Principles of Pharmacogenetics and Pharmacogenomics

The study of pharmacogenetics and pharmacogenomics focuses on how our genes and complex gene systems influence our response to drugs. Recent progress in the science of clinical therapeutics has led to the discovery of new biomarkers that make it technically easier to identify groups of patients that are more or less likely to respond to individual therapies. The aim is to improve personalized medicine— not simply to prescribe the right medicine, but to deliver the right drug at the right dose at the right time. This textbook brings together contributions from leading experts to discuss the latest information on how human genetics has an impact on drug response phenotypes. It presents not only the basic principles of pharmacogenetics, but also clinically valuable examples that cover a broad range of specialties and therapeutic areas. The first section of the book outlines critical concepts in pharmacogenetics and pharmacogenomics, including genetic testing, genotyping technologies, and adverse drug effects. The next section discusses the legal, ethical, and social implications of pharmacogenomics. The second half of the book details many of the main therapeutic areas, including oncologic drugs, cardiovascular drugs, statins, drug-induced long-QT syndrome, diabetes drugs, respiratory drugs, gastrointestinal drugs, rheumatoid arthritis drugs, obstetric drugs, psychiatric drugs, pain and anesthesia drugs, HIV and antiretroviral drugs, pediatrics, and fetal and neonatal medicine. This textbook provides an introduction to pharmacogenetics and pharmacogenomics for health care professionals, medical students, pharmacy students, graduate students, and researchers in the biosciences.

Online resources for this book can be found at www.cambridge.org/altman.

Resources include:

- Link to the Pharmacogenomics Knowledgebase
- Study guides
- Images from the book
- Discussion questions
- Content updates

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Introduction

Health care is moving toward a more individualized approach that has been termed “personalized medicine.” The underlying causes for this transition are many; they include the ability to genotype and sequence DNA, the increasing emphasis on consumerism among patients, and changes in the pharmaceutical industry worldwide and particularly at the U.S. Food and Drug Administration (FDA) and its sister regulatory agencies around the world. Pharmacogenetics and pharmacogenomics both involve the study of how genetics exerts an impact on drug response phenotype. For our purposes, the term “pharmacogenetics” connotes single genes that dominate the effects on a drug response, whereas “pharmacogenomics” connotes systems of many genes that create complex drug response phenotypes. It is clear that pharmacogenetics and pharmacogenomics are the core elements of the future of personalized medicine.

The emergence of robust and effective patient advocacy groups over the past thirty years has led to organized demands by patients for medicines that are more effective and that have fewer side effects. This was fueled by the Institute of Medicine “To Err is Human” report of 1999, which estimated that more than 50,000 Americans die each year because of medical errors, in particular, involving prescription drugs. Health care organizations have registered the clinical and financial dangers inherent in medication errors, and more precise prescribing is now a central part of quality control and even part of the marketing campaigns for hospitals in the United States. The pharmaceutical industry is experiencing the death of the “blockbuster” model of drug development in which one dose of a single medication can be used to treat everyone, including men and women, people of all races, infants, adolescents, adults, and the elderly. The success of therapies that treat a carefully selected subset of the population, such as Herceptin\textsuperscript{TM} in the treatment of breast cancer, demonstrates that focusing a therapy on a population with a better benefit-to-risk ratio need not incur economic calamity. Last, the inexorable progress of science within clinical therapeutics has led to the discovery of new biomarkers for therapeutic effect that make it technically easier to identify groups of patients who are more or less likely to respond to individual therapies. Measures of DNA sequence (both focused genotyping and full sequencing) are the biomarkers whose cost has dropped most precipitously, with an accuracy approaching perfection.

The revolution occurring in the use of biomarkers to assess the risks and benefits of drugs is not confined to new prescription medicines, but includes the entire therapeutic armamentarium. Both the FDA in the United States, through its efforts on age-old medicines such as warfarin and tamoxifen, and the National Institutes of Health, through its funding of basic research (e.g., the Pharmacogenetics Research Network), have shown that they expect all existing therapies to be evaluated for the potential of more targeted use. As a result, health care providers and administrators will rapidly need to understand the optimal selection and use of these new biomarkers to provide the best care possible. Consistent with this need, research and reimbursement agencies are stressing the importance of data on “comparative effectiveness” between existing medications – an emphasis that will inevitably involve the use of validated biomarkers that will soon be integrated into routine medical care.

Although the current focus of pharmacogenomic research is on biomarkers derived from inherited (germline) DNA, there is increasing interest in somatic biomarkers from tumors, proteomics, and metabolomics. The initial focus on DNA is natural: it is relatively stable and easier to handle than other more degradable biologic materials like RNA and protein. In addition, we have a detailed map of the human genome,
and sentinel examples of the use of DNA are already available as role models. These advantages are not enough to move this science into the clinic, however.

For genetic testing to realize its full potential to improve drug selection and dosing, we must integrate the science and communicate its clinical value within the curricula of pharmacy and medical schools. As part of this effort, we recognized the need for a book that presents not only the basic principles of pharmacogenetics, but also the clinically valuable examples that cover a broad range of clinical specialties and therapeutic areas. Our intended audience is medical and pharmacy students, as well as practicing professionals. This book represents our first attempt to create such a text. It represents the work of many scientists and practicing physicians in a wide range of medical specialties, and is designed to provide not only a broad overview of the science underlying this testing, but also a strong, practical element for clinical practice. We are grateful to all these contributors not only for the many hours of toil involved in creating this work, but also for their continued efforts to educate a new generation of health care professionals, not simply to prescribe the right medicine, but to deliver “the right drug at the right dose at the right time.”

Russ B. Altman, Dave Flockhart, and David B. Goldstein