Evidence-Based Diagnosis

Evidence-Based Diagnosis is a textbook about diagnostic, screening, and prognostic tests in clinical medicine. The authors' approach is based on many years of experience teaching physicians in a clinical research training program. Although requiring only a minimum of mathematics knowledge, the quantitative discussions in this book are deeper and more rigorous than those in most introductory texts. The book includes numerous worked examples and 60 problems (with answers) based on real clinical situations and journal articles. The book will be helpful and accessible to anyone looking to select, develop, or market medical tests. Topics covered include:

- The diagnostic process
- Test reliability and accuracy
- Likelihood ratios
- ROC curves
- Testing and treatment thresholds
- Critical appraisal of studies of diagnostic, screening and prognostic tests
- Test independence and methods of combining tests
- Quantifying treatment benefits using randomized trials and observational studies
- Bayesian interpretation of P-values and confidence intervals
- Challenges for evidence-based diagnosis

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Preface

This is a book about diagnostic testing. It is aimed primarily at clinicians, particularly those who are academically minded, but it should be helpful and accessible to anyone involved with selection, development, or marketing of diagnostic, screening, or prognostic tests. Although we admit to a love of mathematics, we have restrained ourselves and kept the math to a minimum – a little simple algebra and only three Greek letters, κ (kappa), α (alpha), and β (beta). Nonetheless, quantitative discussions in this book go deeper and are more rigorous than those typically found in introductory clinical epidemiology or evidence-based medicine texts.

Our perspective is that of skeptical consumers of tests. We want to make proper diagnoses and not miss treatable diseases. Yet, we are aware that vast resources are spent on tests that too frequently provide wrong answers or right answers of little value, and that new tests are being developed, marketed, and sold all the time, sometimes with little or no demonstrable or projected benefit to patients. This book is intended to provide readers with the tools they need to evaluate these tests, to decide if and when they are worth doing, and to interpret the results.

The pedagogical approach comes from years of teaching this material to physicians, mostly fellows and junior faculty in a clinical research training program. We have found that many doctors, including the two of us, can be impatient when it comes to classroom learning. We like to be shown that the material is important and that it will help us take better care of our patients, understand the literature, and improve our research. For this reason, in this book we emphasize real-life examples. When we care for patients and read journal articles, we frequently identify issues that the material we teach can help people understand. We have decided what material to include in this book largely by creating homework problems from patients and articles we have encountered, and then making sure that we covered in the text the material needed to solve them. This explains the disproportionate number of pediatric and emergency medicine examples, and the relatively large portion of the book devoted to problems and answers – the parts we had the most fun writing.

Although this is primarily a book about diagnosis, two of the twelve chapters are about evaluating treatments – both using randomized trials (Chapter 9) and observational studies (Chapter 10). The reason is that evidence-based diagnosis requires not only being able to evaluate tests and the information they provide, but also the *value* of that information – how it will affect treatment decisions, and how those decisions will affect patients' health. For this reason, the chapters about treatments emphasize quantifying risks and benefits. Other reasons for including the material about treatments, which also apply to the material about P-values and confidence intervals in Chapter 11, are that we love to teach it, have lots of good examples, and are able to focus on material neglected (or even wrong) in other books.

After much deliberation, we decided to include in this text answers to all of the problems. However, we strongly encourage readers to think about and even write out the answers to the problems before looking at the answers at the back of the book. The disadvantage of including all of the answers is that instructors wishing to use this book for a course will have to create new problems for any take-home or open-book examinations. Because that includes us, we will continue to write new problems, and will be happy to share them with others who are teaching courses based on this book. We will post the additional problems on the book's Web site: http://www.epibiostat.ucsf.edu/ebd. Several of the problems in this book are adapted from problems our students created in our annual final examination problem-writing contest. Similarly, we encourage readers to create problems and share them with us. With your permission, we will adapt them for the second edition!

Acknowledgments & Dedication

This book started out as the syllabus for a course TBN first taught to Robert Wood Johnson Clinical Scholars and UCSF Laboratory Medicine Residents beginning in 1991, based on the now classic textbook *Clinical Epidemiology: A Basic Science for Clinical Medicine* by Sackett, Haynes, Guyatt, and Tugwell (Sackett et al. 1991). Although over the years our selection of and approach to the material has diverged from theirs, we enthusiastically acknowledge their pioneering work in this area.

