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Genomic Clinical Trials and Predictive Medicine

The late 20th century, Richard Simon writes, was "an era of blockbuster drugs for homogeneous diseases." The focus was on developing treatments that proved effective, on average, when applied broadly to the entire segment of the population with a certain condition. That era, in the opinion of many in the pharmaceutical industry (e.g., Malik 2008), may be largely drawing to a close. The focus of 21st century medical research, by contrast, is likely to consider the heterogeneity of diseases and responses to treatment, and to develop treatments in which some patients will benefit from a treatment while others will not – a paradigm widely referred to as "personalized medicine".

Simon's new book, *Genomic Clinical Trials and Predictive Medicine*, is the latest installment in Cambridge University Press's "Practical Guides to Biostatistics and Epidemiology" series, and the tone of the book is indeed very practical. With the exception of the quote above, Simon's prose never strays too far from the point at hand. His goal is to provide a brief, accessible overview of new approaches to clinical trial design that attempt to simultaneously establish that a treatment is effective as well as determine what kind of patient it is effective for. In doing so, he moves briskly from one practical consideration to the next, covering a rather impressive range of topics in a mere 89 pages (excluding appendices).

This practical bent will not come as a surprise to anyone who has read Simon's articles. As the director of the Biometric Research Branch at the National Cancer Institute, Simon has been influential in industry and government, as well as academia. He has published an impressive and highly-cited body of work concerning clinical trials in the genomic era, particularly in oncology, and throughout, the book is filled not only with discussions of clinical trials in the abstract, but also references to specific trials.

Shifting from developing treatments for an entire patient population to developing treatments for a subset of those patients truly is a significant change in thinking, and brings with it many new considerations. Traditionally, these sorts of concerns have been addressed in post-hoc subset analyses, and used mainly for hypothesis-generating purposes.

In *Genomic Clinical Trials and Predictive Medicine*, these questions are built into the design of the study, so that the resulting conclusions have the same standard of evidence that we have come to expect from confirmatory clinical trials. These approaches, however, involve design considerations that are largely absent from traditional designs.

For example, suppose a new therapy will provide a large benefit to 10% of patients. The Phase III sample size may be 200, but one must screen 2,000 patients to enroll those 200. On the other hand, the effect size may be much larger in the subgroup than in the population as a whole, which reduces the number of patients that must be randomized to treatment or control. There is a lot to think about here in terms of designing an efficient trial, including the cost of the genomic assay, the expense and potential complications of treatment, accrual rates, and so on. Chapter 4 contains a very nice overview of these issues, along with a specific case study involving the drug trastuzumab (Slamon et al., 2001).

The intended target audience includes both statisticians and clinical investigators; by necessity, this means that statisticians reading the book will no doubt find the statistical details lacking in certain sections. In the finished product, however, this is not as critical as you might imagine, since the focus, overwhelmingly, is on design and not, as Simon puts it, "statistically complicated model-based analyses". Relatively speaking, there are not a great number of equations in *Genomic Clinical Trials and Predictive Medicine*. Instead, at least in the first half of the book, we have a lot of flow charts discussing issues such as whether we should randomize prior to collecting genomic information, or after collecting genomic information. These considerations are readily grasped by statisticians and non-statisticians alike, as well as being vitally important for anyone actually planning a genomic clinical trial.

It is worth clarifying what exactly Simon means by "predictive medicine" in the title of his book. It does not, as one might suppose, mean predicting a clinical outcome such as disease-free survival – that would be "prognostic medicine". Simon, generally speaking, is less interested in prognostic prediction than in predicting which subset of patients are likely to benefit (or fail to benefit) from a specific treatment, which is what he means by "predictive medicine". There is a strong case to be made for this focus, however: while patients are often eager to know more about their prognosis, insurance companies are rarely willing to pay for genomic tests merely to satisfy patient curiosity, and such prognostic prediction typically plays little role in medical decision-making. One exception to this occurs in oncology, where a genomic test may reveal that a patient's prognosis is good, and the patient may therefore wish to forego the unpleasant side effects of chemotherapy; Simon provides a sound discussion of this situation in Chapter 2.

Genomic Clinical Trials and Predictive Medicine is something of a hybrid, with Chapters 1-5 presenting a broad overview of the fundamental concepts and ideas of genomic design considerations for Phase II and Phase III clinical trials, with Chapters 6-8 reading more like a monograph, discussing some specific aspects of such trials and focusing largely on Simon's own work. These final chapters would seem to have a shorter shelf life than the rest of the book, as they concentrate on a few specific methods rather than offering a wide perspective on main ideas. Furthermore, some of the methods themselves seem a bit quick-and-dirty, and one would imagine that the next decade will see the development of more sophisticated approaches (i.e, "statistically complicated" models) for dealing with issues like adaptive design and multivariate biomarker signatures. To put it another way, if a second edition of the book were to appear in ten years, I would anticipate Chapters 6-8 requiring substantial revision, while Chapters 1-5 will mostly stand the test of time.

With *Genomic Clinical Trials and Predictive Medicine*, Simon has written an effective and timely book. Its biggest limitation is that, due to its brevity and its wide intended audience, the depth with which it covers many topics is perhaps shallower than some readers may wish. For example, Chapter 1 attempts to cover the basics of clinical trials in six pages. Now, this is a good recap – any author would struggle to cover as much ground in as few pages – although obviously there is a lot left out. Some of what is left out, such as ethical considerations and informed consent, are actually quite complicated issues in the genomic era. When it comes to study design, however, the book is dense with references for further reading for readers who want more details. Overall, I found the book very useful, serving its purpose to quickly familiarize its readers with the main ideas in genomic clinical trials and, just as helpful, providing a guide to the rapidly expanding literature in this important and evolving area.

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