Personalized Medicine for High Blood Pressure

Stephen T. Turner, Gary L. Schwartz, Eric Boerwinkle

“One important characteristic of biology is its diversity, its variation. It’s why personalized medicine is so important.”

Personalized medicine refers to the use of diagnostic and screening methods that exploit knowledge of the patient’s unique molecular or risk profile to achieve optimal health and medical outcome through improved management of the patient’s disease or predisposition toward a disease. High blood pressure (hypertension) is the most common modifiable risk factor for vascular disease, which in turn accounts for more morbidity and mortality than any other category of disease. This invited review attempts to explain why individualized approaches are imperative to improve the detection, evaluation, treatment, and prevention of hypertension; to recount the history of the pursuit of this “holy grail”; and to propose approaches to overcoming the many obstacles to realization of personalized medicine for hypertension.

Rationale for Personalized Medicine for Hypertension

Ischemia of vital organs, especially the brain, heart, and kidneys, causes most of the morbidity and mortality associated with hypertension. Arteriosclerosis is the disease process, encompassing two main patterns, atherosclerosis and arteriolosclerosis, that contribute to thickening of arterial walls, reduction of lumen diameters, and impairment of blood flow leading to ischemia, dysfunction, and ultimately failure of target organs. Because increased resistance to blood flow, ie, the primary vascular disorder of hypertension, involves medial thickening and consequent luminal narrowing in small, muscular arteries and end-arterioles, hypertension emerges as the strongest risk factor, after age, for arteriolosclerotic manifestations of target organ complications (Table).

Whereas mortality attributable to heart attack and stroke are declining, the incidence and prevalence of heart failure and kidney failure are rising. Diabetes and hypertension are the two disorders that account for most of the increase in kidney failure, mainly through consequences of arteriolosclerosis. Likewise, coronary arteriolosclerosis may play a prominent role in the increasing proportion of heart failure cases in which left ventricular function is preserved, and age- and hypertension-related cerebral arteriolosclerosis is recognized as a cause or contributor to a rising prevalence of vascular dementia. Thus, in contrast to the declines in age-specific mortality attributable to atherosclerotic coronary and cerebrovascular disease, the burden of hypertension and its associated arteriosclerotic target organ complications are increasing as the population increases in size, age, and obesity.

Blood pressure levels and patterns of target organ damage may differ among persons not only as a consequence of different exposures to environmental factors (eg, dietary sodium and fat, caloric intake, physical inactivity, psychosocial stress) but also because of genetic variation in susceptibility to develop disease in response to the environment. Genetic and environmental variation also influences responses to interventions applied to lower blood pressure and prevent target organ damage. Therefore, any single method for detection, evaluation, treatment, or prevention of hypertension or its target organ complications is unlikely to be equally successful in all individuals. Strategies tailored to the particular characteristics of individual patients are both intuitively appealing and promise to maximally improve health of the population by optimizing outcomes for each individual patient.

A “revolution” in healthcare has been predicted based on knowledge and technologies evolving from the Human Genome Project. Much of the excitement derives from the promise of applying measurements of thousands of genetic polymorphisms cataloged by the HapMap Project to more individually tailor existing approaches or develop new ones that will more effectively detect, evaluate, treat, and prevent common conditions including hypertension and its target organ complications. Most previous pharmacogenetic studies were limited to relatively small sample sizes; candidate genes from only the best established pathways regulating blood pressure levels were investigated, and the numbers of polymorphisms analyzed per gene was less than required to captured the full extent of nucleotide sequence variation. Although the null hypothesis of no genetic association has been rejected, the effects of variation in single candidate genes appears to be modest (eg, less than one standard deviation around the mean blood pressure response) and accounts for only a small percentage of total variation in response (eg, generally less than 5%). There also appears to be considerable heterogeneity across races and genders in the reported associations. None of the reported associations of candidate genes with antihypertensive responses has been replicated in multiple independent studies.

