

Preface

IN THE EARLY DECADES OF THE TWENTIETH CENTURY, the connection between genetics and phenotypic causality was discussed by many, but elucidated particularly clearly by geneticist, evolutionary biologist, and pioneering statistical methodologist Sewall Wright. In many ways we are only now catching up with him, and this volume is our attempt to contribute in a small way to this process. Sewall Wright introduced path analysis as a form of statistical estimation that allowed causal interpretation if—and only if—there was external causal anchoring, usually provided by the laws of Mendelian inheritance. Sewall Wright also contributed to the development of the instrumental variable method, initially advanced in a book by his father, the economist Philip Wright, in 1928. The bringing together of human genetics and causal inference for deciphering human development and disease is the subject of this book. In particular, the use of causal anchors provided by assayed germline genetic variation, which serve as instrumental variables, provides the basis for Mendelian randomization (MR), an approach discussed in several of the contributions that focus on delineating phenotypic chains of causation. Several other approaches also use genetic information to understand such chains. Natural experiments—twin studies and in vitro fertilization—contribute here, as does the use of family members as “negative controls.” We hope that the mixture of familiar and less familiar methods contributes to the sense that we are probably only scratching the surface of how genetic data will be used to elucidate modifiable pathways to desired states of health and well-being over the coming decades.

We started commissioning chapters for this volume in 2019, obviously unaware that the bulk of the work would be carried out under the shadow of a pandemic. As epidemiologists and researchers engaged in studying human disease and development, it was inevitable that we would become embroiled in COVID-19-related work, as were many of the authors who were writing contributions for us. This has led to a less smooth process than would have been desired. We would not have completed this task—at least not while retaining our sanity—if it had not been for the extraordinary support provided by Barbara Acosta and others at Cold Spring Harbor Laboratory Press. We would also like to acknowledge Julia Mackay for her fantastic administrative support. We are indebted to the authors and reviewers of the contributions for their sharp insights and critiques. A final thanks must go to our families.

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