Evidence-Based lmaging in Pediatrics

L. Santiago Medina, MD, MPH
Co-Director Division of Neuroradiology and Brain Imaging, Director of the Health Outcomes, Policy, and Economics (HOPE) Center, Department of Radiology, Miami Children's Hospital, Miami, FL 33155, USA
santiago.medina@mch.com
Former Lecturer in Radiology, Harvard Medical School, Boston, MA 02114
smedina@post.harvard.edu

Kimberly E. Applegate, MD, MS, FACR
Vice Chair of Quality and Safety, Department of Radiology Emory University School of Medicine, 1364 Clifton Rd NE, Suite D112, Atlanta, GA 30322
keapple@emory.edu

C. Craig Blackmore, MD, MPH
Scientific Director, Center for Health Care Solutions, Department of Radiology, Virginia Mason Medical Center, Seattle, Washington
craig.blackmore@vmmc.org

Evidence-Based lmaging in Pediatrics

Optimizing Imaging in Pediatric Patient Care

With 146 Illustrations, 11 in Full Color

Foreword by Jay E. Berkelhamer, MD, FAAP
Foreword by Bruce J. Hillman, MD

Springer

Editors
L. Santiago Medina, MD, MPH
Co-Director Division of Neuroradiology and Brain Imaging
Director of the Health Outcomes, Policy, and Economics (HOPE) Center
Department of Radiology
Miami Children's Hospital
Miami, FL 33155, USA
santiago.medina@mch.com
Former Lecturer in Radiology
Harvard Medical School
Boston, MA 02114
smedina@post.harvard.edu

C. Craig Blackmore, MD, MPH
Scientific Director, Center for Health Care Solutions
Department of Radiology
Virginia Mason Medical Center
Seattle, WA 98111, USA
craig.blackmore@vmmc.org

Kimberly E. Applegate, MD, MS, FACR
Vice Chair of Quality and Safety
Department of Radiology
Emory University School of Medicine
Atlanta, Georgia 30322, USA
keapple@emory.edu

ISBN 978-1-4419-0921-3 e-ISBN 978-1-4419-0922-0
DOI 10.1007/978-1-4419-0922-0
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2009938480

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

To our patients who are our best teachers
and to the researchers, who made this book possible.
To our families, friends, and mentors.

Foreword

Medical imaging has revolutionized how we care for children and is the fastest growing area of health care today. Every clinician, from generalist to sub-specialist, will order imaging tests on children as he or she determines the course of action in caring for sick children. Given the high cost of health care and the large number of uninsured children who lack access to care, we must optimize how we use imaging to be more sophisticated and more prudent health care providers. Current worldwide economic conditions will cause physicians everywhere to confront more limited resources and weigh the costs and benefits of health care spending: "Medical technology (including radiology) itself is not the problem. It is why, how and how often it is used and by whom which creates the problem."* This book is an important step forward toward optimizing the use of imaging in children.

Most books and resources on imaging focus on how to interpret imaging and on the potential benefits of the newest imaging technologies. Less attention has been given to determining when it is appropriate to image, with what modality, and how to apply the results of imaging to clinical care. This book fills that gap, by defining how imaging can most optimally be used to diagnose or exclude the common conditions in children. Critically, the authors also provide a summary of the supporting evidence and the limitations of today's evidence-based literature.

Chapters 1 and 2 introduce the health care provider to the language, methods, and applications of evidence-based medical care. These chapters describe the common research methods used to study the role of imaging in medicine and reporting. From there, the chapters cover the most prevalent conditions and diseases affecting children in the developed nations, providing an evidence-based summary of the role of imaging in infection, inflammation, congenital disorders, trauma, neoplasm, in utero fetal assessment, and cardiovascular anomalies. Recognized leaders in radiology who understand and use the evidence-based care approach have collaborated to make the book both state of the art and readable for all physicians who care for children. Most of the individual chapters have been written by pediatric radiologists in partnership with pediatricians and other specialist physicians, providing both radiology and clinical perspectives.

Designed as a practical guide for use at the clinic or bedside rather than as a reference tome, the book eloquently captures the nuances of medical practice today and empowers the reader to use the current evidence behind medical imaging. It is a valuable book for all health care providers who care for children, from pediatricians to emergency physicians to family practice clinicians and radiologists.

*Chisholm R. Guidelines for radiological investigations [editorial]. BMJ 1991; 303:797–780.

As can be gathered from the above statements, I have decided to include this book on my "must haves" list and expect that readers will improve their skills as diagnosticians by incorporating the approaches promoted by the authors.

Jay E. Berkelhamer, MD, FAAP
Past President, American Academy of Pediatrics

Foreword

I am honored to write this foreword on several counts. First, the idea of evidence-based imaging is one in which I passionately believe. Our usual acceptance of anecdote and habit as a rationale for clinical imaging decision making is fraught with hazard for both patients and our society. Second, the editors and chapter authors have done an amazing job of putting forth an approach that is philosophically sound—one in which I can believe. Third is the focus of the book. Because of our somewhat belated concern over the long-term effects of increasingly prevalent diagnostic radiation, children and adolescents have become a lightning rod for the potential hazards of marginal and inappropriate imaging care. Finally, a book like this has even greater importance in the context of our current times. As I write this foreword, the world is plunging deep into recession. People are losing their jobs, and, with this, they are losing their health insurance. The new US President, Barack Obama, ran on a platform of instituting universal health care in the United States. What he has proposed is a very expensive plan. Where is the funding to come from? A major target, according to the new administration, is to reduce the amount of care that does not contribute to improving health. As we know, sometimes it can be difficult to distinguish beneficial from unnecessary or harmful imaging care. In this regard, this book provides us with a framework for more cost-effective decision making and direction for determining the most appropriate imaging for specific clinical presentations.

Such direction provides a "just in time" remedy for the ills that regulators and payers believe to be rife in imaging. Relatively few radiologists seem consciously aware of why we are such targets for payment reform, but perceptions that we are doing too little to reduce inappropriate imaging are a major contributor. At the root of our problem is a lack of critical reading and thinking skills. Because of how medical students and trainees are educated—with an emphasis on remembering vast amounts of minutia—too few radiologists have learned to consider critically what they read or hear in the lectures of our field's eminences. Even in our most esteemed journals, literature reviews tend to be exhaustive regurgitations of everything that has been written, without providing much insight into which studies were performed more rigorously. Few take the time to consider what information is unique to the institution generating the data and which is more generalizable to all of our practices. The emphasis remains on reading shadows rather than on what might well be our role in care coordination.

