``Personalizing'' academic medicine: opportunities and challenges in implementing genomic profiling

DAVID J. TWEARDY, and JOHN W. BELMONT

HOUSTON, TEX

BCM faculty members spearheaded the development of a first-generation Personal Genome Profile (Baylor PGP) assay to assist physicians in diagnosing and managing patients in this new era of medicine. The principles that guided the design and implementation of the Baylor PGP were high quality, robustness, low expense, flexibility, practical clinical utility, and the ability to facilitate broad areas of clinical research. The most distinctive feature of the approach taken is an emphasis on extensive screening for rare disease-causing mutations rather than common risk-increasing polymorphisms. Because these variants have large direct effects, the ability to screen for them inexpensively could have a major immediate clinical impact in disease diagnosis, carrier detection, presymptomatic detection of late onset disease, and even prenatal diagnosis. In addition to creating a counseling tool for individual "consumers," this system will fit into the established medical record and be used by physicians involved in direct patient care. This article describes an overall framework for clinical diagnostic array genotyping and the available technologies, as well as highlights the opportunities and challenges for implementation. (Translational Research 2009;154:288–294)

Abbreviations: ADME = absorption, distribution, metabolism, and elimination; BCM = Baylor College of Medicine; IBD = identical by descent; Indel = insertion deletion mutation; SNP = single nucleotide polymorphism

For several years, Baylor College of Medicine (BCM) leadership has envisioned an integrated health care model that actively develops and deploys genetic testing in its personalized medicine strategy. As part of these efforts, BCM, like other leading schools of medicine, became an active member of the Personalized Medicine Coalition, created an infrastructure (the Personalized Medicine Alliance) to coordinate these efforts within the institution, and began planning for a new graduate training curriculum to train the next generation of medical leaders.

As part of this larger strategy, BCM faculty members spearheaded the development of a first-generation Personal Genome Profile (Baylor PGP) assay to assist physicians in diagnosing and managing patients in this new era of medicine. The principles that guided the design and implementation of the Baylor PGP were high quality, robustness, low expense, flexibility, practical clinical utility, and the ability to facilitate broad areas of clinical research. The tests contained within the prototype (Personal Genomic Profile: Version 1) were targeted to strategic areas within the Baylor Clinic and affiliated clinical and translational research programs. Like most other groups developing testing for personalized medicine, we include genetic tests that can aid in risk classification and that are linked to individual responses to pharmacologic agents. The most distinctive feature of our approach is the emphasis on extensive screening for rare disease-causing mutations rather than just common risk increasing polymorphisms. We are developing tools

From the Departments of Medicine (Section of Infectious Diseases) and Molecular and Cellular Biology, Baylor College of Medicine, Houston, Tex; Departments of Molecular and Human Genetics, and Pediatrics, Baylor College of Medicine, Houston, Tex.

Submitted for publication August 23, 2009; revision submitted September 19, 2009; accepted for publication September 22, 2009.

Reprint requests: Davi1d J. Tweardy, Department of Medicine (Section of Infectious Diseases), Baylor College of Medicine, One Baylor Plaza, Room N1317.01, Mail Stop BCM 286, Houston, TX 77030.; e-mail: dtweardy@bcm.edu.

1931-5244/$ – see front matter

doi:10.1016/j.trsl.2009.09.008

for large-scale genotyping for rare mutant alleles already known to be responsible for genetic diseases. Because these variants have large direct effects, we believe that the ability to screen for them inexpensively could have major immediate clinical impact in disease diagnosis, carrier detection, presymptomatic detection of late onset disease, and even prenatal diagnosis. We emphasize that our purpose is not exclusively to create a counseling tool for individual ''consumers'' but rather to develop a system that fits into the established medical record and that can be used by physicians involved in direct patient care.

In this article, we will describe an overall framework for clinical diagnostic array genotyping, describe the available technologies, and highlight the challenges for implementation.

WHAT SHOULD BE INCLUDED IN A PERSONAL GENOME PROFILE?

Our simple answer to this question is that the content should include genetic markers that have a clear clinical interpretation. We give greatest priority to results that would have a practical and direct effect on diagnosis, prognosis, and clinical decision making. We do not believe that risk counseling based on the results from common polymorphisms is yet understood well enough to convert to routine clinical practice—with a few notable exceptions.

COMMON POLYMORPHISMS: DISEASE RISK MODIFIERS AND PHARMACOGENETIC EFFECTS

During the last 3 years, there has been a steady stream of publications that have identified associations between disease risk and common single nucleotide polymorphisms (SNPs).[1] These studies have been tremendously successful in the sense that for the first time there are epidemiologically robust and statistically sound demonstrations of the effect of these common variants on disease. On the one hand, a remarkable result has been the identification of previously unsuspected pathogenic mechanisms that are likely to provide important avenues for novel interventions and drug development.[2,3] On the other hand, the impact of knowing the specific pattern of variants in individuals is not clear. A recent publication from Brautbar et al[2] demonstrates how the incorporation of a single genetic variant into a well-established risk prediction model for coronary artery disease might be used to aid the decision whether to start statin therapy in individuals with otherwise moderate risks. The general concept that genetic tests can be incorporated into clinical decision algorithms is attractive. In contrast, vague assertions about lifestyle counseling based on genetic risks raise many questions about acceptability, cost, efficacy, and application.

A handful of loci and genetic variants exist for which convincing data indicate that they affect drug metabolism and/or risk of drug-induced toxicity (http://www.pharmgkb.org/). Genetic variants that influence the absorption, distribution, metabolism, and elimination (ADME) of various drugs have been associated with individual differences in pharmacokinetics.[3] In addition, some genetic variants have also been associated with the risk of drug side effects and toxicities.[4-6] The broad problem of pharmacogenetics is beyond the scope of this short commentary, but it is clear that there are a limited number of such markers with large effects and only a few in which testing might be ready to incorporate into clinical practice. Nevertheless, we recognize that pharmacogenetic testing is one of the most important potential applications for diagnostic genotyping. At the time of the design of our assay, clinical pharmacogenetic testing was offered by at least 1 laboratory for 32 different genes. A review of the literature suggests that only a subset of these are supported by studies with adequate sample sizes, consistently defined effects on drug metabolism or toxicity, repeated independent replication of the claimed genetic effect, and unambiguously defined risk alleles or haplotypes. Although we have incorporated genetic analysis of all these candidate genes in our version 1.0 assay, we plan to report only a subset of proven markers to referring physicians. Key examples are the CYP2D9 and VKORC loci, which have been shown to have large effects on the metabolism of warfarin.[7] Table I shows some examples of the gene representation on the assay and the drugs whose metabolism is known to be affected by common variants in these loci. Another example relates to the predictive association of HLA-B*5701 and hypersensitivity to the reverse transcriptase inhibitor, abacavir, used to treat HIV-1 infection. HLA-B*5701 is in tight linkage with SNP HCP5, which is included in the Baylor PGP: Version 1.

THE CASE FOR INCLUDING MUTATIONS THAT CAUSE SINGLE-GENE DISORDERS

The lifetime risk of being affected with a genetic disorder has been estimated to be at least 8%.[8] Although most physicians tend to dismiss these conditions as ''zebras'' because individually they are relatively rare, the aggregate effect of these conditions is large. In the past 20 years, almost 3000 human genes responsible for Mendelian (single gene) disease have been identified. A role for some of these mutations is strongly suspected in more common disorders and shown to be risk factors in multiple diseases,[9-17] but to date, there has been no systematic studies that address how much rare mutations contribute to common diseases.

There are virtually no higher prevalence single-gene disorders in which the genes(s) responsible have eluded