Genomic Clinical Trials and Predictive Medicine

Genomics is having a major impact on therapeutics development in medicine. This book contains up-to-date information on the use of genomics in the design and analysis of therapeutic clinical trials with a focus on novel approaches that provide a reliable basis for identifying what kinds of patients are likely to benefit from the test treatment. It is oriented to both statisticians and clinical investigators. For clinical investigators, it includes background information on clinical trial design and statistical analysis. For statisticians and others who want to go deeper, it covers state-of-the-art adaptive designs and the development and validation of probabilistic classifiers. The author describes the development and validation of prognostic and predictive biomarkers and their integration into clinical trials that establish their clinical utility for informing treatment decisions for future patients.

Dr. Richard M. Simon is chief of the Biometric Research Branch of the National Cancer Institute, where he is head statistician for the Division of Cancer Treatment and Diagnosis. He is the lead author of the textbook *Design and Analysis of DNA Microarray Experiments* and has more than 450 publications. Dr. Simon has been influential in promoting excellence in clinical trial design and analysis. He has served on the Oncologic Advisory Committee of the U.S. Food and Drug Administration and is a frequent advisor to government, academic, and industry organizations involved with developing improved treatments and diagnostics for patients with cancer. In 1998, Dr. Simon established the Molecular Statistics and Bioinformatics Section of the National Cancer Institute, a multidisciplinary group of scientists developing and applying methods for the application of genomics to cancer therapeutics. He is the architect of BRB-ArrayTools software for the analysis of microarray expression and copy number data.

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Contents

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Introduction

Genomics is having a major impact on therapeutics development in medicine. In oncology, the impact is particularly profound. Cancer is a set of diseases resulting from DNA alterations, and each tumor is almost unique with regard to the somatic alterations that it harbors. In fact, not only do any two tumors differ with regard to their DNA alterations but each tumor is composed of subclones of cells, and the subclones differ from each other with regard to their mutational spectrum. Although the discovery of these DNA changes provides a rich source of potential molecular targets, the development and evaluation of therapeutics based on re-regulating these targets poses profound challenges, many of which are the topic of this monograph.

Our focus will be heavily on oncology, where the personalization of therapy is primarily based on the tumor DNA genome that has undergone somatic alterations. The material here should be of value, however, in the study of other diseases for which the candidate characteristics for disease personalization are often based on germ line polymorphisms or phenotypic measures of disease heterogeneity.

The randomized clinical trial has been a fundamentally important contribution to medicine. Randomized clinical trials have permitted us to distinguish the minority of new regimens that are effective from the majority of proposed interventions that are ineffective, harmful, and expensive. The history of medicine contains many examples of harmful treatments that persisted for decades based on erroneous expert opinion. Clinical trials attempt to make the opinion of medical authorities evidence based. Of course, we all know that data can be as misleading as authorities, and so clinical trials are rigidly structured to avoid the bias and errors of many data analyses. As a result, however, clinical trials

tend to be rather crude tools for answering simple questions. One of the challenges is whether they can be adapted to the more complex questions involved in the personalization of therapeutics, while retaining the high level of reliability in the conclusions that we have come to expect from randomized clinical trials.

In addition to addressing the development of therapeutics, this monograph is about the development and evaluation of diagnostic tests for enabling the right drug to be used for the right patient. There is currently an enormous amount of confusion, hype, and misinformation published about personalized medicine biomarkers.

Although this monograph is not a primer on clinical trials, I have included an introductory chapter that may serve as a useful introduction for some readers and be skipped by others. I include an appendix that covers the basic statistical background needed for the material in this text for nonstatistical readers. The second chapter addresses biomarkers, prognostic classifiers, and the evaluation of diagnostic tests. The subsequent chapters describe designs and analysis strategies for the use of genomics in prospective clinical trials. Chapter 7 also includes material on the development and validation of multivariate predictive classifiers for identifying patients whose prognosis is better on a specified treatment than a control. Most of the analysis methods described in Chapter 7 and Appendix B are available in the BRB-ArrayTools software (Simon et al. 2007) available at http://brb.nci.nih.gov. Chapter 8 describes the prospective–retrospective approach to evaluate the medical utility of prognostic and predictive biomarkers based on previously conducted clinical trials. I also include an appendix on the development and validation of prognostic biomarkers using high-dimensional data such as gene expression profiles.

The target audience of the monograph includes statisticians, clinical investigators, and translational scientists. The focus is on new approaches to the design of clinical trials with prospectively specified analysis plans that provide a reliable basis for identifying what kinds of patients are likely to benefit from the test treatment. The focus is not on statistically complicated model-based analyses. There is abundant literature on post hoc analysis of clinical trials using complex statistical models. The problem is that the post hoc approach does not result in the kind of reliable

conclusion that we expect from phase III clinical trials, so those analyses are considered exploratory and hypothesis generating for future trials. Here we emphasize designing a clinical trial and prespecifying an analysis plan so that one obtains information about whether the test treatment has any benefit and, if so, whether a reliable classifier that characterizes the patients who are most likely to benefit from the test treatment can be obtained.

The book includes novel designs and novel approaches that have been developed in the past several years. Web-based programs are available at http://brb.nci.nih.gov for utilizing some of the designs. For some of the designs discussed, sufficient time has not passed for there to be published examples. These designs are currently of considerable interest in oncology drug development. I hope that the monograph contains accessible material of importance for readers of diverse backgrounds and that it can help in our efforts to develop more effective treatments for debilitating diseases.