The aim of *Evidence-Based Imaging in Pediatrics* is nothing less than to begin to reverse these conditions. The editors and chapter authors are well positioned to accomplish this end. They are the anomalies in our field who have seen modern imaging practice and think we could do better. Reading *Evidence-Based Imaging in Pediatrics* provides a window into how they think as they evaluate the literature and arrive at their conclusions, which we can use as models for our own improvement. Importantly, the editors have designed a uniform approach for each chapter and held the

authors' feet to the fire to adhere to it. As a result, we do not have to adapt to a different framework as we move from gastrointestinal disease to musculoskeletal conditions to abnormalities of the vascular system. The literature reviews that follow are selective and critical, rating the strength of the literature to provide insight into the degree of confidence the reader might have in reviewing the conclusions. At the end of each chapter, the authors present the imaging approaches best supported by the evidence and what gaps exist that should give us pause for further consideration.

The outcome is a highly approachable text that suits the needs of both the busy practitioner who wants a quick consultation on a patient with whom he or she is actively engaged and of the radiologist who wishes a comprehensive, in-depth view of an important topic. Most importantly, from my perspective, the book goes counter to the current trend of "dumbing down" radiology, a trend so abhorrent in many modern textbooks. To the contrary, *Evidence-Based Imaging in Pediatrics* is an intelligent effort that respects the reader's potential to think for one's self.

Bruce J. Hillman, MD
Theodore E. Keats Professor
Department of Radiology
The University of Virginia
Charlottesville, VA

Preface

"All is flux, nothing stays still.
Nothing endures but change."
Heraclitus, 540–480 B.C.

Certainly, Heraclitus' philosophy is apparent to those who care for children: we watch them grow and change continually, and yet each child does so at different rates and in different ways. Medical imaging has grown exponentially in the last three decades with the development of many promising and often non-invasive diagnostic studies and therapeutic modalities. The corresponding medical literature has also exploded in volume, leading to information overload for health care providers. In addition, the literature varies in scientific rigor and clinical applicability, and publications on the same topic may contradict each other. The purpose of this book is to employ stringent evidence-based medical criteria in order to systematically review the evidence defining the appropriate use of medical imaging in infants and children and to present to the reader a concise summary of the best medical imaging choices for the care of infants and children.

The 41 chapters cover the most prevalent conditions and diseases that affect children in developed countries. Most of the chapters have been written by pediatric radiologists in close collaboration with pediatric clinical physicians and surgeons in order to provide a balanced analysis of the different medical topics and the role of imaging. We cannot answer all the questions we face in the clinical care of children today—medical imaging is a delicate balance of science and art, often without data for guidance—but we can empower the reader with the current evidence behind medical imaging.

To make the book user friendly and to enable fast access to pertinent information, we have organized all of the chapters in the same format. The chapters are framed around important and provocative clinical questions relevant to the daily physician's practice. A short listing of issues at the beginning of each chapter helps three different tiers of users: (1) the busy physician searching for a quick guidance, (2) the meticulous physician seeking deeper understanding, and (3) the medical-imaging researcher requiring a comprehensive resource. Key points and summarized answers to the important clinical issues are at the beginnings of the chapters, so the busy clinician can understand the most important evidence-based imaging data in seconds. This fast bottom-line information is also available in an electronic fully searchable format so that an expeditious search can be done using a handheld device on the run or a computer at the medical office, hospital, or at home. Each important question and summary is followed by a detailed discussion of the supporting evidence so that the meticulous physician can have a clear understanding of the science behind the evidence.

In each chapter, the evidence discussed in the chapter is presented in Take Home Tables and Figures, which provide an easy review in the form of summary tables and flow charts. The Imaging Case Studies highlight the strengths and limitations of the different imaging studies with vivid examples. Toward the ends of the chapters, the best imaging protocols are described to assure that the imaging studies are well standardized and done with the highest available quality. The final sections of the chapters are called Future Research; here, provocative questions are raised for physicians and non-physicians interested in advancing medical imaging.

Not all research and not all evidences are created equal. Accordingly, throughout the book, we use a four-level classification detailing the strength of the evidence and based on the Oxford Criteria: Level I (strong evidence), Level II (moderate evidence), Level III (limited evidence), and Level IV (insufficient evidence). The strength of the evidence is presented in parenthesis throughout the chapters so the reader gets immediate feedback on the weight of the evidence behind each topic.

Finally, we had the privilege of working with a group of outstanding contributors from major medical centers and universities in North America and Europe. We believe that the authors' expertise, breadth of knowledge, and thoroughness in writing different chapters provide a valuable source of information and can guide decision making for physicians and patients. In addition to guiding practice, the evidence summarized in the chapters may have policy-making and public health implications. Finally, we hope that the book highlights key points and generates discussion, promoting new ideas for future research.

L. Santiago Medina, MD, MPH
Kimberly E. Applegate, MD, MS
C. Craig Blackmore, MD, MPH

Contents

Contributors

Nolan Altman, MD
Chief, Department of Radiology, Miami Children's Hospital, Miami, FL 33155, USA

Sudha Anupindi, MD
Assistant Professor of Radiology, Department of Radiology, at the Children's Hospital of University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA

Yoshimi Anzai, MD, MPH
Professor, Department of Radiology, University of Washington Medical Center, Seattle, WA 98195, USA

Kimberly E. Applegate, MD, MS, FACR
Vice Chair of Quality and Safety, Department of Radiology, Emory University School of Medicine, Atlanta, Georgia 30322, USA

Stephen Ashwal, MD
Chief, Division of Pediatric Neurology, Department of Pediatrics, Loma Linda University, Loma Linda, CA 92350, USA

Rama Ayyala, MD
Department of Internal Medicine, Mount Sinai Medical Center, New York, NY 10029, USA

Martha C. Ballesteros, MD
Pediatric Radiologist, Department of Radiology, Miami Children's Hospital, Miami, FL 33155, USA

Carol E. Barnewolt, MD
Assistant Professor, Department of Radiology, Harvard Medical School, Co-Director, Division of Ultrasound, Department of Radiology, Children's Hospital Boston, Boston, MA 02115, USA

D. Gregory Bates, MD
Clinical Assistant Professor of Radiology, Department of Radiology, The Ohio State University College of Medicine and Public Health, Nationwide Children's Hospital, Columbus, OH 43205, USA

Barry R. Berch, MD
Department of Pediatric Surgery, Vanderbilt University School of Medicine, Nashville, TN 37232, USA

Byron Bernal, MD, CCTI
Neuroscientist, Department of Radiology, Miami Children's Hospital, Miami, FL 33155, USA

Rob A.C. Bilo, MD
Department of Forensic Pathology, Netherlands Forensic Institute, 2497GB, The Hague, The Netherlands

G. Brian Black, MD, FRCS(C), FACS
Professor of Surgery, Paediatric Orthopedic Surgeon, Department of Surgery (Orthopedics), Winnipeg Children's Hospital, University of Manitoba, Winnipeg, MB R3A 1S1, Canada

C. Craig Blackmore, MD, MPH
Scientific Director, Center for Health Care Solutions, Department of Radiology, Virginia Mason Medical Center, Seattle, WA 98111, USA

