

## 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](http://www.cambridge.org/altman).

Resources include:


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

**RUSS B. ALTMAN** is Chairman of the Bioengineering Department and Professor of Bioengineering, Genetics, and Medicine at Stanford University. His primary research interests are in the application of computing technology to basic molecular biological problems of relevance to medicine. His group builds the PharmGKB ([www.pharmgkb.org](http://www.pharmgkb.org)).

**DAVID FLOCKHART** is the Harry and Edith Gladstein Chair in Cancer Genomics and Professor of Medicine, Medical Genetics and Pharmacology at the Indiana University School of Medicine in Indianapolis. He is also the Director of the Division of Clinical Pharmacology. His research is focused on clinically relevant applications of pharmacogenetics and drug interactions.

**DAVID B. GOLDSTEIN** is the Richard and Pat Johnson Distinguished University Professor and Director of the Center for Human Genome Variation at Duke University. He is also Professor of Molecular Genetics and Microbiology at Duke. His principal interests include human genetic diversity, the genetics of disease, and pharmacogenetics.

# Principles of Pharmacogenetics and Pharmacogenomics



Edited by

**Russ B. Altman**

*Stanford University*

**David Flockhart**

*Indiana University*

**David B. Goldstein**

*Duke University*

Cambridge University Press  
978-0-521-88537-9 — Principles of Pharmacogenetics and Pharmacogenomics  
Edited by Russ B. Altman , David Flockhart , David B. Goldstein  
Frontmatter  
[More Information](#)

CAMBRIDGE UNIVERSITY PRESS  
Cambridge, New York, Melbourne, Madrid, Cape Town,  
Singapore, São Paulo, Delhi, Tokyo, Mexico City  
Cambridge University Press  
32 Avenue of the Americas, New York, NY 10013-2473, USA  
[www.cambridge.org](http://www.cambridge.org)  
Information on this title: [www.cambridge.org/9780521885379](http://www.cambridge.org/9780521885379)

© Cambridge University Press 2012

This publication is in copyright. Subject to statutory exception  
and to the provisions of relevant collective licensing agreements,  
no reproduction of any part may take place without the written  
permission of Cambridge University Press.

First published 2012

Printed in China by Golden Cup

*A catalog record for this publication is available from the British Library.*

*Library of Congress Cataloging in Publication data*

Principles of pharmacogenetics and pharmacogenomics / [edited by] Russ B. Altman, David Flockhart,  
David B. Goldstein.  
p. ; cm.  
Includes bibliographical references and index.  
ISBN 978-0-521-88537-9 (hardback)  
1. Pharmacogenetics. I. Altman, Russ. II. Flockhart, David A. III. Goldstein, David B.  
[DNLM: 1. Pharmacogenetics. 2. Pharmacological Phenomena – genetics. QV 38]

RM301.3.G45P76 2012  
615'.7–dc23 2011018883

ISBN 978-0-521-88537-9 Hardback

Additional resources for this publication at [www.cambridge.org/altman](http://www.cambridge.org/altman)

Cambridge University Press has no responsibility for the persistence or accuracy of URLs for external or  
third-party Internet Web sites referred to in this publication and does not guarantee that any content on such  
Web sites is, or will remain, accurate or appropriate.

Every effort has been made in preparing this book to provide accurate and up-to-date information that is in  
accord with accepted standards and practice at the time of publication. Although case histories are drawn from  
actual cases, every effort has been made to disguise the identities of the individuals involved. Nevertheless, the  
authors, editors, and publishers can make no warranties that the information contained herein is totally free from  
error, not least because clinical standards are constantly changing through research and regulation. The authors,  
editors, and publishers therefore disclaim all liability for direct or consequential damages resulting from the use  
of material contained in this book. Readers are strongly advised to pay careful attention to information provided  
by the manufacturer of any drugs or equipment that they plan to use.

## Contents

---

<i>Contributors</i>	page vii
<i>Introduction</i> <i>Russ B. Altman, David Flockhart, and David B. Goldstein</i>	xi
<b>Part I: Critical Concepts</b>	
1. Introduction to Population Diversity and Genetic Testing <i>Michael D. Caldwell, Ingrid Glurich, Kimberly Pillsbury, and James K. Burmester</i>	3
2. Genotyping Technologies <i>Cristi R. King and Sharon Marsh</i>	12
3. Pharmacokinetics: Absorption, Distribution, Metabolism, Excretion Overview Chapter <i>Terrence Blaschke</i>	21
4. Overview: Adverse Drug Reactions <i>Matthew R. Nelson</i>	27
5. PharmGKB, a Centralized Resource for Pharmacogenomic Knowledge and Discovery <i>Li Gong and Teri E. Klein</i>	38
6. DrugBank <i>David S. Wishart</i>	55
7. Ethical Considerations for Pharmacogenomics: Privacy and Confidentiality <i>Sandra Soo-Jin Lee</i>	66
8. Informed Consent in Pharmacogenomic Research and Treatment <i>Mark A. Rothstein</i>	74
9. Legal Trends Driving the Clinical Translation of Pharmacogenomics <i>Barbara J. Evans</i>	81
<b>Part II: Therapeutic Areas</b>	
10. Oncologic Drugs <i>Uchenna O. Njiaju and M. Eileen Dolan</i>	97

