

COMMENTARIES

Getting personal: the promises and pitfalls of personalized medicine

JEFFREY LAURENCE

NEW YORK

Abbreviations: FDA = U.S. Food and Drug Administration; HCV = hepatitis C virus; INR = international normalized ratio; PPI = proton pump inhibitor; SNP = single-nucleotide polymorphisms

Margaret Atwood, who is a novelist, cultural activist, and winner of the first Arthur C. Clarke Award for science fiction, had her own commentary on the utility and dangers of our entry into an age of personalizing the molecular. “We’ve just opened the biggest toy box in the world, which is the genetic code,” she quipped. That “toy box,” and its potential for refining and defining the way we will eventually diagnose and prevent disease, as well as target, test, and prescribe new medications, is the theme of this special issue of *Translational Research*.

All of medicine, from its origins, might be considered personal, with each diagnosis and treatment tailored to an individual, qualified only by the background, skill, and art of the physician. But with new tools at hand, courtesy of molecular biology, that physician can now access a panoply of genetic data in Ms. Atwood’s box. Indeed, although Dr. Brewer argues in this issue for more resources focused on the rare “orphan” diseases based on comprehensive, individualized research and treatment, and Drs. Ginsburg and Willard emphasize that the molecular would best be combined with current clin-

ical tools to refine the risk of developing disease as well as screening, diagnosis, prognosis, and therapeutic selection, “personalized medicine” commonly refers only to gene-based health care. There are new specialty journals to herald it, which bear titles such as *Genome Medicine* and *Journal of Pharmacogenetics and Personalized Medicine*. Yet there are very few specific examples of its utility in the clinic, and among those gene-based tests that are used, many issues are far from settled.

Edward Abrahams, PhD, Executive Director of the Personalized Medicine Coalition, noted that federal regulatory agencies are integrating genetic testing into prescribing information, and virtually every new drug development project incorporates information on genetic variation and its impact on safety and efficacy.¹ In our special issue, Dr. Downing emphasizes that genomic medicine must be integrated into total health care practices to be successful. He provides an overview that includes consumer use and demand, health information technology, and ultimately, cost effectiveness. Abrahams, in his description of 6 features critical to the success of personalized medicine, views the potential for reducing health care costs among all of them.¹ Abrahams’s 6 features are as follows:

1. A shift in emphasis from reaction to prevention. Already some 1,300 gene-based tests describe the susceptibility to a variety of syndromes and diseases, some of which promise targeted prevention, treatment, or earlier diagnostic options.
2. Selection of optimal therapies for existing conditions. On average, any single current U.S. Food and Drug Administration (FDA)-approved drug is effective for only half of the people from whom it is prescribed.
3. Avoidance of adverse drug reactions. Currently 5.3% of U.S. hospital admissions are associated with adverse drug reactions; most are linked to

From the Division of Hematology/Oncology, Weill Cornell Medical College, New York, NY.

Submitted for publication September 29, 2009; accepted for publication September 29, 2009.

Reprint requests: Jeffrey Laurence, MD, Division of Hematology/Oncology, Weill Cornell Medical College, New York Blood Center, 310 East 67th Street, New York, NY 10065; e-mail: jlaurenc@med.cornell.edu.

Translational Research 2009;154:269–271.

1931-5244/\$ – see front matter

© 2009 Mosby, Inc. All rights reserved.

doi:10.1016/j.trsl.2009.09.010

variations in cytochrome (c) P450 genes related to drug metabolism.

4. Increased patient compliance and medication adherence; a corollary of point number 3.
5. Reduction in the time and cost of clinical trials. I had argued in an earlier editorial² that a restructuring of phase I and II clinical trials to improve their predictive value and mitigate the expense and waste of inadequately structured or targeted phase III studies was essential. In oncology, only one quarter of phase III trials are successful despite their being based on identical “positive” phase II trials. Better ways of preidentifying subsets of patients or tumors most likely to respond could be predicated on personalized patient and/or tumor gene profiles.
6. Revival of drugs failing in clinical trials.

These goals also argue for correlating gene polymorphisms to subsets of specific diseases, patients, and therapeutic responses among disparate populations worldwide. Distinctions in the prevalence of single-nucleotide polymorphisms (SNP) based on ethnicity and race are important to acknowledge as we move into ever increasing pools of potential research participants. For example, to enroll patients fully for all current phase III cancer trials, it would take 5.8 years if restricted to the United States, but only 1.9 years through accession of global pools of patients.³ Pharmaceutical companies are not waiting around for the former.