Two vendors of genotyping platforms, Affymetrix and Illumina, now make genomewide association studies feasible
in which hundreds of thousands of single nucleotide polymorphisms can be measured in large numbers of unrelated individuals. “Proof of principal” that such an approach can be successful for a common, complex phenotype influenced by multiple genetic and environmental factors has been demonstrated recently by the identification of novel risk loci for type 2 diabetes mellitus. Using the Illumina platform, the investigators tested the association of 392,930 single nucleotide polymorphisms in a French case–control cohort. Four novel loci were identified, in addition to confirming the previously well replicated association with the TCF7L2 gene. The novel loci included a nonsynonymous polymorphism in the zinc transporter SLC30A8, which is expressed exclusively in insulin producing beta cells, and appeared to account for a substantial portion of risk for type 2 diabetes. Success of comparable genome-wide association studies in identifying multiple genetic and environmental factors has been demonstrated consistently in favor of standardized “one-size-fits-all” approaches.

On the heels of the genetic revolution are complementary expectations for proteomic, metabolomic, and other “-omic” markers of disease, including molecular imaging. Because antihypertensive drug responses may be influenced by a host of nongenetic factors (eg, diet, activity, drug compliance) and interactions between the effects of genes and environments, full realization of personalized medicine will undoubtedly require more precise and comprehensive characterizations of individual environmental exposures and measurements from multiple levels across the biological hierarchy. Nevertheless, the technologies that have emerged from the Human Genome Project and HapMap Project are available now and scalable to a degree not approached by other complementary approaches. Consequently, genomic approaches are now poised to initially impact the development of personalized medicine. The potential to connect genes and drug action with human diseases is exemplified by the first installment of a reference collection of gene-expression profiles from cultured human cells treated with bioactive small molecules, referred to as a “connectivity map.”

History of Personalized Medicine for Hypertension

Appreciation of the need for individualization of hypertension care is documented in the Joint National Committee (JNC) Reports on the Detection, Evaluation, and Treatment of High Blood Pressure. In the 1970s, secondary causes of hypertension were recognized to require different diagnostic and therapeutic approaches. The remaining majority of cases of so-called “essential hypertension” had been described by Page as a “mosaic” of heterogeneous mechanisms contributing to the elevation of blood pressure. Furthermore, Guyton and colleagues modeled the redundant and counterbalancing multiplicity of physiological and biochemical systems interacting to regulate blood pressure, long before “systems biology” came into vogue. Although blood pressure lowering in response to mono or combination drug therapies had been shown to differ widely among individuals, the first JNC report in 1977 recommended that the initial diagnostic evaluation be limited to patient history and physical examination. Notwithstanding the admonition that “all patients must receive individualized therapy programs,” a standardized, stepped-care approach to treatment was advocated for all patients, beginning with a thiazide diuretic. The measured patient characteristics, namely, blood pressure levels, age and sex, race, presence of target organ damage (eg, left ventricular hypertrophy), and comorbidities (eg, diabetes) were considered in the decision whether to initiate drug therapy, not drug selection. Moreover, there was no discussion of matching of drug mechanism of action to the mechanism of blood pressure elevation.

Subsequent JNC reports have not deviated substantially from the initially proposed approach. In the “individualized” approach now encouraged, treatment is chosen based on age, race, comorbidities, and issues of cost and potential side effects, but still without other information that may increase the likelihood of selecting an efficacious drug by virtue of matching its mechanism of action with the underlying pathophysiologic disturbance. The latest JNC report, for example, states that “testing for identifiable causes of hypertension is not indicated generally unless blood pressure control is not achieved or the clinical and routine laboratory evaluation strongly suggests an identifiable secondary cause.” Furthermore, “thiazide-type diuretic should be used as initial therapy for most patients, either alone or in combination with one of the other classes.” Thus, despite the long-standing appreciation of the ideal of personalized medicine, controversies surrounding the practicality and expense have been resolved consistently in favor of standardized “one-size-fits-all” approaches.

