evolutionary terms, to most drugs only for a relatively short period of time and that limited genetic selection pressures have been applied *(4)*. Accordingly, exploiting the marked interaction of the genome with drug response represents an exceptional opportunity to enhance the precision and lower the costs of prescription medications. This opportunity has been enhanced by the plummeting cost of sequencing and the recent precedents of accelerated regulatory drug approvals for breakthrough medications developed with genomic guidance *(5)*. Although pharmacogenomics offers the prospect of distinct improvements in drug development and utilization, it is appropriate to ask whether this approach will be cost-effective.

In this issue of *Clinical Chemistry*, Arnaout et al. describe a cost-effectiveness analysis of the costs and time scales involved in the discovery of pharmacogenomic variants, their validation, and their incorporation into future clinical guidelines *(3)*. A selection of 8 currently approved drugs—including warfarin, clopidogrel, statins, and carbamazepine—that already have evidence for pharmacogenomic guidance was the basis of a quantitative model designed to simulate future time scales and development costs for a set of hypothetical drugs. Cost calculations were based on factors that included cost per genomic association, number of associations per adverse outcome, and estimates of costs to produce a clinical guideline based on the previously selected prescription drugs. Calculations of time-scale parameters were based on the time from variant discovery to inclusion in a set of validated clinical guidelines. Given estimates that up to 83% of adverse drug events are nonpreventable and therefore potentially genetic in origin, a value of 60% was chosen as an estimate of the potential reduction in the incidence of adverse drug events. Simulations were run for each hypothetical drug to estimate the time and costs to discover, validate, and produce a validated guideline for reducing an adverse event. This process was repeated until adverse events for that particular drug were reduced by at least 50%. It is interesting that the single greatest determinant of total cost was the extent to which genomic variants influenced the likelihood of an adverse drug event—a component that is likely only to improve over time. The authors estimate that an overall reduction in adverse events by 25% to 50%, would require an investment in the single-digit billions of dollars for a period of up to 20 years *(3)*.

Arnaout et al. have addressed hypothetically the issue of costs associated with pharmacogenomic drug development. As they acknowledge, there is considerable variation and uncertainty associated with their model. We believe that the projected worst-case scenario of a cost of up to $6 billion over 20 years is justifiable, given the pharmaceutical costs of misdirected therapies of >$100 billion in the US alone, whether for engendering noxious side effects or for lack of efficacy in patients *(4)*. Pharmacogenomics is ideally positioned to address such wasted costs and potentially avoidable adverse effects of drugs. Our belief is that all future drug development will be genomically or biomarker (including biosensor) guided and that its large-scale adoption will lead to more efficacious and safer drugs that are delivered at considerably lower costs.

The question of pharmacogenomic cost-effectiveness has previously been addressed with respect to other prescription medications, such as warfarin, but such studies suffer, as do the calculations by Arnaout et al.,

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Received January 21, 2013; accepted January 24, 2013.
Previously published online at DOI: 10.1373/clinchem.2012.200386

from the distortion arising from using historical data alone. Warfarin dosing was deemed cost-ineffective on the basis of quality-adjusted life-year costs of >$170 000. It is important to note, however, that the primary determinant of this figure was the genotyping cost of $400 per patient, a cost that is now on the order of pennies. If the study were performed today, the quality-adjusted life-year costs would be only a fraction of those of the original calculation. Second, genotyping can now be routinely performed at the point of care, in a matter of minutes, whereas the mean turnaround time for genotyping in the warfarin study was 3 to 5 days in a central laboratory *(6, 7)*.

Additionally, cheaper whole-genome and whole-exome sequencing will facilitate a transition away from the more narrow focus of common sequence variants (via genomewide association studies) to the lower-frequency and rare variants that have even more pronounced impacts. This integration of genetic information may not be facilitated via DNA sequence variants alone but is likely to be delivered by an integrated panel of transcriptomic, metabolomic, proteomic, and epigenomic data. For example, recent evidence suggests that epigenomic methylation changes may guide drug choice for patients with rheumatoid arthritis *(8)*.

Although the majority of the data on pharmacogenomics has been retrospectively collected for drugs that are currently approved, even greater benefits could be achieved if it were applied to earlier phases of drug development in efforts to reduce trial costs and duration. This strategy of genomic trial enrichment, now encouraged by the US Food and Drug Administration (FDA)[3], has already demonstrated considerable success with the genomically guided trials of the use of HER2 (human epidermal growth factor receptor 2) positivity status for selecting trastuzumab-suitable patients with breast cancer and with the use of *BRAF* (v-raf murine sarcoma viral oncogene homolog B1) gene mutations to identify melanoma patients appropriate for vemurafenib therapy *(9, 10)*. Notably, the use of such therapies as trastuzumab for HER2-positive patients not only allows patients with the greatest likelihood of response to receive the drug but also, importantly, prevents patients who are unlikely to respond from being exposed to its potential cardiotoxic side effects. Many companies in the life science industry are now developing genomic companion diagnostics in parallel with their active drugs to facilitate drug approval *(9)*.

[3] Nonstandard abbreviations: FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2.

The benefits of such an approach were demonstrated in the pivotal phase 3 randomized control trial of ivacaftor, a drug used to treat a genomically distinct group of cystic fibrosis patients. The trial was conducted in only 48 weeks and with as few as 167 patients *(5)*. Another example of pursuing this strategy of genomically guided trials is everolimus, a newer mTOR inhibitor, which in only 4 years has been approved for 5 separate indications. Several more indications are expected in the near future *(11)*. Because such trials are being conducted over such short time periods, require fewer patients, and yield far more drug approvals, their costs will be miniscule compared with the expenses of conducting large, genomically blinded randomized controlled trials.

Pursuing nongenomically targeted drug development not only exposes patients to potential harm but also puts pharmaceutical companies at significant financial risk. Merck's recall of rofecoxib in 2004 has cost nearly $6 billion in litigation-related expenses alone. Searle's 2005 recall of Bextra (valdecoxib) has cost >$2 billion in legal awards and expenses. Neither of these recalls, however, can compare with the $21 billion cost of Wyeth's fenfluramine recall in 1997 *(12)*. The adoption of genomically guided drugs not only might avoid such consequences but also could be used to rescue compounds that had previously failed phase 1 and phase 2 trials because of adverse events. Identifying and fully characterizing the sequence variants (or other "omics") for subsequent compound screening for the potential of major side effects holds considerable promise.

Although in the future we are likely to benefit from prospective, genomically trialed drugs and to have clear guidance as to how such drugs should be prescribed, that is not the case today. With 10% of all currently available drugs already with genomic labeling, it is clear that in the absence of preceding genomically guided trials, the FDA will not be awaiting the development of physician guideline consensus on the actions required of such information *(9)*. Therefore, physicians will need to consider adapting their prescribing practices on the basis of genomic drug labeling, often in the absence of definitive data.

Ultimately, how drugs will be developed and used in the future is about to undergo a fundamental shift. Drug development will be streamlined so that short, genomically targeted trials will identify the patients most likely to respond and least likely to experience an adverse event. We believe that the synergistic effects of higher-resolution omics data, rapid point-of-care testing, and reductions in the costs of genotyping and conducting trials—coupled with avoiding costly drug recalls—will translate into substantial future net savings and patient benefit. Pharmacogenomics is pro-

foundly altering the future of medicine. The question remaining, however, is how quickly we embrace it and at what cost.

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 author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: E.J. Topol, Quest Diagnostics.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: Clinical and Translational Science Award (CTSA) funding to Scripps Translational Science Institute (NIH/NCATS UL1 TR000109).
Expert Testimony: None declared.
Patents: None declared.

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