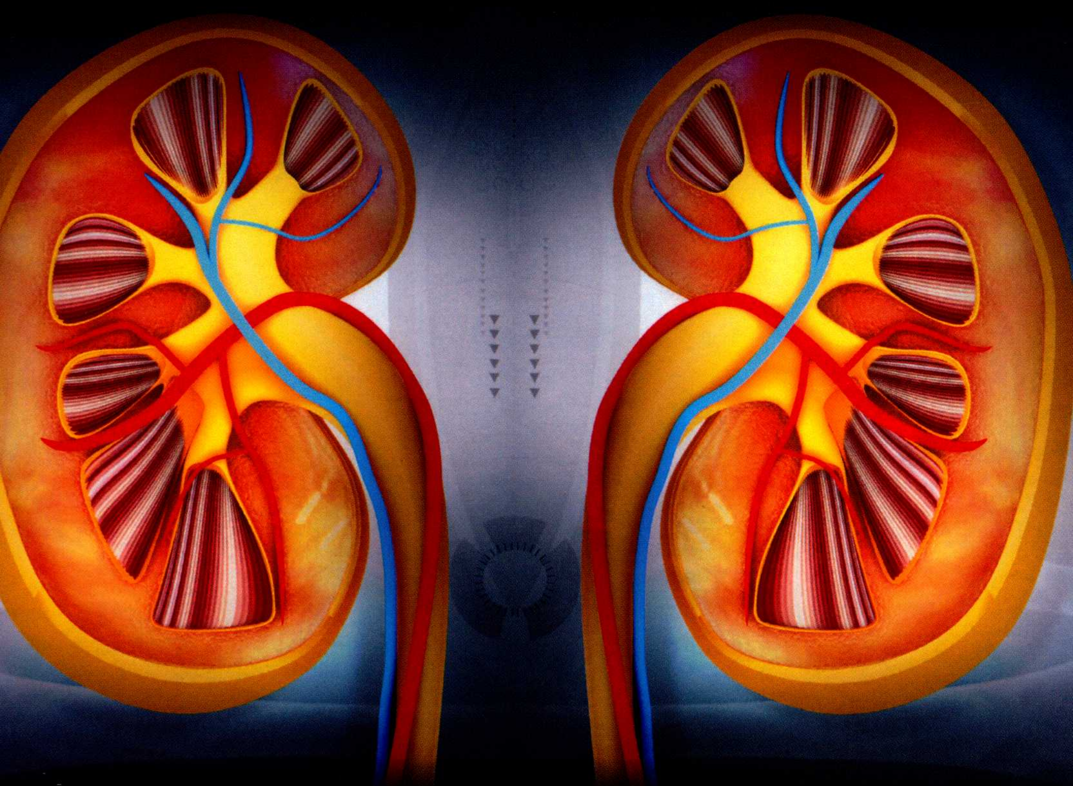
SECOND EDITION

BIOMARKERS OF KIDNEY DISEASE



EDITED BY

CHARLES L. EDELSTEIN

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To my family
Freda, Craig, Jeremy, and Joy.

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PREFACE

Developing and defining biomarkers of kidney diseases that can be used for early diagnosis, assessment of severity, assessment of short- and long-term prognosis and risk-stratification is extremely important for the practicing physician. Biomarkers can help physicians in determining the timely prevention, severity, more effective treatment, prognosis and response to therapy of disease. Biomarkers of disease are a fertile area of research for scientists.

During the last 6 years since the first edition of the book, there has continued to be exponential growth in research on biomarkers of kidney diseases and as a result, we can now bring preclinical studies to the bedside and diagnose certain kidney diseases at earlier stages than was possible with conventional tests. One of the most important advances has been NephroCheck, the first FDA-approved biomarker of acute kidney injury (AKI). NephroCheck uses a combination of urinary insulin-like growth factor-binding protein-7 (IGF-BP7) and tissue inhibitor of metalloproteinases-2 (TIMP2) and with its approval, early diagnosis and treatment of kidney diseases has now become a reality in clinical practice.

The second edition of the book provides an update of biomarkers of kidney diseases that are of particular importance to the practicing physician while remaining the most comprehensive work published on this crucial topic. New chapters include "Biomarkers of Extra-Renal Complications of AKI," "Diagnostic and Prognostic Biomarkers in Autosomal Dominant Polycystic Kidney Disease," and "Biomarkers of Cardiovascular Risk in Chronic Kidney Disease." In addition, the second edition expands coverage of certain diseases, including AKI, CKD, kidney transplant rejection, delayed kidney allograft function, polycystic kidney disease, renal cell cancer, glomerular disease, diabetic nephropathy, and preeclampsia.