We thank our colleagues in the Department of Epidemiology and Biostatistics, particularly Steve Hulley for his mentoring and steadfast support. We are particularly indebted to Dr. Andrea Marmor, a stellar clinician, teacher, and colleague at UCSF, and Lauren Cowles, our editor at Cambridge University Press, both of whom made numerous helpful suggestions on every single chapter. We also thank our students, who have helped us develop ways of teaching this material that work best, and who have enthusiastically provided examples from their own clinical areas that illustrate the material we teach.

TBN: I would like to thank my wife, Johannah, and children, David and Rosie, for their support on the long road that led to the publication of this book. I dedicate this book to my parents, Ed and Carol Newman, in whose honor I will donate my share of the royalties to Physicians for Social Responsibility, in support of its efforts to rid the world of nuclear weapons.

MAK: I thank my wife, Caroline, and children, Emily, Jake, and Kenneth, and dedicate this book to my parents, Martin and Jean Kohn.

Sackett, D. L., R. B. Haynes, et al. (1991). *Clinical epidemiology: a basic science for clinical medicine*. Boston, MA, Little Brown.

Abbreviations/Acronyms

AAA	abdominal aortic aneurysm
ACI	acute cardiac ischemia
ALT	alanine transaminase
ANOVA	analysis of variance
ARR	absolute risk reduction
AST	aspartate transaminase
AUROC	area under the ROC curve
BMD	bone mineral density
BNP	B-type natriuretic peptide
CACS	Coronary Artery Calcium Score
CCB	calcium channel blocker
CDC	Centers for Disease Control
CHD	congenital heart disease
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase–MB fraction
CMV	cytomegalovirus
CP	chest pain
CSF	cerebrospinal fluid
CT	computed tomography
CV	coefficient of variation
D−	disease negative
D+	disease positive
DFA	direct fluorescent antibody
dL	deciliter
DRE	digital rectal examination
DS	Down syndrome
DXA	dual-energy x-ray absorptiometry

EBM	evidence-based medicine
ECG	electrocardiogram
ESR	erythrocyte sedimentation rate
FRS	Framingham Risk Score
GCS	Glasgow Coma Scale
GP	general practitioner
H_0	null hypothesis
H_A	alternative hypothesis
HAART	highly active antiretroviral therapy
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HEDIS	Health Plan Employer Data and Information Set
HHS	Health and Human Services
HPF	high power field
ICD-9	International Classification of Diseases, 9th revision
IU	international unit(s)
IV	intravenous
IVIG	intravenous immune globulin
LD	lactate dehydrogenase
ln	natural logarithm
LR	likelihood ratio
mg	milligram(s)
MI	myocardial infarction
mm	millimeter(s)
MS	multiple sclerosis
NBA	nasal bone absent
NEXUS	National Emergency X-radiology Utilization Study
NIH	National Institutes of Health
NNH	number needed to harm
NNT	number needed to treat
NPV	negative predictive value
NS	not significant
NSAID	non-steroidal anti-inflammatory drug
NT	nuchal translucency
OIA	optical immunoassay
OM	otitis media
OME	otitis media with effusion
OR	odds ratio
pCO2	partial pressure of carbon dioxide
PCR	polymerase chain reaction
PE	pulmonary embolism
PPV	positive predictive value
PSA	prostate-specific antigen
P_{TT}	treatment threshold probability

PVC	premature ventricular contraction
qCT	quantitative computed tomography
ROC	receiver operating characteristic
RR	relative risk
RRR	relative risk reduction
SK	streptokinase
SROC	summary receiver operating characteristic
tPA	tissue plasminogen activator
TSA	Transportation Safety Administration
UA	urinalysis
US	ultrasound
UTI	urinary tract infection
V/Q	ventilation/perfusion
VCUG	voiding cystourethrogram
WBC	white blood cell
WHO	World Health Organization

Greek letters

α	alpha
β	beta
κ	kappa