An alternative framework for personalization of antihypertensive drug therapy was articulated by Laragh and colleagues several years before the first JNC report. This “vasoconstriction-volume analysis” was based on the concept that the renin–angiotensin–aldosterone system determines blood pressure levels by regulating vascular tone and intravascular volume. Based on measurements of plasma renin activity, 3 main subtypes of essential hypertension were described: low (27% of the population), normal (57%), and high (16%). When aldosterone excretion was measured, 8 of 9 theoretically possible hormonal patterns could be identified that were proposed to define “criteria for more rational drug therapy, specifically tailored to correct a particular abnormal biochemical profile.” This construction was proposed to have “etiologic, prognostic, and therapeutic implications.” In particular, volume expanded and low renin hypertension, “with presumably more open arterial bed and better tissue perfusion,” was thought to be “less prone to
cardiovascular complications” and to “respond to diuretics alone.”22 In contrast, “vasoconstrictor hypertension (high renin and some normal renin) respond to anti-renin–aldosterone therapy alone.”22

One large, carefully conducted study has tested the utility of the renin-based approach to personalization of antihypertensive drug therapy in men.24 The plasma renin profile, indexed for urinary sodium excretion, was compared with an age-race subgroup method for predicting response to single-drug therapy in 1031 ambulatory men with stage 1 and 2 hypertension (ie, diastolic blood pressure of 95 to 109 mm Hg), who were randomized to 1 of 6 antihypertensive drugs: hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem, or prazosin.24 The expected differences in renin profiles were observed among age-race subgroups: blacks tended toward a low-renin profile whereas whites tended toward medium and high-renin profiles. However, the comparison of renin profiling and age-race subgroup methods for selection of an initial antihypertensive drug did not reveal a significant difference in predictive ability between the two methods. Because age-race subgrouping is cost-free and requires no sample collection or laboratory testing, renin-sodium profiling could not be recommended.24

To our knowledge, no other measurement proposed to characterize the hypertensive phenotype or guide antihypertensive drug selection has begun to approach the notoriety of plasma renin activity, nor has the cost-effectiveness of any been demonstrated, including plasma renin activity. Other approaches proposed for the selection of antihypertensive drug therapy are empirical and do not depend on biochemical measurements.25 Such limited progress in developing more individualized therapy for hypertension is remarkable in light of the extensive understanding of anatomic, physiological, and biochemical mechanisms regulating blood pressure, and corresponding successes of the pharmaceutical industry in developing drugs that safely target these mechanisms to lower blood pressure. Major obstacles appear to have been the difficulty and expense of directly measuring relevant processes within cells, tissues, and organs of individual patients in vivo. The need to make direct measurements may in part be overcome by measures of genomic variation, which influences the relevant processes in remote compartments, but can be performed on the DNA extracted from easily accessible cells.

Future Directions

Biomarker Discovery

Biomarkers are biological measures that are in the causal pathway of disease or have utility for risk stratification. Consequently, biomarkers are key to implementation of at least 3 aspects of personalized medicine: detection and diagnosis of disease, risk assessment and prognosis, and prediction of responses to therapeutic or preventative interventions. The value of established cohorts and ongoing clinical trials could potentially be enhanced by applying existing high throughput genomic technologies that appear to have the greatest near-term likelihood of leading to discovery and validation of novel biomarkers useful in the detection, evaluation, treatment, and prevention of disease. Serving as a model for the application of this recommendation to hypertension, the GENetics of Hypertension Associated Treatment (GenHAT) study is determining whether variants in hypertension susceptibility genes interact with antihypertensive medication to modify coronary heart disease risk in hypertensives. GenHAT is an ancillary study of the Antihypertensive and Lipid Lowering Treatment to prevent Heart Attack Trial (ALLHAT), a double-blind, randomized trial of 42 418 hypertensives, 55 years of age or older, with systolic or diastolic hypertension and 1 or more risk factors for cardiovascular disease.26 The large sample size and representation of women and minorities make this established cohort a valuable resource not only for biomarker discovery but also validation of drug-by-genotype interactions reported from smaller, less representative cohorts. Given the inverse correlation between age and plasma renin activity, the GenHAT cohort is expected to be enriched for low renin hypertension (ie, based on the age inclusion criterion >55 years) and, therefore, may offer enhanced power to detect drug-by-biomarker interactions within and across strata defined by plasma renin activity.

Research Structure

Full realization of the opportunities for personalized medicine will require changes in the structure and design of research studies and collaborations. Specifically, more comprehensive biobanks and registries for existing clinical trials and population-based cohorts would ideally provide accessible data enclaves, examples for standardization of phenotyping methods, and the analytical tools necessary to mine these data and integrate new results from individual investigator-initiated studies. One relevant example of such a data resource is the online, public-use database of the Family Blood Pressure Program (http://www.biostat.wustl.edu/fbpp/FBPP.shtml). The first release of this data set includes measurements from 11 079 participants in 3993 families and is arguably the most diverse family-based study of hypertension by virtue of including 3 major ethnic groups: blacks, whites, and hispanics. Another example is the Pharmacogenetics Knowledge Base (www.PharmGKB.org), which is an information resource about pharmacogenomics for both the lay public and scientific community. These examples reflect a movement in biomedical research toward making primary data more accessible to the scientific community, while maintaining participant and patient confidentiality.