Yet many have argued that personal genomic tests hold great potential, unfulfilled. Muin Khoury, MD, director of the National Office of Public Health Genomics at the Centers for Disease Control and Prevention, believes the field “is evolving, but it’s still in its infancy. If you look at the clinical validity and utility of these tests, it’s clear that we haven’t crossed a certain threshold of evidence that would allow these tests to be used in the context of primary care.”⁴ Several authors in this issue address this challenge. Dr. Dorn, in his discussion of the pharmacogenomics of β -blockers, argues for “pre-prescription genotyping” to guide the use of these drugs in specific cardiovascular diseases. Dr. Ely, in reviewing cancer chemotherapeutics having precise targets—atypical for most current antineoplastic agents, he admits—and Dr. Jozic, in discussing the antiplatelet thienopyridine clopidogrel, also argue otherwise, at least with restrictions in their restricted arenas. Drs. Tweardy and Belmont extend these models, advocating for clinical diagnostic array profiling limited to those genetic markers that have a “clear” clinical interpretation. But there is the rub. Screening for rare disease-causing mutations, rather than searching for common disease risk-increasing SNPs, seems clear cut. David Goldstein, PhD, noted that most common gene variants implicated by genome-wide association studies are responsible for a small

fraction of known genetic variation, “and common variation is packing much less of a phenotypic punch than expected.”⁵ Small effect sizes for common variants demand shunning the “recreational genomics” provided by most genomics companies, Goldstein notes.⁶ Instead, with Drs. Tweardy and Belmont, he believes that a focus on the rare variants is needed. Which is fine, although which SNP or SNPs can be “clearly” linked to a drug reaction or therapeutic response may be open to debate, as illustrated by warfarin and clopidogrel, examples raised by several of our authors and briefly noted below.

There is also a lot of genetic information we are therapeutically not ready for. Persistent hepatitis C virus (HCV) infection afflicts some 170 million people worldwide and 4 million in the United States alone.⁷ Apart from leading to cirrhosis and hepatocellular carcinoma, it can be a significant impediment to treatment of those coinfecting with the AIDS virus HIV. Of its 3 major genotypes, genotype 1 is successfully treated only half the time.⁷ Three recent studies identified SNPs near the IL28B gene on chromosome 19; these results correlated with the ability to respond to the mainstay of HCV therapy, which is interferon- α plus ribavirin.⁸⁻¹⁰ Regardless of race or ethnicity, 80% of individuals homozygous for these SNPs cleared the virus and were considered cured. The same variant studied by 1 group is also associated with spontaneous clearance of HCV.⁷ However, it was emphasized in a commentary that although these observations raised the “tantalizing prospect of a more personalized approach to treating HCV by tailoring treatment to patients who are most likely to benefit, the reality is more sobering... clinical decision-making will be clouded by the fact that the effect of this advantageous variant is not absolute.... Furthermore, there is currently no alternative to interferon therapy for the HCV-infected population.”⁷

Another example relates to what was purported to be, just 2 years ago, a major breakthrough in confirmation of the utility of personalized medicine. In August 2007, the FDA announced that the product label for the oral anticoagulant and vitamin K antagonist warfarin would include the potential benefits of genetic testing to guide treatment.¹¹ A month later, the FDA granted clearance to the first genetic test of warfarin sensitivity.¹¹ Warfarin is given to 2 million people in the United States alone, as prophylaxis against venous thromboembolism and myocardial infarction,¹¹ yet it has an extraordinarily low therapeutic index, with a broad range of dosing required to achieve appropriate anticoagulation and avoid bleeding complications.¹² Currently, dosing is based on assessment of the prothrombin time with calculated international normalized ratio (INR). Lawrence Lesko, PhD, Director of the FDA’s Office of Clinical Pharmacology, noted that “The approach over the past 50 years

has been trial and error” in using this drug. New genetic information promised a prescribing method that involved a more science-based trial and less error. Yet comparative studies showed that these tests for cP450 gene CYP2C9 and vitamin K epoxide reductase VKORC1 SNPs linked to warfarin and vitamin K metabolism, respectively, added little value over careful monitoring of the INR.¹³ With cost effectiveness not established and limited evidence that bleeding and thrombosis might be impacted,¹⁴ the American College of Chest Physicians argued against their use,¹² and in mid-2009 Medicare decided not to pay for those tests.

