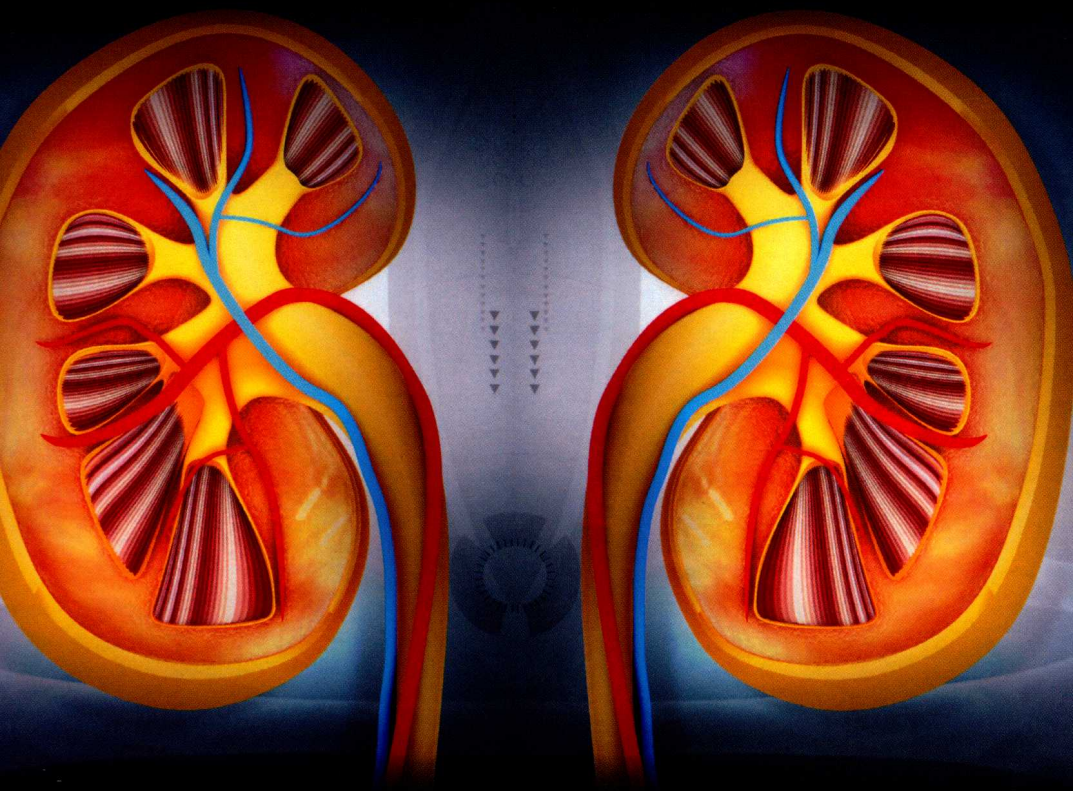


SECOND EDITION

BIOMARKERS OF KIDNEY DISEASE



EDITED BY
CHARLES L. EDELSTEIN



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CHARLES L. EDELSTEIN, MD, PhD

Division of Renal Diseases and Hypertension

University of Colorado Denver

Aurora, CO, United States



Amsterdam • Boston • Heidelberg • London
New York • Oxford • Paris • San Diego
San Francisco • Singapore • Sydney • Tokyo
Academic Press is an imprint of Elsevier



Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

ISBN: 978-0-12-803014-1

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Publisher: Mica Haley

Acquisition Editor: Tari Broderick

Editorial Project Manager: Lisa Eppich

Production Project Manager: Karen East and Kirsty Halterman

Designer: Mark Rogers

Typeset by Thomson Digital

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

LIST OF CONTRIBUTORS

J.M. Arthur, MD, PhD

Division of Nephrology, University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, United States

R.E. Banks, PhD

Biomedical Proteomics, Clinical and Biomedical Proteomics Group, Leeds Institute of Cancer and Pathology, St James's University Hospital, Leeds, United Kingdom

M.R. Bennett, PhD

Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, University of Cincinnati, College of Medicine, Cincinnati, OH, United States

U. Christians, MD, PhD

iC42 Clinical Research and Development, Department of Anesthesiology, University of Colorado, Anschutz Medical Campus, Aurora, CO, United States

P. Devarajan, MD, FAAP

Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, University of Cincinnati, College of Medicine, Cincinnati, OH, United States

C.L. Edelstein, MD, PhD

Division of Renal Diseases and Hypertension, University of Colorado Denver, Aurora, CO, United States

E. Elnagar, MBBS, MPH

Division of Nephrology, University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, United States

Z.H. Endre, BScMed, MBBS, PhD, RACP, FASN

Department of Nephrology, Prince of Wales Hospital and Clinical School, University of New South Wales, Sydney, NSW; School of Medicine, University of Queensland, Brisbane, QLD, Australia; Department of Medicine, University of Otago, Christchurch, New Zealand

