Clinical and Statistical Considerations in Personalized Medicine

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“While nothing is more uncertain than a single life, nothing is more certain than the average duration of a thousand lives”—Elizur Wright (1804–1885, sometimes described as the “father of life insurance” for his pioneering work on actuarial tables; http://en.wikipedia.org/wiki/Elizur_Wright)

The science of statistics has long been very good at predicting the average paths of a thousand lives, but this mastery can come as cold comfort when the owner of a particular life is faced with its specific medical needs. With the recent dawn of personalized medicine, statistics has turned its attention to the details within single lives, deciphering information on the makeups of individuals and applying this information to tailor the most effective treatments for a specific individual.

Achieving the ultimate goal of personalized medicine requires synergetic advancements in biology and statistics. This message is the mission of Clinical and Statistical Considerations in Personalized Medicine, which delivers both current biological and statistical developments as described by experts in Biomedicine (e.g., Cardini) and Biostatistics (e.g., Menon and Chang).

The first four chapters deal mainly with the biology portion, presenting introductory-level information on the identification and utilization of biomarkers: types, history and characteristics of biomarkers, and their value in foretelling the effectiveness of a specific medicine (Chapter 1); the contributions and challenges in using RNA interference (RNAi) as biomarkers, which has revolutionized drug target identification in human genome (Chapter 2); interactions between genetic code and the environment in which it is manifested—epigenetics—and how epigenetic patterns and signatures can be used as biomarkers for diseases (Chapter 3); and the process of identifying appropriate biomarkers in order to develop and evaluate treatments for rare diseases (Chapter 4).

Credit should be given to the authors specializing in biomedical research for adhering to the analytical and applicability aspects of these fascinating molecules.

The second half of the book contains balanced coverage between study design and statistical analysis issues at the forefront of drug development and evaluation. Chapters 5 and 6 each present novel approaches which have been recently proposed and submitted for peer-reviewed publication; these are treated in the detail befitting original works, with problem statements followed by theories, models, examples, and even R-code to calculate stopping boundaries. Chapter 5 introduces a two-level correlation model to
assess the biomarker-informed adaptive design, and Chapter 6 discusses an adaptive staggered dose design which starts with a subset of doses and expands the set based on early study results. Chapter 7 focuses on statistical approaches for identifying and confirming classifiers, i.e., predictive biomarkers, of a specific therapy. For design and decision strategies, the authors of this chapter not only cover the hypothesis testing approach for a transition between the proof-of-concept and confirmation stages, but also apply cost–benefit ratio analysis as an aid for decision-making. This sets the stage nicely for Chapter 8, which offers statistical models and methods for meeting the various challenges in biomarker identification. In particular, sufficient information is offered to readers to understand and use the SIDES algorithm (subgroup identification based on differential effect search) developed by the chapter authors (Lipcovich et al., 2011). Chapter 9 deals with multiplicity issues in pharmacogenomics research. Typical multiplicity issues, particularly inflation of family-wise error rate (FWER), can be severe in pharmacogenomics, where thousands of genes often need to be analyzed in parallel; this chapter gives a concise account of rationales and procedures in controlling FWER and gFWER (generalized FWER). Widely adopted and less conservative procedures aimed at controlling false discovery rate and false discovery proportion are also discussed. The chapter’s appendix offers step-by-step implementations of all methods discussed in the chapter, including code for analyzing a microarray experiment in R, SAS, and East®. Chapter 10 gives a high-level overview of the patient-reported outcome and its use as a data collection tool in comparative effective research. Specific topics, such as instrument development and validation, factor analysis, mediation models, and item response theory, are touched upon. To close out the book, Chapter 11 turns to the regulatory issues in using biomarkers during drug development. The author of this chapter, FDA/CBER statistician Aloka G. Chakravarty, emphasizes the role of the biomarker as “a surrogate to clinical evidence” in the regulatory decision-making process.

The editors of this book successfully maintain a focus on those biomarkers used in the development of new drugs, with related applications—personalized diagnostics and intelligent medical devices—mostly left to the publications that will doubtlessly follow.

Any statistician or scientist who seeks to wield pharmaceutical biomarkers on the quest for personalized medical certainty will find this book a timely and useful reference on a most important and fastest evolving subject.

The Table of Contents of Clinical and Statistical Considerations in Personalized Medicine can be viewed on the publisher’s website: http://www.crcpress.com/product/isbn/9781466593862

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