Clinical Decision Making

Personalized medicine has the potential to leverage novel genomics findings to provide additional diagnostic and prognostic information that will supplement established disease markers of biologically relevant pathways. Collaborative efforts among public and private institutions will be required to validate the impact of biomarkers on clinical outcomes and clinical decision making, including evaluation of efficacy, cost-effectiveness, and safety outcomes; optimization of medication dosing to minimize adverse effects and maximize therapeutic benefits; and identification of high priority areas, eg, those plagued by high-costs and poor outcomes. Given the
present paucity of validated biomarkers for hypertension, such collaborative efforts are particularly germane as we look forward to the increasingly rapid rate at which novel “-omic” biomarkers are likely to be discovered.27

Data Analysis and Bioinformatics
Biomedical and healthcare research, in general, and personalized medicine, in particular, increasingly require processing and analyses of large volumes of data as electronic medical records, biomedical imaging, genomics, and other “-omic” technologies advance into more widespread application. To realize the full utility of these data will require partnerships between biomedical researchers, statisticians, and computer scientists, as well as involvement of the information technology experts. There is a critical need for development and dissemination of analytical methods tailored for large numbers of interrelated yet distinct variables (eg, genomic variation and metabolomic profiles), and validation of their ability to predict response to disease treatment and preventive lifestyle modifications. Meeting this need may be facilitated by adopting appropriate methods from other fields, such as economics and meteorology that are both data and analysis intensive, but may also require de novo development of novel methodologies. Relevant examples of present needs include analyses of “-omic” and outcome data being generated from large, integrated healthcare networks; analyses of therapeutic and adverse responses in large clinical trials; analyses of gene-by-environment interactions in observational cohort studies, as well as in observational outcome studies conducted by large, integrated healthcare networks.

Training
Development and implementation of personalized medicine to reduce the public health burden of hypertension and its target organ complications will also require greater training in contemporary “-omics” technologies for not only biomedical researchers and physicians but also for other stakeholders including patients, legislators, healthcare agencies, and consumers. In particular, targeting of educational activities in the area of the “-omics” toward new and established investigators should emphasize team approaches by including experts from other areas with relevant expertise (eg, economics and meteorology). Identification of early successes will facilitate the development of a compelling story for personalized medicine that is broadly understandable to all stakeholders. In turn, this would facilitate the transition of personalized medicine to become a central principal of medical education and lead to greater reliance on predictive models than on case studies.

Perspectives
The notion of personalized medicine for high blood pressure is not new, as the first JNC report in 1977 explicitly articulated the goal of personalization of the therapy of hypertension. What has changed is the scope and power of the tools at our disposal to characterize individual differences at the molecular level. For common diseases such as hypertension, the etiology of the phenotype is heterogeneous, variably related to effects of multiple genes acting in the context of the genetic background and interacting with multiple environ-

mental factors. Sorting out which characteristics of individual-specific “-omic” profiles can serve as a useful biomarkers in the detection, evaluation, treatment, and prevention of hypertension remains an arduous process beyond the discovery stage, which is just beginning for pharmacogenomics. Although the “holy grail” of medicine that is uniquely personalized for each patient may never be practical, progress can certainly be made toward an intermediate goal of identifying smaller population subgroups with more homogeneous pathophysiology and greater likelihood of favorable responses to particular therapeutic and preventative interventions.

Acknowledgments
We thank our colleagues and collaborators for discussions that have contributed to the views expressed regarding personalized medicine for high blood pressure.

Sources of Funding
This work was supported by HL 53330, HL 74735, GM 74492, and Mayo Clinic.

Disclosures
None.

References
11. Schwartz GL, Turner ST, Chapman AB, Boerwinkle E. Interacting effects of gender and genotype on blood pressure response to hydrochlorothia-

Disclosures
None.