S. Faubel, MD

Medicine, Division of Renal Diseases and Hypertension, University of Colorado Denver, Veteran Affairs Medical Center, Denver, CO, United States

G. Fick-Brosnahan, MD

Division of Renal Diseases and Hypertension, Anschutz Medical Campus, Aurora, CO, United States

A. Grubb, MD, PhD

Department of Clinical Chemistry and Pharmacology, University Hospital, Lund University, Lund, Sweden

S. Jain, PhD

University of Colorado, Aurora, CO, United States

A. Jani, MD

University of Colorado, Aurora; Denver Veteran Affairs Medical Center, Denver, CO, United States

N. Karakala, MD

Division of Nephrology, University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, United States

S.A. Karumanchi, MD

Department of Medicine, Obstetrics and Gynecology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, United States

J. Klawitter, PhD

iC42 Clinical Research and Development, Department of Anesthesiology, University of Colorado, Anschutz Medical Campus, Aurora, CO, United States

J. Klawitter, PhD

iC42 Clinical Research and Development, Department of Anesthesiology, University of Colorado, Anschutz Medical Campus, Aurora, CO, United States

J. Klepacki, PhD

iC42 Clinical Research and Development, Department of Anesthesiology, University of Colorado, Anschutz Medical Campus, Aurora, CO, United States

J.B. Klein, MD, PhD

Robley Rex Veterans Administration Medical Center, Louisville, KY, United States

M.L. Merchant, PhD

Division of Nephrology and Hypertension, Department of Medicine, University of Louisville, Louisville, KY, United States

C.R. Parikh, MD, PhD

Program of Applied Translational Research, Department of Medicine, Yale University, New Haven; Veterans Affairs Medical Center, West Haven, CT, United States

H. Thiessen Philbrook, MMath, AStat

Program of Applied Translational Research, Department of Medicine, Yale University, New Haven; Veterans Affairs Medical Center, West Haven, CT, United States

B.Y. Reed, PhD

Division of Renal Diseases and Hypertension, Anschutz Medical Campus, Aurora, CO, United States

N.S. Vasudev, MD, PhD

Medical Oncology, Clinical and Biomedical Proteomics Group, Leeds Institute of Cancer and Pathology, St James's University Hospital, Leeds, United Kingdom

R.J. Walker, MBChB, MD, FRACP, FASN, FAHA

Department of Nephrology, Dunedin Hospital and University of Otago, Dunedin, New Zealand

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

<i>List of Contributors</i>	<i>xiii</i>
<i>Preface</i>	<i>xv</i>
1. Characteristics of an Ideal Biomarker of Kidney Diseases	1
M.R. Bennett and P. Devarajan	
The Discovery of Biomarkers	1
Characteristics of an Ideal Biomarker	4
Biomarkers in AKI	7
Biomarkers in CKD	12
Conclusions and Future Directions	16
References	16
2. Statistical Considerations in Analysis and Interpretation of Biomarker Studies	21
C.R. Parikh and H. Thiessen Philbrook	
Introduction	21
Planning a Study	23
Metrics for Prediction Performance	24
Sample-Size Calculations	28
Evaluating Incremental Value	28
Summary	31
References	31
3. The Role of Metabolomics in the Study of Kidney Diseases and in the Development of Diagnostic Tools	33
U. Christians, J. Klawitter, J. Klepacki and J. Klawitter	
Introduction	34
Metabolic Mapping of the Kidney	40
Nontargeted and Targeted Metabolomics	42
The Sample	48
Analytical Technologies	50
Metabolic Molecular Marker Discovery and Development	68
Metabolomics in Renal Research: Kidney Function, Disease, and Injury Markers	71
Metabolomics as a Clinical Diagnostic Tool in Nephrology	94
References	100

4. The Role of Proteomics in the Study of Kidney Diseases and in the Development of Diagnostic Tools	119
U. Christians, J. Klawitter, J. Klepacki and J. Klawitter	
Introduction	120
Nontargeted and Targeted Proteomics	124
Proteins and the Kidney	127
The Proteomics Sample	131
Analytical Technologies	134
Proteomics in Renal Research and as a Marker for Kidney Function, Disease, and Injury	158
Proteomics as Clinical Diagnostic Tool in Nephrology	196
References	202
 5. Cystatin C as a Multifaceted Biomarker in Kidney Disease and Its Role in Defining "Shrunken Pore Syndrome"	 225
A. Grubb	
Factors Influencing the Diagnostic Performance of Cystatin C- or Creatinine-Based GFR-Estimating Equations and Causing the Plethora of Equations: The Concepts of "Internal" or "External" Validation	226
Optimizing the Use of Cystatin C- and Creatinine-Based GFR-Estimating Equations	228
Cystatin C and Creatinine (eGFR _{cystatin C} and eGFR _{creatinine}) as Markers of End-Stage Renal Disease (ESRD), Hospitalization, Cardiovascular Disease, and Death	230
Identification of "Shrunken Pore Syndrome": Its Influence on Mortality	231
Cystatin C as an Indicator of the Circadian Rhythm of GFR	234
Cystatin C as an Indicator of "Renal Reserve"	237
References	237
 6. Biomarkers in Acute Kidney Injury	 241
C.L. Edelstein	
Introduction	242
Definition and Classification of AKI	243
Serum Creatinine in AKI	245
Biology of Biomarkers	247
Biomarkers for the Differential Diagnosis of AKI	254
Biomarkers for the Early Diagnosis of AKI	259
Biomarkers That Predict Short-Term Outcomes	272