Dorothy I. Bulas, MD
Professor of Radiology and Pediatrics, Department of Diagnostic Imaging and Radiology, George Washington University School of Medicine and Health Sciences, Children's National Medical Center, Washington DC 20010, USA

Luisa F. Cervantes, MD
Pediatric Radiologist, Department of Radiology, Miami Children's Hospital, Miami, FL 33155, USA

Soonmee Cha, MD
Associate Professor, Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA 94143, USA

Pranav Chitkara, BS, MD
Department of Internal Medicine, Baylor College of Medicine, Houston, TX 77030, USA

Garry Choy, MD, MS
Department of Radiology, Massachusetts General Hospital, Boston, MA 02114, USA

Leonard P. Connolly, MD
Assistant Professor of Radiology, Associate Radiologist, Department of Nuclear Medicine/ Radiology, Harvard Medical School, Massachusetts General Hospital, Boston, MA 02114, USA

Erin A. Cooke, MD
Department of Radiology, Virginia Mason Medical Center, Seattle, WA 98101, USA

Andrea Doria, MD, PhD, MSc
Clinician Scientist/General Radiologist, Department of Diagnostic Imaging, The Hospital for Sick Children, Toronto, ON 5MG 1X8, Canada

Carlos R. Estrada, MD
Instructor in Surgery (Urology), Department of Urology, Harvard Medical School, Children's Hospital Boston, Boston, MA 02115, USA

Lynn Ansley Fordham, MD
Associate Professor and Chief of Pediatric Imaging, Department of Radiology, University of North Carolina School of Medicine, North Carolina Children's Hospital, Chapel Hill, NC 27599, USA

Donald P. Frush, MD
Professor of Radiology and Pediatrics, Division of Pediatric Radiology, Department of Radiology, Duke Medical Center, Durham, NC 27710, USA

Debbie S. Gipson, MD, MS
Associate Professor, Division of Nephrology and Hypertension, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

Joel A. Gross, MD, MS
Associate Professor, Chief, and Fellowship Director, Emergency Radiology, Department of Radiology, Harborview Medical Center, University of Washington School of Medicine, Seattle, WA 98104, USA

Brian E. Grottkau, MD
Chief of Pediatric Orthopaedics, Department of Orthopaedic Surgery, Massachusetts General Hospital for Children/Harvard Medical School, Boston, MA 02114, USA

Jeffrey C. Hellinger, MD
Assistant Professor of Radiology, Department of Radiology, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA

Marta Hernanz-Schulman, MD
Professor, Radiology and Pediatrics, Radiology Vice-Chair in Pediatrics, Radiologist-in-Chief and Medical Director, Department of Diagnostic Imaging, Vanderbilt Children's Hospital, Monroe Carell Jr Children's Hospital at Vanderbilt, Nashville, TN 37232, USA

Barbara A. Holshouser, PhD
Associate Professor, Department of Radiology, Loma Linda University Medical Center, Loma Linda, CA 92354, USA

Diego Jaramillo, MD, MPH
Radiologist-in-Chief, Department of Radiology, The Children's Hospital of Philadelphia, Professor of Radiology, Department of Radiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA

Boaz Karmazyn, MD
Department of Pediatric Radiology, Assistant Professor of Radiology, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, IN 46202, USA

Marc S. Keller, MD
Professor of Clinical Radiology, Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

Judith Kelsen, MD
Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

Geetika Khanna, MD, MS
Assistant Professor, Washington University School of Medicine, 510 S. Kings highway, Campus Box 8131-MIR, St Louis, MO 63110

John Y. Kim, MD
Chairman, Department of Radiology, Texas Health Presbyterian Hospital of Plano, Plano, TX 75093, USA

Jaroslaw Krejza, MD, PhD
Associate Professor of Radiology, Department of Radiology, Division of Neuroradiology, University of Pennsylvania, Philadelphia, PA 19104, USA; Department of Nuclear Medicine, University of Gdansk, Gdansk, Poland

Rajesh Krishnamurthy, MB, BS
Assistant Professor of Radiology, EB Singleton Department of Diagnostic Imaging, Texas Children's Hospital, Baylor College of Medicine, Houston, TX 77030, USA

Edward Y. Lee, MD, MPH
Assistant Professor of Radiology, Department of Radiology, Children's Hospital Boston, Harvard Medical School, Boston, MA 02115, USA

Petar Mamula, MD
Director of Kohl's Endoscopy Suite, Assistant Professor of Pediatrics, Department of Pediatrics, University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

F.A. Mann, MD
Department of Medical Imaging, Seattle Radiologists, Swedish Medical Center, Seattle, WA 98104, USA

Amit M. Mathur, MBBS, MD
Associate Professor of Pediatrics, Department of Pediatrics/Newborn Medicine, Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, MO 63110, USA

Robert C. McKinstry, MD, PhD
Associate Professor, Department of Pediatric Radiology, St. Louis Children's Hospital, Washington University, St. Louis, MO 63017, USA

L. Santiago Medina, MD, MPH
Co-Director Division of Neuroradiology and Brain Imaging, Director of the Health Outcomes, Policy, and Economics (HOPE) Center, Department of Radiology, Miami Children's Hospital, Miami, FL 33155, USA; Former Lecturer in Radiology, Harvard Medical School, Boston, MA 02114

Elias R. Melhem, MD, PhD
Professor of Radiology, Department of Radiology, Division of Neuroradiology, University of Pennsylvania, Philadelphia, PA 19104, USA

Elka Miller, MD
Pediatric Radiologist, Department of Radiology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada

Toshio Moritani, MD, PhD
Assistant Professor, Department of Radiology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, USA

Wallace W. Neblett III, MD
Professor of Pediatric Surgery and Pediatrics, Chairman, Department of Surgery; Department of Pediatric Surgery, Vanderbilt University School of Medicine, Nashville, TN 37232, USA

Els L.F. Nijs, MD
Assistant Professor of Radiology, Department of Radiology, Children's Hospital of Philadelphia, Philadephia, PA 19104, USA

Huub G.T. Nijs, MD, PhD
Department of Forensic Pathology, Netherlands Forensic Institute, Lann Van Ypenburg 6, 2497GB, The Hague, The Netherlands

Natan Noviski, MD
Chief, Pediatric Critical Care Medicine, Massachusetts General Hospital, Associate Professor of Pediatrics, Harvard Medical School, Department of Pediatric Critical Care Medicine, Boston, MA 02114, USA

Udochukwu E. Oyoyo, MPH
Department of Radiology, Loma Linda University Medical Center, Loma Linda, CA 92354, USA

Esperanza Pacheco-Jacome, MD
Co-Director of Neuroradiology and Brain Imaging, Department of Radiology, Miami Children's Hospital, Miami, FL 33155, USA