Successful biomarker candidates are now being advanced as tools for personalized and predictive approaches to kidney disease. Prasad Devarajan provides a brief review of how novel biomarkers are discovered and validated, and what the general characteristics of an ideal biomarker are.

For the physician interpreting or planning biomarker studies, Chirag R. Parikh and Heather Thiessen Philbrook, both experts in the field, discuss traditional and emerging statistical methods for evaluating the prediction performance of diagnostic biomarkers.

Proteomic and metabolomic profiling of body fluids and tissues has great potential to advance our understanding of kidney diseases and drug effects, to advance clinical diagnostics and to be an important tool in the individualization of treatment. Dr. Uwe Christians, who has state-of-the-art laboratories at the University of Colorado for biomarker discovery, has updated his comprehensive chapter on the use of metabolomics and proteomics in kidney diseases with the most exciting studies in the field in the last 6 years.

BUN and serum creatinine are not very sensitive and specific markers of kidney function in AKI as they are influenced by many renal and non-renal factors independent of kidney function. Charles L. Edelstein reviews the new biomarkers for the diagnosis and prognosis of AKI that have been discovered over the last 6 years including newly FDA-approved biomarkers. Dr. Alkesh Jani, a transplant nephrologist, has updated the chapter on biomarkers for the early diagnosis of delayed kidney graft function, kidney rejection, and polyoma virus infection.

Clinical and experimental data indicate that AKI contributes to distant organ injury. Thus, the high mortality of AKI may be due to deleterious systemic effects of AKI. In a new addition to the book, Dr. Sarah Faubel discusses the inflammatory and pulmonary complications of AKI as well as their potential biomarkers.

We are fortunate to have Dr. Grubb, who helped isolate and sequence the "mysterious protein" cystatin C that was discovered in the urine in 1961, write the chapter on cystatin C as a biomarker in kidney diseases. The updated chapter includes the role of cystatin C in identifying the novel "Shrunken Pore Syndrome."

Determining prognosis for individual patients with renal cell cancer is important to allow targeting of high-risk patients for trials of adjuvant therapy and more intensive follow-up. The current field of renal cancer biomarkers is comprehensively reviewed by Dr. Roz E. Banks and Dr. Naveen S. Vasudev.

Diabetic nephropathy and glomerulonephritis are the commonest causes of ESRD in the USA. Dr. Jon B. Klein and colleagues update the evolving role that proteomics has played in expanding our understanding of the natural history of diabetic nephropathy. The most promising candidate biomarkers for the early diagnosis, early prediction of flares and prediction of outcome in patients with glomerulonephritis like membranous GN, FSGS, and IgA nephropathy are reviewed by Dr. John M. Arthur and colleagues.

In an exciting new addition to the book, Zoltan H. Endre and Robert J. Walker review traditional markers of kidney disease, traditional markers of cardiovascular disease, and novel markers of kidney damage as markers of cardiovascular risk in subjects with CKD.

Autosomal dominant polycystic kidney disease (ADPKD) is the commonest hereditary kidney disease. Drs. Berenice Y. Reed and Godela Fick-Brosnahan, well-known researchers in ADPKD, have written a unique new addition to the book. A prognostic biomarker predicting the disease course at an early age would be helpful for patient counseling, selecting those patients most likely to benefit from an intervention and could serve as a surrogate endpoint in clinical trials testing new therapeutic interventions in ADPKD. Total kidney volume is qualified as a biomarker by the FDA for ADPKD Trials.

Preeclampsia can be a devastating disease and is a leading cause of maternal and perinatal morbidity and mortality. Dr. S. Ananth Karumanchi, a world expert on this topic, has updated his chapter to include new angiogenic factors, placental protein-13 (PP-13), and combinations of these and other parameters with Doppler analysis that hold promise for future predictive testing for preeclampsia.

The advances in our knowledge of biomarkers of kidney disease continue to grow and I believe that the use of novel biomarkers of kidney disease has become a reality in clinical practice. It is my pleasure and privilege to edit the second edition of a book written by distinguished authors that continue to contribute to the exciting advances in our knowledge of biomarkers of kidney disease.

Charles L. Edelstein

CONTENTS

CHAPTER ONE

Characteristics of an Ideal Biomarker of Kidney Diseases

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Contents

THE DISCOVERY OF BIOMARKERS

The quest for biomarkers is as old as medicine itself. From the earliest days of diagnostic medicine in ancient Egypt, to the misguided science of phrenology (the belief that skull measurements could predict personality traits), to the powerful discoveries of modern science, we have been searching for measurable biologic cues that will give us an insight into the physiologic workings of the human organism. In its simplest definition, a biomarker is anything that can be measured to extract information about a biologic state or process. The NIH Biomarkers Definitions Working Group has defined a biologic marker (biomarker) as "A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [1]."

