

Pharmacogenomics and Public Health

D. Veenstra^{a, b} W. Burke^{b, c}

^aDepartment of Pharmacy, ^bCenter for Genomics and Healthcare Equality, and ^cDepartment of Bioethics and Humanities, University of Washington, Seattle, Wash., USA

Testing for genetic variation in drug response, in order to improve the safety and efficacy of drug therapy, is both intuitively appealing and scientifically grounded. The impact on health care could be significant, given the potentially disruptive effect of pharmacogenomic testing on clinical practice, reimbursement policies, research and development, and perhaps most significantly, on the approach of patients to their own health care, as argued by Carlson in this issue [1]. But as with many scientific innovations, transformation into medical applications has proven complicated. Though many gene variants are known to play a role, drug response is a complex phenomenon, influenced by factors such as diet, co-morbidities, and even other drugs. Thus, the predictive value of many potential pharmacogenomic tests remains small, and their clinical utility is generally not yet established. These considerations lead Garrison to argue that the impact of pharmacogenomics is likely to be moderate – an evolution or refinement rather than a revolution – and as with most new healthcare technologies, change will take decades to fully work through the healthcare system [2].

Given these uncertainties, it is not yet possible to forecast the public health impact of pharmacogenomics. It is clear, however, that important scientific, social, and policy issues need to be addressed to optimize the potential benefits to patients and the public's health. These include careful consideration of incentives – such as research funding, partnership development, and reimbursement

mechanisms – and oversight. The needs and expectations of both clinicians and patients must be considered, and unanticipated consequences, such as the potential 'nocebo' effect described by Haga and colleagues [3], must be considered. And as with other genomic research, limitations in study design or analysis may lead to overly simplistic interpretations of population differences in drug response, with potential adverse consequences for how tests and drugs are used [4]. The papers in this special issue illustrate the broad range of scientific, ethical, and social issues to be considered as the field develops.

Pharmacogenomics has different potential applications and the settings that offer the greatest opportunities are difficult to predict. To some extent, opportunities will be influenced by the nature of the scientific and clinical challenge. Given the adverse effects and variable responses associated with cancer chemotherapy and the somatic genetic variation inherent in the biology of cancer, it is not surprising that some of the most promising applications of pharmacogenomics are found in oncology [5, 6]. In general, though, the benefits of pharmacogenomics may relate most to issues of service delivery. Patients receiving 'state of the art' care from clinicians, involving close follow-up, monitoring for adverse effects, and appropriate dose adjustments and drug changes, may be least likely to benefit from pharmacogenomic guidance. But if patients receiving less than ideal care stand to receive the greatest benefit, we are faced with the conun-

drum that these patients are typically the least likely to have access to ‘fancy’ new technologies. The good news is that testing costs for many well-known pharmacogenomic variants as well as genome-wide scanning are dropping dramatically. And logistical aspects of actual testing have evolved to the point of direct patient access and ‘mail-in’ testing. These observations underscore the importance of rigorous health services research to explore the potential for pharmacogenomics to be truly cost-saving, or at a minimum, cost-effective.

In this context, how might pharmacogenomics improve public health specifically? Two examples, one involving drug safety and the other drug effectiveness, provide useful examples. Warfarin is a widely used drug with a narrow therapeutic index: approximately 3–10% of warfarin users experience a serious bleeding event each year, and some of these events are fatal. Testing for variants in the *CYP2C9* and *VKORC1* genes identifies individuals with lower warfarin dosing requirements and could provide a means to prescribe the drug more safely [7]. Even a small reduction in bleeding episodes could have a positive effect on public health. However, the ability of testing to improve outcomes beyond those achieved in a ‘state of the art’ anticoagulation clinic has not been shown to date, and indeed may prove to be challenging. Therefore, evaluation of pharmacogenomic applications in diverse patient populations and settings will be important to determine where they provide most value. The populations likely to benefit the most may also be the most challenging to collaborate with because of logistical issues, cultural barriers, and difficulties conducting research studies in real-world settings. Research partnerships that promote community participation and shared governance may be an important component of successful pharmacogenomic research.