Angelisa Paladin, MD, MS
Associate Professor, Department of Radiology, University of Washington, Seattle, WA 98195, USA

Andres H. Peña, MD
Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

Michelle Perez, BS, LPN
Health Outcomes, Policy and Economics (HOPE) Center, Department of Radiology, Miami Children's Hospital, Miami, FL 33155, USA

Tina Young Poussaint, MD
Associate Professor of Radiology, Department of Radiology, Harvard Medical School, Attending Neuroradiologist, Department of Radiology, Children's Hospital Boston, Boston, MA 02115, USA

Stefan Puig, MD MSc
Associate Professor, Head of Department, Research Programm on Evidence-Based Medical Diagnostics, Institute of Public Health, Paracelsus Private Medical University, Salzburg A-5020, Austria

James G. Ravenel, MD
Chief of Thoracic Imaging, Department of Radiology, The Medical University of South Carolina, Charleston, SC 29425, USA

Martin H. Reed, MD, FRCP(C)
Head, Section of Pediatric Radiology, Department of Diagnostic Imaging, University of Manitoba Health Sciences Centre/Children's Hospital, Winnipeg, MB R3A 1S1, Canada

Ricardo Restrepo, MD
Pediatric Radiologist, Fellowship Director, Department of Radiology, Miami Children's Hospital, Miami, FL 33155, USA

Yutaka Sato, MD
Professor of Radiology, Department of Radiology, University of Iowa, Iowa City, IA 52242, USA

Christopher Schettino, MD
Department of Radiology, Miami Children's Hospital, Miami, FL 33155, USA

Marilyn J. Siegel, MD
Professor of Radiology and Pediatrics, Mallinckrodt Institute of Radiology, Washington University Medical School, St. Louis, MO 63110, USA

Gerard A. Silvestri MD, MS
Professor of Medicine, Department of Medicine, Medical University of South Carolina, Charleston, SC 29425, USA

Richard W. Sutherland, MD
Associate Professor, Department of Surgery, Division of Urology, University of North Carolina Children's Hospital, Chapel Hill, NC 27599, USA

Maciej Swiat, MD, PhD
Department of Neurology, Aging, Degenerative and Cerebrovascular Diseases, Medical University of Silesia/Central University Hospital, Katowice, Poland; Department of Radiology, Division of Neuroradiology, University of Pennsylvania, Philadelphia, PA 19104, USA

Maciej Tomaszewski, MD, PhD
Department of Radiology, Division of Neuroradiology, University of Pennsylvania, Philadelphia, PA 19104, USA

Karen A. Tong, BSc, MD
Associate Professor, Department of Radiology, Loma Linda University, Loma Linda, CA 92354, USA

Neil Vachhani, MD
Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

Rick R. van Rijn, MD, PhD
Pediatric Radiologist, Department of Radiology, Emma Children's Hospital/Academic Medical Centre Amsterdam, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands

Elza Vasconcellos, MD
Director, Headache Disorders Clinic, Department of Neurology, Miami Children's Hospital, Miami, FL 33155

Daniel N. Vinocur, MD
Department of Radiology, Children's Hospital Boston. Harvard Medical School. Boston, Massachusetts

Sjirk J. Westra, MD
Associate Professor, Department of Radiology, Harvard Medical School, Massachusetts General Hospital, Boston, MA 02114, USA

Phoebe H. Yager, MD
Pediatric Intensivist, Massachusetts General Hospital, Assistant in Pediatrics, Harvard Medical School, Department of Pediatric Critical Care Medicine, Boston, MA 02114, USA

Part I

Principles, Methodology, and Radiation Risk

1

Principles of Evidence-Based Imaging

L. Santiago Medina, C. Craig Blackmore, and Kimberly E. Applegate

Medicine is a science of uncertainty and an art of probability.

Sir William Osler

Issues

I. What is evidence-based imaging?
II. The evidence-based imaging process
  a. Formulating the clinical question
  b. Identifying the medical literature
  c. Assessing the literature
    1. What are the types of clinical studies?
    2. What is the diagnostic performance of a test: sensitivity, specificity, and receiver operating characteristic (ROC) curve?
    3. What are cost-effectiveness and cost-utility studies?
  d. Types of economic analyses in medicine
  e. Summarizing the data
  f. Applying the evidence
III. How to use this book

I. What Is Evidence-Based Imaging?

The standard medical education in Western medicine has emphasized skills and knowledge learned from experts, particularly those encountered in the course of postgraduate medical education, and through national publications and meetings. This reliance on experts, referred to by Dr. Paul Gerber of Dartmouth Medical School as "eminence-based medicine"

L.S. Medina (✉)
Co-Director Division of Neuroradiology and Brain Imaging, Director of the Health Outcomes, Policy, and Economics (HOPE) Center, Department of Radiology, Miami Children's Hospital, Miami, FL 33155, USA
e-mail: santiago.medina@mch.com

This chapter is based on a previous chapter titled "Principles of Evidence-Based Imaging" by LS Medina and CC Blackmore that appeared in *Evidence-Based Imaging: Optimizing Imaging in Patient Care* edited by LS Medina and CC Blackmore. New York: Springer Science+Business Media, 2006.

L.S. Medina et al. (eds.), *Evidence-Based Imaging in Pediatrics*,
DOI 10.1007/978-1-4419-0922-0_1, © Springer Science+Business Media, LLC 2010

(1), is based on the construct that the individual practitioner, particularly a specialist devoting extensive time to a given discipline, can arrive at the best approach to a problem through his or her experience. The practitioner builds up an experience base over years and digests information from national experts who have a greater base of experience due to their focus in a particular area. The evidence-based imaging (EBI) paradigm, in contradistinction, is based on the precept that a single practitioner cannot through experience alone arrive at an unbiased assessment of the best course of action. Assessment of appropriate medical care should instead be derived through evidence-based process. The role of the practitioner, then, is not simply to accept information from an expert, but rather to assimilate and critically assess the research evidence that exists in the literature to guide a clinical decision (2–4).

Fundamental to the adoption of the principles of EBI is the understanding that medical care is not optimal. The life expectancy at birth in the United States for males and females in 2005 was 75 and 80 years, respectively (Table 1.1). This is slightly lower than the life expectancies in other industrialized nations such as the United Kingdom and Australia (Table 1.1). The United States spends at least 15.2% of the gross domestic product in order to achieve this life expectancy. This is significantly more than the United Kingdom and Australia, which spend about half that (Table 1.1). In addition, the U.S. per capita health expenditure is $6096, which is twice the expenditures in the United Kingdom or Australia. In conclusion, the United States spends significantly more money and resources than other industrialized countries to achieve a similar outcome in life expectancy. This implies that a significant amount of resources is wasted in the U.S. health care system. The United States in 2007 spent $2.3 trillion in health care. By 2016, the U.S. health percent of the gross domestic product is expected to grow to 20% or $4.2 trillion (5). Recent estimates prepared by the Commonwealth Fund Commission (USA) on a High Performance Health System indicate that $1.5 trillion could be saved over a 10-year period if a combination of options, including evidence-based medicine and universal health insurance, was adopted (6).