Biomarkers for Risk Stratification of Patients With Existing AKI	278
Biomarkers of AKI and Long-Term Outcomes	280
Biomarkers of Subclinical AKI	280
The Effect of Interventions on Biomarkers of AKI	283
Biomarkers of AKI in the ICU	285
Urinary Stability Studies for Biomarkers of AKI	295
Combinations of AKI Biomarkers	296
TIMP2 and IGFBP7	298
Conclusions	302
References	303
7. Biomarkers of Extra-Renal Complications of AKI	317
S. Faubel	
AKI and Inflammation	319
Serum Cytokines are Increased in Patients With AKI	321
Pulmonary Complications of AKI	324
Summary	329
References	329
8. Biomarkers in Kidney Transplantation	335
S. Jain and A. Jani	
Biomarkers: An Overview	336
Biomarkers of AKI Posttransplantation	336
Biomarkers of Acute Rejection	348
Biomarkers of Chronic Allograft Nephropathy	378
Biomarkers of Polyoma Virus Infection	388
Summary	393
References	410
9. Biomarkers of Renal Cancer	421
N.S. Vasudev and R.E. Banks	
Renal Cancer	421
Cancer Biomarkers—General Concepts	429
Renal Cancer Biomarkers	430
Conclusions	455
Acknowledgments	456
References	456

10. Proteomics and Advancements in Urinary Biomarkers of Diabetics Kidney Disease	469
M.L. Merchant and J.B. Klein	
Introduction	469
Urinary Peptides as Biomarkers of Diabetic Kidney Disease	475
Future Developments and Applications of Proteomics for Biomarker Discovery	481
References	482
11. Biomarkers of Cardiovascular Risk in Chronic Kidney Disease	485
Z.H. Endre and R.J. Walker	
Introduction	485
The Definition of CKD and the Risk of Cardiovascular Diseases:	
GFR, Albuminuria, and Proteinuria	486
Cardiac Biomarkers in CKD	497
Summary	507
References	508
12. Diagnostic and Prognostic Biomarkers in Autosomal Dominant Polycystic Kidney Disease	513
G. Fick-Brosnahan and B.Y. Reed	
Genetic Testing for Diagnosis and Prognosis	513
Total Kidney Volume	515
Renal Blood Flow	518
Serum and Urine Biomarkers	519
References	526
13. Biomarkers in Glomerular Disease	531
J.M. Arthur, E. Elngar and N. Karakala	
Biomarkers in Glomerular Diseases	532
Predictors of Outcome in Glomerular Diseases	532
Biomarkers in Lupus Nephritis	533
Predictors of Lupus Nephritis Class	533
Biomarkers that Predict Renal Lupus Flares	534
Membranous Nephropathy	536
Focal Segmental Glomerulosclerosis	540
Minimal Change Disease	542
CD80/B7-1 in Minimal Change and FSGS	543

IgA Nephropathy	544
Discovery of New Biomarkers Using Proteomics	547
References	550
14. Biomarkers in Preeclampsia	555
S.A. Karumanchi	
Definition and Prevalence of the Disease	555
Pathophysiology and Mechanisms	557
Clinical Manifestations	558
Diagnosis	563
Biomarkers	565
Novel Biomarkers and Future Perspectives	579
Conclusions	583
References	585
Index	595

Characteristics of an Ideal Biomarker of Kidney Diseases

M.R. Bennett, PhD and P. Devarajan, MD, FAAP

Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, University of Cincinnati, College of Medicine, Cincinnati, OH, United States

Contents

The Discovery Of Biomarkers	1
Characteristics of an Ideal Biomarker	4
Biomarkers in AKI	7
Biomarkers in CKD	12
Conclusions and Future Directions	16
References	16



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

Table 1.1 Phases of biomarker discovery, translation, and validation

Phase	Terminology	Action steps
Phase 1	Preclinical discovery	<ul style="list-style-type: none"> • Discover biomarkers in tissues or body fluids • Confirm and prioritize promising candidates
Phase 2	Assay development	<ul style="list-style-type: none"> • Develop and optimize clinically useful assay • Test on existing samples of established disease
Phase 3	Retrospective study	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Use biomarker to screen population • Identify extent and characteristics of disease • Identify false-referral rate
Phase 5	Disease control	<ul style="list-style-type: none"> • 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,