In addition to reducing adverse events, pharmacogenomics might also improve the efficacy of drug treatment. Tamoxifen is a widely used adjuvant treatment to prevent the recurrence of early stage breast cancer. Tamoxifen is actually a ‘pro-drug’ – that is, it needs to be activated via the body’s metabolic enzymes. Studies have indicated that variants of *CYP2D6* may be associated with the risk of breast cancer recurrence: women with a low-activity variant of *CYP2D6* have less active metabolites of tamoxifen and thus may have lower effectiveness [8]. There is no effective approach to monitoring women for their response to tamoxifen over time. Fortunately, there is a good drug alternative, aromatase inhibitors, which have been shown to be at least equally efficacious, but these are significantly more expensive than tamoxi-

fen. The clinical and patient impact of breast cancer recurrence is obviously significant, and *CYP2D6* testing with tamoxifen therapy would appear to be an ideal application of pharmacogenomics, especially in resource-limited situations. Several questions must be resolved: Is the genetic association with disease recurrence (and/or survival) valid? And what level of evidence would be required to recommend testing? Does genetic testing provide a means to optimize the use of a less expensive drug in a cost-effective manner, and if so, will clinicians and patients find this an acceptable approach? As with drug safety, effective strategies for community-based research are needed.

The promise of pharmacogenomics will not be realized without effective leadership. Despite rapid growth of the pharmacogenomic literature, research addressing clinical outcomes is still very limited [9]. And with costs dropping, collaborative effort is needed to minimize the dangers of premature translation. For example, analysis of a test marketed as a means to reduce the risk of hearing loss from aminoglycosides indicated little scientific evidence of benefit, lack of cost effectiveness, and a potential for net harm [10]. Leadership is needed to assure oversight mechanisms that either prevent such tests from reaching the marketplace or assure that clinicians and consumers are well informed of their limitations when they do. At the same time, reimbursement policies that provide appropriate incentives for development are needed, with reasonable standards for clinical utility [11]. Perhaps most important, infrastructures will be required to assure adequate evaluation of pharmacogenomic testing in a range of routine clinical settings so that meaningful evaluation of the risks and benefits (both clinical and social) can occur. Robust partnerships between industry and academia [12], careful attention to research ethics [13], and methods to incorporate patient perspectives [14] will all be important in this effort. If researchers, health care leaders, policy makers, and test developers can work cooperatively and in concert with patients to achieve these goals, benefits to public health are likely.

Acknowledgement

This work was supported in part by the Center for Genomics and Healthcare Equality (NIH Grant P50HG003374).

References

- 1 Carlson RJ: The disruptive nature of personalized medicine technologies: implications for the health care system. *Public Health Genomics* 2009;12:180–184.
- 2 Garrison LP: Will pharmacogenomics disrupt the US health care system? No. *Public Health Genomics* 2009;12:185–190.
- 3 Haga SB, Warner LR, O'Daniel J: The potential of a placebo/nocebo effect in pharmacogenetics. *Public Health Genomics* 2009;12:158–162.
- 4 Lee SSJ: Pharmacogenomics and the challenge of health disparities. *Public Health Genomics* 2009;12:170–179.
- 5 Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, Cronin M, Baehner FL, Watson D, Bryant J, Costantino JP, Geyer CE Jr, Wickerham DL, Wolmark N: Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006;24:3726–3734.
- 6 Wang L, Weinshilboum R: Thiopurine S-methyltransferase pharmacogenetics: insights, challenges and future directions. *Oncogene* 2006;25:1629–1638.
- 7 Limdi NA, Veenstra DL: Warfarin pharmacogenetics. *Pharmacotherapy* 2008;28:1084–1097.
- 8 Goetz MP, Kamal A, Ames MM: Tamoxifen pharmacogenomics: the role of CYP2D6 as a predictor of drug response. *Clin Pharmacol Ther* 2008;83:160–166.
- 9 Guessous I, Gwinn M, Yu W, Yeh J, Clyne M, Khoury MJ: Trends in pharmacogenomic epidemiology: 2001–2007. *Public Health Genomics* 2009;12:142–148.
- 10 Veenstra DL, Harris J, Gibson RL, Rosenfeld M, Burke W, Watts C: Pharmacogenomic testing to prevent aminoglycoside-induced hearing loss in cystic fibrosis patients: potential impact on clinical, patient, and economic outcomes. *Genet Med* 2007;9:695–704.
- 11 Deverka PA: Pharmacogenomics, evidence, and the role of payers. *Public Health Genomics* 2009;12:149–157.
- 12 Gurwitz D, Zika E, Hopkins MM, Gaisser S, Ibarreta D: Pharmacogenetics in Europe: barriers and opportunities. *Public Health Genomics* 2009;12:134–141.
- 13 Avar D, Silverstein T, Sillon G, Joly Y: Researchers' perceptions of the ethical implications of pharmacogenomics research with children. *Public Health Genomics* 2009;12:191–201.
- 14 Issa AM, Tufail W, Hutchinson J, Tenorio J, Baliga MP: Assessing patient readiness for the clinical adoption of personalized medicine. *Public Health Genomics* 2009;12:163–169.