Simultaneous with the increase in health care costs has been an explosion in available medical information. The National Library of Medicine PubMed search engine now lists over 18 million citations. Practitioners cannot maintain familiarity with even a minute subset of this literature without a method of filtering out publications that lack appropriate methodological quality. Evidence-based imaging is a promising method of identifying appropriate information to guide practice and to improve the efficiency and effectiveness of imaging.

Evidence-based imaging is defined as medical decision making based on clinical integration of the best medical imaging research evidence with the physician's expertise and with patient's expectations (2–4). The best medical imaging research evidence often comes from the basic sciences of medicine. In EBI, however, the basic science knowledge has been translated into patient-centered clinical research, which determines the accuracy and role of diagnostic and therapeutic imaging in patient care (3). New evidence may make current diagnostic tests obsolete and new ones more accurate, less invasive, safer, and less costly (3).

Table 1.1. Life expectancy and health care spending in three developed countries

	Life expectancy at birth (2005)		Percentage of GDP in health care (2003) (%)	Per capita health expenditure (2007)
	Male	Female		
United States	**753**	**803**	**15.2**	**$6,096**
United Kingdom	**774**	**814**	**7.8**	**$2,560**
Australia	**795**	**845**	**9.2**	**$3,123**

GDP, gross domestic product.

Sources: Organization for Economic Cooperation and Development Health Data File 2002, www.oecd.org/els/health; United Kingdom Office of National Statistics; Australian Bureau of Statistics; Per capita expenditures: *Human Development Report, 2007,* United Nations, hdr.undp.org; Life expectancy: Kaiser Family Foundation web site with stated source: WHO, World Health Statistics 2007, available at: http://www.who.int/whosis/en/.

The physician's expertise entails the ability to use the referring physician's clinical skills and past experience to rapidly identify high-risk individuals who will benefit from the diagnostic information of an imaging test (4). Patient's expectations are important because each individual has values and preferences that should be integrated into the clinical decision making in order to serve our patients' best interests (3). When these three components of medicine come together, clinicians and imagers form a diagnostic team, which will optimize clinical outcomes and quality of life for our patients.

II. The Evidence-Based Imaging Process

The evidence-based imaging process involves a series of steps: (A) formulation of the clinical question, (B) identification of the medical literature, (C) assessment of the literature, (D) summary of the evidence, and (E) application of the evidence to derive an appropriate clinical action. This book is designed to bring the EBI process to the clinician and imager in a user-friendly way. This introductory chapter details each of the steps in the EBI process. Chapter 2 discusses how to critically assess the literature. The rest of the book makes available to practitioners the EBI approach to numerous key medical imaging issues. Each chapter addresses common pediatric disorders ranging from congenital anomalies to asthma to appendicitis. Relevant clinical questions are delineated, and then each chapter discusses the results of the critical analysis of the identified literature. The results of this analysis are presented with meta-analyses where appropriate. Finally, we provide simple recommendations for the various clinical questions, including the strength of the evidence that supports these recommendations.

A. Formulating the Clinical Question

The first step in the EBI process is formulation of the clinical question. The entire process of evidence-based imaging arises from a question that is asked in the context of clinical practice. However, often formulating a question for the EBI approach can be more challenging than one would believe intuitively. To be approachable by the EBI format, a question must be specific to a clinical situation, a patient group, and an outcome or action. For example, it would not be appropriate to simply ask which imaging technique is better—computed tomography (CT) or radiography. The question must be refined to include the particular patient population and the action that the imaging will be used to direct. One can refine the question to include a particular population (which imaging technique is better in pediatric victims of high-energy blunt trauma) and to guide a particular action or decision (to exclude the presence of unstable cervical spine fracture). The full EBI question then becomes, In pediatric victims of high-energy blunt trauma, which imaging modality is preferred, CT or radiography, to exclude the presence of unstable cervical spine fracture? This book addresses questions that commonly arise when employing an EBI approach for the care of children and adolescents. These questions and issues are detailed at the start of each chapter.

B. Identifying the Medical Literature

The process of EBI requires timely access to the relevant medical literature to answer the question. Fortunately, massive on-line bibliographical references such as PubMed are available. In general, titles, indexing terms, abstracts, and often the complete text of much of the world's medical literature are available through these on-line sources. Also, medical librarians are a potential resource to aid identification of the relevant imaging literature. A limitation of today's literature data sources is that often too much information is available and too many potential resources are identified in a literature search. There are currently over 50 radiology journals, and imaging research is also frequently published in journals from other medical subspecialties. We are often confronted with more literature and information than we can process. The greater challenge is to sift through the literature that is identified to select that which is appropriate.

C. Assessing the Literature

To incorporate evidence into practice, the clinician must be able to understand the published literature and to critically evaluate the strength of the evidence. In this introductory chapter on the process of EBI, we focus on discussing types of research studies. Chapter 2 is a detailed discussion of the issues in determining the validity and reliability of the reported results.

1. What Are the Types of Clinical Studies?

An initial assessment of the literature begins with determination of the type of clinical study: descriptive, analytical, or experimental (7). *Descriptive* studies are the most rudimentary, as they only summarize disease processes as seen by imaging, or discuss how an imaging modality can be used to create images. Descriptive studies include case reports and case series. Although they may provide important information that leads to further investigation, descriptive studies are not usually the basis for EBI.

Analytic or *observational* studies include cohort, case–control, and cross-sectional studies (Table 1.2). Cohort studies are defined by risk factor status, and case–control studies consist of groups defined by disease status (8). Both case–control and cohort studies may be used to define the association between an intervention, such as an imaging test, and patient outcome (9). In a cross-sectional (prevalence) study, the researcher makes all of his measurements on a single occasion. The investigator draws a sample from the population (i.e., asthma in 5- to 15-year-olds) and determines distribution of variables within that sample (7). The structure of a cross-sectional study is similar to that of a cohort study except that all pertinent measurements (i.e., PFTs) are made at once, without a follow-up period. Cross-sectional studies can be used as a major source for health and habits of different populations and countries, providing estimates of such parameters as the prevalence of asthma, obesity, and congenital anomalies (7, 10).

Table 1.2. Study design

	Prospective follow-up	Randomization of subjects	Controls
Case report or series	No	No	No
Cross-sectional study	No	No	Yes
Case–control study	No	No	Yes
Cohort study	Yes/no	No	Yes
Randomized controlled trial	Yes	Yes	Yes

Reprinted with the kind permission of Springer Science+Business Media from by Medina and Blackmore (40).