The utility of pharmacogenetic testing has also arisen in the context of clopidogrel. Loss of function alleles in the cP450 gene CYP2C19, required to bioactivate the drug, seem to be important risk factors that predict clopidogrel treatment failure.¹⁵ This is part of what has become known as high-risk pharmacokinetics: a risk of serious drug toxicity when drug levels are dependent on the activity of a single metabolic pathway.¹⁵ Two other agents in this class are codeine, activated to its active metabolite morphine by CYP2D6, and tamoxifen, bioactivated by the same pathway (albeit also by other mechanisms).¹⁵ The CYP2C19 association became of great clinical concern given the fact that the widely used proton pump inhibitor (PPI) omeprazole is a potent inhibitor of CYP2C19; this concern was supported by database studies indicating a higher thrombotic event rate among clopidogrel-treated patients taking PPIs.¹⁵ However, an analysis of 2 randomized trials of clopidogrel and another antiplatelet agent prasugrel showed that the PPI treatment did not affect the clinical outcome for either drug, even though it attenuated the pharmacodynamic effects of clopidogrel, and to a lesser extent those of prasugrel.¹⁶

Despite these setbacks, about 200 drugs currently contain some information relating genes to drug response.¹⁷ More might be forthcoming and validated if clinical trials were to be performed. The FDA has maintained the position that prospective, randomized clinical trials are the ideal method to validate a genomic test.¹⁷ But many test developers and pharmaceutical companies argue that these data are costly and time consuming to collect, and instead rely on a post-hoc analysis of completed clinical trials.¹⁷ One also needs to apply legitimately any information that is validated. Consider Herceptin (trastuzumab), which is an inhibitor of the membrane receptor Her2 that is overexpressed on a subset—about 10%—of breast cancers. It is effective only in women who bear this marker. The Herceptin model was thought to be rev-

olutionary, pointing the way to conduct later phase clinical trials only in a select population that is likely to respond to the drug, thereby speeding drug approval and perhaps recovering an ostensibly ineffective agent for the subgroup that can benefit.¹⁸ But this model has not been repeated successfully. And in 2005, 7 years since Herceptin was FDA approved, UnitedHealthcare found that 8% of women who received the drug had tested negative for the required genetic marker, and 4% had not been tested at all.¹⁷

REFERENCES

1. Abrahams E. Personalized medicine realizing its promise. *Gen Eng Biotech News* 2009;29(15):70–3.
2. Laurence J. No more boring science, no more waste in clinical trials. *Transl Res* 2009;153:1–3.
3. Peddicord D. Access to global populations speeds trials. *Gen Eng Biotech News* 2009;29(15):18.
4. Khoury M. A conversation about personal genomic tests. *NCI Cancer Bull* 2009;6:5–6.
5. Goldstein DB. Common genetic variation and human traits. *N Engl J Med* 2009;360:1696–8.
6. Wade N. Study of genes and diseases at an impasse. *New York Times*, 2009. p. A1.
7. Iadonato SP, Katze MG. Hepatitis C gets personal. *Nature* 2009; 461:357–8.
8. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; 461:399–402.
9. Suppiah V, Moldovan M, Ahlenstiel G, et al. *IL28B* is associated with response to chronic hepatitis C interferon- α and ribavirin therapy. *Nature Gen* 2009;41:1100–4.
10. Tanaka Y, Nishida N, Sugiyama M, et al. Genome-wide association of *IL28B* with response to pegylated interferon- α and ribavirin therapy for chronic hepatitis. *C. Nature Gen* 2009;41:1105–9.
11. Jones D. Steps on the road to personalized medicine. *Nature Rev Drug Disc* 2007;6:770–1.
12. Rosove MH, Grody WW. Should we be applying warfarin pharmacogenetics to clinical practice? No, not now. *Ann Intern Med* 2009;151:270–3.
13. Anderson JL, Horne BD, Stevens SM, et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation* 2007;116:2563–70.
14. Wadelius M, Chen LY, Lindh JD, et al. The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood* 2009;113:784–92.
15. Roden DM, Stein CM. Clopidogrel and the concept of high-risk pharmacokinetics. *Circulation* 2009;119:2127–30.
16. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomized trials. *Lancet* 2009;374:989–97.
17. Pollack A. Patient's DNA may be signal to tailor drugs. *New York Times*, 2008. p. A1.
18. Garber K. Trial offers early test case for personalized medicine. *J Natl Cancer Inst* 2009;101:136–8.