11. Pharmacogenetics and Pharmacogenomics of Cardiovascular Disease <i>Daniel Kurnik and C. Michael Stein</i>	115
12. Statin-Induced Muscle Toxicity <i>Russell A. Wilke, Melissa Antonik, Elenita I. Kanin, QiPing Feng, and Ronald M. Krauss</i>	125
13. Genomics of the Drug-Induced Long-QT Syndrome <i>Dan M. Roden, Prince J. Kannankeril, Stefan Kääh, and Dawood Darbar</i>	136
14. Pharmacogenetics of Diabetes <i>Mark C. H. de Groot and Olaf H. Klungel</i>	145
15. Pharmacogenetics – Therapeutic Area – Respiratory <i>Kelan Tantisira and Scott Weiss</i>	154
16. Pharmacogenomics Associated with Therapy for Acid-Related Disorders <i>Takahisa Furuta</i>	175
17. Pharmacogenetics of Rheumatology: Focus on Rheumatoid Arthritis <i>Robert M. Plenge, Yvonne C. Lee, Soumya Raychaudhuri, and Daniel H. Solomon</i>	188
18. Pharmacogenetics of Obstetric Therapeutics <i>David Haas and Jamie Renbarger</i>	202
19. Pharmacogenomics of Psychiatric Drugs <i>David Mrazek</i>	217
20. Pain and Anesthesia <i>Konrad Meissner and Evan D. Kharasch</i>	224
21. HIV and Antiretroviral Therapy <i>Amalio Telenti</i>	238
22. Application of Pharmacogenetics and Pharmacogenomics in Pediatrics: What Makes Children Different? <i>Jennifer A. Lowry and J. Steven Leeder</i>	249
23. Fetal and Neonatal Pharmacogenomics <i>Yair Blumenfeld</i>	263

## Contributors

---

**Russ B. Altman**

Chairman  
Department of Bioengineering  
Stanford University  
Stanford, CA

**Melissa Antonik**

Division of Endocrinology and Metabolism  
Department of Medicine  
Medical College of Wisconsin  
Milwaukee, WI

**Terrence Blaschke**

Professor Emeritus  
Stanford School of Medicine  
Stanford University  
Stanford, CA

**Yair Blumenfeld**

Division of Maternal-Fetal Medicine  
Department of Obstetrics and Gynecology  
Stanford University  
Stanford, CA

**James K. Burmester**

Marshfield Clinic, Research Foundation  
Marshfield, WI

**Michael D. Caldwell**

Principal Investigator  
Marshfield Clinic, Research Foundation  
Marshfield, WI

**Dawood Darbar**

Division of Cardiovascular Medicine  
Vanderbilt University School of Medicine  
Nashville, TN

**Mark C. H. de Groot**

Heart and Lung Institute  
University Hospital  
Utrecht  
The Netherlands

**M. Eileen Dolan**

Department of Medicine  
Comprehensive Cancer Research Center  
The University of Chicago  
Chicago, IL

**Barbara J. Evans**

Health Law and Policy Institute  
University of Houston Law Center  
Houston, TX

**QiPing Feng**

Division of Clinical Pharmacology  
Department of Medicine  
Vanderbilt University Medical Center  
Nashville, TN

**David Flockhart**

Harry and Edith Gladstein Chair in Cancer  
Genomics  
Division of Clinical Pharmacology  
Indiana University School of Medicine  
Indianapolis, IN

**Takahisa Furuta**

Center for Clinical Research  
Hamamatsu University School of Medicine  
Hamamatsu  
Japan

**Ingrid Glurich**

Marshfield Clinic, Research Foundation  
Marshfield, WI

**David B. Goldstein**

The Richard and Pat Johnson Distinguished  
University Professor  
Director, Center for Human Genome Variation  
Duke University Medical Center  
Durham, NC

**Li Gong**

Department of Genetics  
 Stanford University Medical Center  
 Stanford University  
 Stanford, CA

**David Haas**

Indiana University School of Medicine  
 Division of Clinical Pharmacology  
 Wishard Memorial Hospital  
 Indianapolis, IN

**Stefan Kääh**

Department of Medicine  
 Vanderbilt University School of Medicine  
 Nashville, TN