In *experimental studies* or *clinical trials*, a specific intervention is performed and the effect of the intervention is measured by using a control group (Table 1.2). The control group may be tested with a different diagnostic test and treated with a placebo or an alternative mode of therapy (7, 11). Clinical trials are epidemiologic designs that can provide data of high quality that resemble the controlled experiments done by basic science investigators (8). For example, clinical trials may be used to assess new diagnostic tests (e.g., high-resolution CT for cystic fibrosis) or new interventional procedures (e.g., stenting for coronary artery anomalies).

Studies are also traditionally divided into retrospective and prospective (Table 1.2) (7, 11). These terms refer more to the way the data are gathered than to the specific type of study design. In *retrospective studies*, the events of interest have occurred before study onset. Retrospective studies are usually done to assess rare disorders, for pilot studies, and when prospective investigations are not possible. If the disease process is considered rare, retrospective studies facilitate the collection of enough subjects to have meaningful data. For a pilot project, retrospective studies facilitate the collection of preliminary data that can be used to improve the study design in future prospective studies. The major drawback of a retrospective study is incomplete data acquisition (10). Case–control studies are usually retrospective. For example, in a case–control study, subjects in the case group (patients with perforated appendicitis) are compared with subjects in a control group (nonperforated appendicitis) to determine factors associated with perforation (e.g., duration of symptoms, presence of appendicolith, size of appendix) (10).

In *prospective studies*, the event of interest transpires after study onset. Prospective stud-

ies, therefore, are the preferred mode of study design, as they facilitate better control of the design and the quality of the data acquired (7). Prospective studies, even large studies, can be performed efficiently and in a timely fashion if done on common diseases at major institutions, as multicenter trials with adequate study populations (12). The major drawback of a prospective study is the need to make sure that the institution and personnel comply with strict rules concerning consents, protocols, and data acquisition (11). Persistence, to the point of irritation, is crucial to completing a prospective study. Cohort studies and clinical trials are usually prospective. For example, a cohort study could be performed in children with splenic injury in which the risk factor of presence of arterial blush is correlated with the outcome of failure of nonmedical management, as the patients are followed prospectively over time (10).

The strongest study design is the prospective randomized, blinded clinical trial (Table 1.2) (7). The randomization process helps to distribute known and unknown confounding factors, and blinding helps to prevent observer bias from affecting the results (7, 8). However, there are often circumstances in which it is not ethical or practical to randomize and follow patients prospectively. This is particularly true in rare conditions, and in studies to determine causes or predictors of a particular condition (9). Finally, randomized clinical trials are expensive and may require many years of follow-up. Not surprisingly, randomized clinical trials are uncommon in radiology. The evidence that supports much of radiology practice is derived from cohort and other observational studies. More randomized clinical trials are necessary in radiology to provide sound data to use for EBI practice (3).

2. *What Is the Diagnostic Performance of a Test: Sensitivity, Specificity, and Receiver Operating Characteristic (ROC) Curve?*

Defining the presence or absence of an outcome (i.e., disease and nondisease) is based on a standard of reference (Table 1.3). While a perfect standard of reference or so-called gold standard can never be obtained, careful attention should be paid to the selection of the standard that should be widely believed to offer the best approximation to the truth (13).

Table 1.3. Two-way table of diagnostic testing

	Disease (gold standard)	
Test result	**Present**	**Absent**
Positive	**a (TP)**	**b (FP)**
Negative	**c (FN)**	**d (TN)**

FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reprinted with the kind permission of Springer Science+Business Media from by Medina and Blackmore (40).

In evaluating diagnostic tests, we rely on the statistical calculations of sensitivity and specificity (see Appendix 1). Sensitivity and specificity of a diagnostic test are based on the two-way (2 × 2) table (Table 1.3). Sensitivity refers to the proportion of subjects with the disease who have a positive test and is referred to as the true positive rate (Fig. 1.1). Sensitivity, therefore, indicates how well a test identifies the subjects with disease (7, 14).

Specificity is defined as the proportion of subjects without the disease who have a negative index test (Fig. 1.1) and is referred to as the true negative rate. Specificity, therefore, indicates how well a test identifies the subjects with no disease (7, 11). It is important to note that the sensitivity and specificity are characteristics of the test being evaluated and are therefore usually independent of the prevalence (proportion of individuals in a population who have disease at a specific instant) because the sensitivity only deals with the diseased subjects, whereas the specificity only deals with the nondiseased subjects. However, sensitivity and specificity both depend on a threshold point for considering a test positive and hence may change according to which threshold is selected in the study (11, 14, 15) (Fig. 1.1A). Excellent diagnostic tests have high values (close to 1.0) for both sensitivity and specificity. Given exactly the same diagnostic test, and exactly the same subjects confirmed with the same reference test, the sensitivity with a low threshold is greater than the sensitivity with a high threshold. Conversely, the specificity with a low threshold is less than the specificity with a high threshold (Fig. 1.1B) (14, 15).

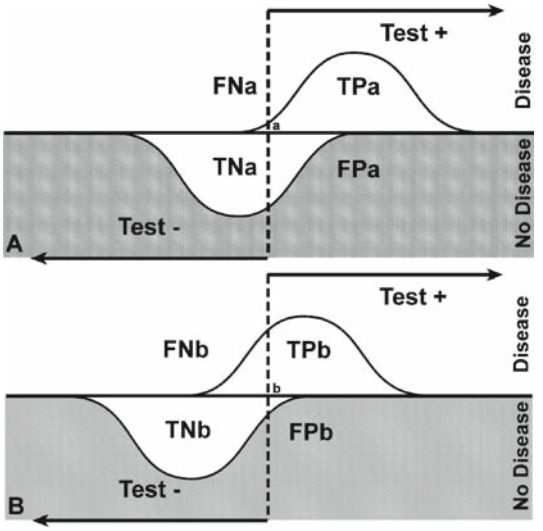

Figure 1.1. Test with a low (A) and high (B) threshold. The sensitivity and specificity of a test change according to the threshold selected; hence, these diagnostic performance parameters are threshold dependent. Sensitivity with low threshold (TPa/diseased patients) is greater than sensitivity with a higher threshold (TPb/dis-eased patients). Specificity with a low threshold (TNa/nondiseased patients) is less than specificity with a high threshold (TNb/nondiseased patients). FN, false negative; FP, false positive; TN, true negative; TP, true positive. (Reprinted with permission of the American Society of Neuroradiology from Medina (11).)