Biomarkers appear in every form. Body temperature, in the form of a fever, can signal infection. Blood pressure and cholesterol levels can predict cardiovascular risk. Tracking biomarkers, such as, height and weight can give clues about normal human growth and development. Such general biomarkers have been used for decades or even centuries and have remained powerful tools for tracking general biologic activity. However, the era of personalized medicine is well on us. Ushered in by the remarkable genomic

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Table 1.1 Phases of biomarker discovery, translation, and validation

Phase	Terminology	Action steps
Phase 1	Preclinical discovery	• Discover biomarkers in tissues or body fluids • Confirm and prioritize promising candidates
Phase 2	Assay development	• Develop and optimize clinically useful assay • Test on existing samples of established disease
Phase 3	Retrospective study	• Test biomarker in completed clinical trial • Test if biomarker detects the disease early • Evaluate sensitivity, specificity and receiver operating characteristic (ROC)
Phase 4	Prospective screening	• Use biomarker to screen population • Identify extent and characteristics of disease • Identify false-referral rate
Phase 5	Disease control	• Determine impact of screening on reducing disease burden

Source: Adapted from States DJ, Omenn GS, Blackwell TW, Fermin D, Eng J, Speicher DW, Hanash SM. Challenges in deriving high-confidence protein identifications from data gathered by a HUPO plasma proteome collaborative study. Nat Biotechnol 2006;24(3):333–8 [7].

and proteomic advances in our understanding of health and disease, personalized medicine promises a more precise determination of disease predisposition, diagnosis, and prognosis, earlier preventive and therapeutic interventions, a more efficient drug development process, and a safer and more fiscally responsive approach toward medicine. Biomarkers are the essential tools for the implementation of personalized medicine. The quest for the advancement of personalized medicine pushes us further and further into the realm of molecular medicine to discover biomarkers with increasing sensitivity and specificity. For most of our history, biomarker discovery has relied on the intimate knowledge of the pathophysiology of the diseases being studied. Biologic substances, which we knew were related to a disease state, were investigated to see if they could serve as diagnostic markers, provide a target for therapy, or lend further insight into the etiology of the disease. While this can be tedious, and relies heavily on prior knowledge of the disease mechanism, this hypothesis-driven method of research almost always provides useful scientific results, whether positive or negative.

The biomarker-development process has typically been divided into five phases, as shown in Table 1.1. The preclinical discovery phase requires high-quality, well-characterized tissue or body fluid samples from carefully chosen animal or human models of the disease under investigation. In the last 20 years, the ready availability of powerful tools that scan both the genome and the proteome of an organism have revolutionized and greatly accelerated biomarker discovery. Transcriptome profiling, using complementary DNA (cDNA) microarrays that can measure the entire complement of messenger RNA (mRNA) in a given sample type, has yielded a number of promising biomarkers of kidney disease, as well as, novel disease mechanisms in many fields [2–4]. This approach can be combined with other techniques, such as laser capture, microdissection, to target specific areas of a diseased tissue to give mechanistic clues that was not possible just a decade ago. Even with this level of specificity, these techniques can yield a daunting array of data that must be sifted through for relevance. A shortcoming of transcriptomic profiling approaches is that it cannot be performed directly in biologic fluids. Another problem with this approach is that ultimately the mRNA does not always reflect protein levels or activity, which must be further confirmed at the protein level prior to larger validation studies. Despite these limitations, transcriptome-profiling studies have been extensively utilized to study models of acute kidney injury (AKI) [5]. A metaanalysis of gene-expression profiles from 150 distinct microarray experiments from 21 different models of AKI identified several upregulated genes previously known to be associated with AKI [6]. The most consistently and most highly upregulated gene has been neutrophil gelatinase-associated lipocalin (NGAL), whose protein product has now successfully passed through the preclinical, assay development, and clinical testing stages of the biomarker-development process.

In the last 5 years, deep sequencing techniques, such as, RNAseq have supplanted microarrays as the preferred transcriptomic "shotgun" method for biomarker discovery, though it is not without limitations in terms of clinical utility. RNAseq uses deep sequencing technologies to sequence the RNA in a given sample as opposed to hybridizing mRNA onto a known cDNA array [8]. This gives a more precise measurement of the level of transcripts and sequence variations [8]. The difficulties with this technology lies not only at the bioinformatic level—as there needs to be the ability to deal with massive amounts of data and narrow them down to a usable format—but also at a cost level. The deeper the sequencing, the more expensive it is to run, and that limits the utility in a clinical environment to large institutions that can afford the specialized equipment, but that also have the bioinformatic capabilities to interpret the resulting profiles.

Proteomic approaches move a step beyond genomic studies and screen the actual proteins and peptides present in a sample. This approach allows one to go beyond simple translation of mRNA into protein and allows a look into protein regulation, posttranslational modifications (such as,