**Elenita I. Kanin**

University of Wisconsin Hospital and  
 Clinics  
 Madison, WI

**Prince J. Kannankeril**

Department of Pediatrics  
 Vanderbilt University School of Medicine  
 Nashville, TN

**Evan D. Kharasch**

Russell D. and Mary B. Shelden Professor of  
 Anesthesiology  
 Department of Anesthesiology  
 Washington University in St. Louis  
 St. Louis, MO

**Cristi R. King**

Faculty of Pharmacy and Pharmaceutical  
 Sciences  
 University of Alberta  
 Edmonton, Alberta  
 Canada

**Teri E. Klein**

Department of Genetics  
 Stanford University Medical Center  
 Stanford University  
 Stanford, CA

**Olaf H. Klungel**

Division of Pharmacoepidemiology  
 Utrecht Institute for Pharmaceutical Sciences  
 Utrecht University  
 Utrecht  
 The Netherlands

**Ronald M. Krauss**

Senior Scientist and Director, Atherosclerosis  
 Research  
 Children's Hospital Oakland Research Institute  
 Oakland, CA

**Daniel Kurnik**

Departments of Medicine and Pharmacology  
 Division of Clinical Pharmacology  
 Vanderbilt University School of Medicine  
 Nashville, TN

**Sandra Soo-Jin Lee**

Stanford Center for Biomedical Ethics  
 Stanford University  
 Stanford, CA

**Yvonne C. Lee**

Division of Rheumatology, Immunology, and  
 Allergy  
 Brigham and Women's Hospital  
 Boston, MA

**J. Steven Leeder**

Division of Clinical Pharmacology and Medical  
 Toxicology  
 Department of Pediatrics  
 Children's Mercy Hospitals and Clinics  
 Kansas City, MO

**Jennifer A. Lowry**

Division of Clinical Pharmacology and Medical  
 Toxicology  
 Department of Pediatrics  
 Children's Mercy Hospitals and Clinics  
 Kansas City, MO

**Sharon Marsh**

Department of Internal Medicine  
 Washington University in St. Louis  
 St. Louis, MO

**Konrad Meissner**

Department of Anesthesiology and Intensive Care  
 Medicine  
 Universitätsklinikum Greifswald  
 der Ernst-Moritz-Arndt-Universität Greifswald AÖR  
 Greifswald  
 Germany

**David Mrazek**

Chair of Department of Psychiatry and Psychology  
 and Director of the SC Johnson Genomics of  
 Addictions Program  
 Mayo Clinic  
 Rochester, MN

**Matthew R. Nelson**

Pharmacogenetics  
 GlaxoSmithKline  
 Research Triangle Park, NC

**Uchenna O. Njiaju**

Department of Medicine  
 Comprehensive Cancer Research Center  
 The University of Chicago  
 Chicago, IL

**Kimberly Pillsbury**

Marshfield Clinic, Research Foundation  
Marshfield, WI

**Robert M. Plenge**

Brigham and Women's Hospital  
Harvard Medical School  
Boston, MA

**Soumya Raychaudhuri**

Division of Rheumatology, Immunology, and  
Allergy  
Brigham and Women's Hospital  
Boston, MA

**Jamie Renbarger**

Indiana University School of Medicine  
Division of Pediatrics  
Wishard Memorial Hospital  
Indianapolis, IN

**Dan M. Roden**

Department of Medicine  
Vanderbilt University School of Medicine  
Nashville, TN

**Mark A. Rothstein**

Herbert F. Boehl Chair of Law and Medicine  
Institute for Bioethics, Health Policy, and Law  
University of Louisville School of Medicine  
Louisville, KY

**Daniel H. Solomon**

Brigham and Women's Hospital  
Harvard Medical School  
Boston, MA

**C. Michael Stein**

Departments of Medicine and Pharmacology  
Division of Clinical Pharmacology  
Vanderbilt University School of Medicine  
Nashville, TN

**Kelan Tantisira**

Channing Laboratory  
Brigham and Women's Hospital  
Harvard Medical School  
Cambridge, MA

**Amalio Telenti**

Institute of Microbiology  
University Hospital Center  
University of Lausanne  
Lausanne  
Switzerland

**Scott Weiss**

Channing Laboratory  
Brigham and Women's Hospital  
Harvard Medical School  
Cambridge, MA

**Russell A. Wilke**

Division of Clinical Pharmacology  
Department of Medicine  
Vanderbilt University Medical Center  
Nashville, TN

**David S. Wishart**

Departments of Computing Science and Biological  
Sciences  
University of Alberta  
Edmonton, Alberta  
Canada



## 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<sup>TM</sup> 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 rep-

resents 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