The effect of threshold on the ability of a test to discriminate between disease and nondisease can be measured by a receiver operating characteristic (ROC) curve (11, 15). The ROC curve is used to indicate the trade-offs between sensitivity and specificity for a particular diagnostic test and hence describes the discrimination capacity of that test. An ROC graph shows the relationship between sensitivity (*y*-axis) and 1–specificity (*x*-axis) plotted for various cutoff points. If the threshold for sensitivity and specificity are varied, an ROC curve can be generated. The diagnostic performance of a test can be estimated by the area under the ROC curve. The steeper the ROC curve, the greater the area and the better the discrimination of the test (Fig. 1.2). A test with perfect discrimination has an area of 1.0, whereas a test with only random discrimination has an area of 0.5 (Fig. 1.2). The area under the

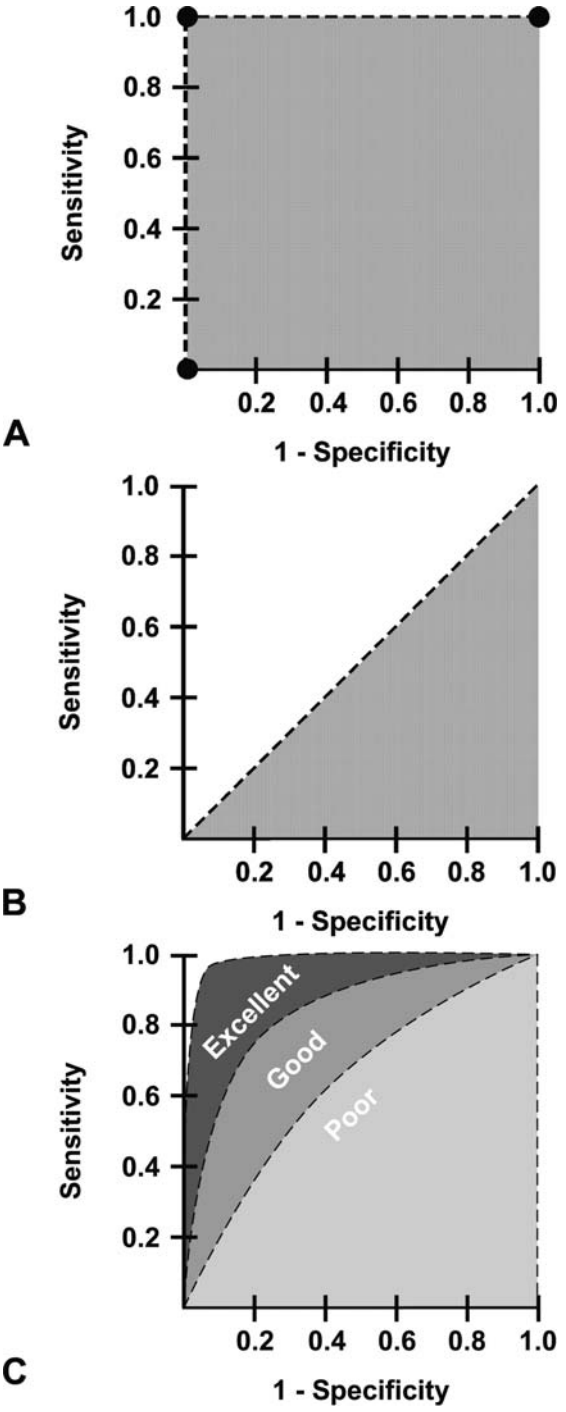

Figure 1.2. The perfect test (A) has an area under the curve (AUC) of 1. The useless test (B) has an AUC of 0.5. The typical test (C) has an AUC between 0.5 and 1. The greater the AUC (i.e., excellent > good > poor), the better the diagnostic performance. (Reprinted with permission of the American Society of Neuroradiology from Medina (11).)

ROC curve usually determines the overall diagnostic performance of the test independent of the threshold selected (11, 15). The ROC curve is threshold independent because it is generated by using varied thresholds of sensitivity and specificity. Therefore, when evaluating a new imaging test, in addition to the sensitivity and specificity, an ROC curve analysis should be done so that the threshold-dependent and threshold-independent diagnostic performance can be fully determined (10).

3. What Are Cost-Effectiveness and Cost-Utility Studies?

Cost-effectiveness analysis (CEA) is an objective scientific technique used to assess alternative health care strategies on both cost and effectiveness (16–18). It can be used to develop clinical and imaging practice guidelines and to set health policy (19). However, it is not designed to be the final answer to the decision-making process; rather, it provides a detailed analysis of the cost and outcome variables and how they are affected by competing medical and diagnostic choices.

Health dollars are limited regardless of the country's economic status. Hence, medical decision makers must weigh the benefits of a diagnostic test (or any intervention) in relation to its cost. Health care resources should be allocated so the maximum health care benefit for the entire population is achieved (10). Cost-effectiveness analysis is an important tool to address health cost-outcome issues in a cost-conscious society. Countries such as Australia usually require robust CEA before drugs are approved for national use (10).

Unfortunately, the term *cost-effectiveness* is often misused in the medical literature (20). To say that a diagnostic test is truly cost-effective, a comprehensive analysis of the entire short- and long-term outcomes and costs needs to be considered. Cost-effectiveness analysis is an objective technique used to determine which of the available tests or treatments are worth the additional costs (21).

There are established guidelines for conducting robust CEA. The U.S. Public Health Service formed a panel of experts on cost-effectiveness in health and medicine to create detailed standards for cost-effectiveness analysis. The panel's recommendations were published as a book in 1996 (21).

D. Types of Economic Analyses in Medicine

There are four well-defined types of economic evaluations in medicine: cost-minimization studies, cost–benefit analyses, cost-effectiveness analyses, and cost-utility analyses. They are all commonly lumped under the term *cost-effectiveness analysis*. However, significant differences exist among these different studies.

Cost-minimization analysis is a comparison of the cost of different health care strategies that are assumed to have identical or similar effectiveness (16). In medical practice, few diagnostic tests or treatments have identical or similar effectiveness. Therefore, relatively few articles have been published in the literature with this type of study design (22). For example, a recent study demonstrated that functional magnetic resonance imaging (MRI) and the Wada test have similar effectiveness for language lateralization, but the later is 3.7 times more costly than the former (23).

Cost–benefit analysis (CBA) uses monetary units such as dollars or euros to compare the costs of a health intervention with its health benefits (16). It converts all benefits to a cost equivalent and is commonly used in the financial world where the cost and benefits of multiple industries can be changed to only monetary values. One method of converting health outcomes into dollars is through a contingent valuation or willingness-to-pay approach. Using this technique, subjects are asked how much money they would be willing to spend to obtain, or avoid, a health outcome. For example, a study by Appel et al. (24) found that individuals would be willing to pay $50 for low osmolar contrast agents to decrease the probability of side effects from intravenous contrast. However, in general, health outcomes and benefits are difficult to transform to monetary units; hence, CBA has had limited acceptance and use in medicine and diagnostic imaging (16, 25).

Cost-effectiveness analysis (CEA) refers to analyses that study both the effectiveness and cost of competing diagnostic or treatment strategies, where effectiveness is an objective measure (e.g., intermediate outcome: number of strokes detected; or long-term outcome: life-

years saved). Radiology CEAs often use intermediate outcomes, such as lesion identified, length of stay, and number of avoidable surgeries (16, 18). However, ideally, long-term outcomes such as life-years saved (LYS) should be used (21). By using LYS, different health care fields or interventions can be compared.

Cost-utility analysis is similar to CEA except that the effectiveness also accounts for quality of life issues. Quality of life is measured as utilities that are based on patient preferences (16). The most commonly used utility measurement is the quality-adjusted life year (QALY). The rationale behind this concept is that the QALY of excellent health is more desirable than the same 1 year with substantial morbidity. The QALY model uses preferences with weight for each health state on a scale from 0 to 1, where 0 is death and 1 is perfect health. The utility score for each health state is multiplied by the length of time the patient spends in that specific health state (16, 26). For example, let us assume that a patient with a congenital heart anomaly has a utility of 0.8 and he spends 1 year in this health state. The patient with the cardiac anomaly would have a 0.8 QALY in comparison with his neighbor who has a perfect health and hence a 1 QALY.

Cost-utility analysis incorporates the patient's subjective value of the risk, discomfort, and pain into the effectiveness measurements of the different diagnostic or therapeutic alternatives. In the end, all medical decisions should reflect the patient's values and priorities (26). That is the explanation of why cost-utility analysis is becoming the preferred method for evaluation of economic issues in health (19, 21). For example, in low-risk newborns with intergluteal dimple suspected of having occult spinal dysraphism, ultrasound was the most effective strategy with an incremented cost-effectiveness ratio of $55,100 per QALY. In intermediate-risk newborns with low anorectal malformation, however, MRI was more effective than ultrasound at an incremental cost-effectiveness of $1000 per QALY (27).

Assessment of Outcomes: The major challenge to cost-utility analysis is the quantification of health or quality of life. One way to quantify health is descriptively. By assessing what patients can and cannot do, how they feel, their mental state, their functional independence, their freedom from pain, and any number of other facets of health and well-being that are referred to as domains, one can summarize their overall health status. Instruments designed to measure these domains are called health status instruments. A large number of health status instruments exist, both general instruments, such as the SF-36 (28), and instruments that are specific to particular disease states, such as the Roland scale for back pain. These various scales enable the quantification of health benefit. For example, Jarvik et al. (29) found no significant difference in the Roland score between patients randomized to MRI versus radiography for low back pain, suggesting that MRI was not worth the additional cost. There are additional issues in applying such tools to children, as they may be too young to understand the questions being asked. Parents can sometimes be used as surrogates, but parents may have different values and may not understand the health condition from the perspective of the child.

Assessment of Cost: All forms of economic analysis require assessment of cost. However, assessment of cost in medical care can be confusing, as the term *cost* is used to refer to many different things. The use of charges for any sort of cost estimation, however, is inappropriate. Charges are arbitrary and have no meaningful use. Reimbursements, derived from Medicare and other fee schedules, are useful as an estimation of the amounts society pays for particular health care interventions. For an analysis taken from the societal perspective, such reimbursements may be most appropriate. For analyses from the institutional perspective or in situations where there are no meaningful Medicare reimbursements, assessment of actual direct and overhead costs may be appropriate (30).

Direct cost assessment centers on the determination of the resources that are consumed in the process of performing a given imaging study, including *fixed costs* such as equipment and *variable costs* such as labor and supplies. Cost analysis often utilizes activity-based costing and time motion studies to determine the resources consumed for a single intervention in the context of the complex health care delivery system. *Overhead*, or *indirect cost*, assessment includes the

costs of buildings, overall administration, taxes, and maintenance that cannot be easily assigned to one particular imaging study. Institutional cost accounting systems may be used to determine both the direct costs of an imaging study and the amount of institutional overhead costs that should be apportioned to that particular test. For example, Medina et al. (31) in a vesicoureteral reflux imaging study in children with urinary tract infection found a significant difference (p <0.0001) between the mean total direct cost of voiding cystourethrography ($112.7 ± $10.33) and radionuclide cystography ($64.58 ± $1.91).

E. Summarizing the Data

The results of the EBI process are a summary of the literature on the topic, both quantitative and qualitative. *Quantitative analysis* involves, at minimum, a descriptive summary of the data and may include formal *meta-analysis* where there is sufficient reliably acquired data. *Qualitative analysis* requires an understanding of error, bias, and the subtleties of experimental design that can affect the reliability of study results. Qualitative assessment of the literature is covered in detail in Chapter 2; this section focuses on meta-analysis and the quantitative summary of data.

The goal of the EBI process is to produce a single summary of all of the data on a particular clinically relevant question. However, the underlying investigations on a particular topic may be too dissimilar in methods or study populations to allow for a simple summary. In such cases, the user of the EBI approach may have to rely on the single study that most closely resembles the clinical subjects upon whom the results are to be applied or may be able only to reliably estimate a range of possible values for the data.

Often, there is abundant information available to answer an EBI question. Multiple studies may be identified that provide methodologically sound data. Therefore, some method must be used to combine the results of these studies in a summary statement. *Meta-analysis* is the method of combining results of multiple studies in a statistically valid manner to determine a summary measure of accuracy or effectiveness (32, 33). For diagnostic studies, the summary estimate is generally a summary sensitivity and specificity, or a summary ROC curve.

The process of performing meta-analysis parallels that of performing primary research. However, instead of individual subjects, the meta-analysis is based on individual studies of a particular question. The process of selecting the studies for a meta-analysis is as important as unbiased selection of subjects for a primary investigation. Identification of studies for meta-analysis employs the same type of process as that for EBI described above, employing Medline and other literature search engines. Critical information from each of the selected studies is then abstracted usually by more than one investigator. For a meta-analysis of a diagnostic accuracy study, the numbers of true positives, false positives, true negatives, and false negatives would be determined for each of the eligible research publications. The results of a meta-analysis are derived not just by simply pooling the results of the individual studies, but instead by considering each individual study as a data point and determining a summary estimate for accuracy based on each of these individual investigations. There are sophisticated statistical methods of combining such results (34).

Like all research, the value of a meta-analysis is directly dependent on the validity of each of the data points. In other words, the quality of the meta-analysis can only be as good as the quality of the research studies that the meta-analysis summarizes. In general, meta-analysis cannot compensate for selection and other biases in primary data. If the studies included in a meta-analysis are different in some way, or are subject to some bias, then the results may be too heterogeneous to combine in a single summary measure. Exploration for such heterogeneity is an important component of meta-analysis.

The ideal for EBI is that all practice be based on the information from one or more well-performed meta-analyses. However, there is often too little data or too much heterogeneity to support formal meta-analysis.

F. Applying the Evidence

The final step in the EBI process is to apply the summary results of the medical literature to