

Contents

1 Introduction	1
Definitions	1
Historical Aspects of Biomarkers	2
Classification of Biomarkers	3
Biological Marker as Response to Therapeutic Intervention	3
Pharmacokinetic/Pharmacodynamics Biomarkers	4
Predictive Biomarkers	4
Valid Biomarkers	5
Types of Biomarkers	5
Genes as Biomarkers	6
Proteins as Biomarkers	6
Proteomics	7
DNA Biomarkers	7
Mitochondrial DNA	7
Mitochondrial Mutations	8
RNA Biomarkers	8
Transcriptomics	9
MicroRNAs	10
Metabolomics	10
Glycomics	11
Single-Nucleotide Polymorphisms	12
Haplotyping	12
Cell Biomarkers of Disease	13
Stem Cell Biomarkers	13
Cancer Stem Cell Biomarkers	14
Endoglin as a Functional Biomarker of Stem Cells	14
p75NTR as a Biomarker to Isolate Adipose Tissue-Derived Stem Cells	15
Protein Expression Profile as Biomarker of Stem Cells	15
STEMPRO® EZChek™ for Analysis of Biomarkers of hESCs	15
SSEA-4 as Biomarker of MSCs	16
Autoantibodies as Biomarkers of Autoimmune Diseases	16

The Ideal Biomarker	17
Biomarkers and Systems Biology	18
Systems Biology Approach to Biomarker Identification	19
Relation of Biomarkers to Other Technologies and Health care	20
Biomarkers and Translational Medicine	20
Limitations of Use of Biomarkers in Health Care	20
2 Technologies for Discovery of Biomarkers	23
Introduction	23
Detection of Biomarkers in Tissues and Body Fluids	23
Disease Biomarkers in Breath	23
Portable Breath Test for Volatile Organic Compounds	24
Detection of Breath Biomarkers by Sensation Technology	24
Detection of Breath Biomarkers Optical Frequency Comb Spectroscopy	25
Genomic Technologies	25
Gene Expression	25
Tissue Microarrays for Study of Biomarkers	28
Epigenomic Technologies	28
Discovery of Methylation Biomarkers	29
Proteomic Technologies	30
2D GE	31
Isotope-Coded Affinity Tags	32
Mass Spectrometry	33
Liquid Chromatography–MS Combination	37
Protein Tomography	37
Protein Biochips/Microarrays and Biomarkers	38
Real-Time PCR for Quantification of Protein Biomarkers	39
Magnetic Beads for Protein Biomarker Discovery	40
CellCarta [®] Proteomics Platform	40
MASStermind [™]	41
Search for Biomarkers in Body Fluids	41
Challenges and Strategies for Discovery of Protein Biomarkers in Plasma	41
Biomarkers in the Urinary Proteome	47
Peptides in Body Fluids and Tissues as Biomarkers of Disease	47
Verification for Interlaboratory Reproducibility of Protein Biomarkers	49
Significance of Similar Protein Biomarkers in Different Tissues	50
Glycomic Technologies	51
Metabolomic Technologies	51
Mass Spectrometry-Based Kits for Discovery of Metabolic Biomarkers in Plasma	52
Urinary Profiling by Capillary Electrophoresis	52
Lipid Profiling	53

Role of Metabolomics in Biomarker Identification and Pattern Recognition	53
Validation of Biomarkers in Large-Scale Human Metabolomics Studies	54
Lipidomics	54
Fluorescent Indicators for Biomarkers	55
Molecular Imaging Technologies	56
Computer Tomography	56
Magnetic Resonance Imaging	57
Positron Emission Tomography	57
Advantages of Imaging Biomarkers	58
Monitoring In Vivo Gene Expression by Molecular Imaging	58
Molecular Imaging In Vivo as a Biomarker	59
Challenges and Future Prospects of Molecular Imaging	59
Molecular Imaging in Clinical Practice	60
Nuclear Magnetic Resonance	61
Chemical Derivatization to Enhance Biomarker Detection by NMR	61
Fluxomics by Using NMR	62
Nanobiotechnology	62
Nanomaterials for Biolabeling	63
Nanoproteomics and Biomarkers	65
Nanoparticles for Molecular Imaging	66
Nanoparticles for Discovering Biomarkers	67
Nucleoprotein Nanodevices for Detection of Cancer Biomarkers	67
Future Prospects of Application of Nanobiotechnology for Biomarkers	67
Bioinformatics	68
Biomarker Workflow Guide	68
Analysis of Microarray Data for Selecting Useful Biomarkers	68
Role of Bioinformatics in Discovery of Proteomic Biomarkers	69
Role of Bioinformatics in Detection of Cancer Biomarkers	70
Biomarker Databases	70
Gene Networks as Biomarkers	71
Pitfalls in the Discovery and Development of Biomarkers	71
3 Biomarkers and Molecular Diagnostics	73
Introduction	73
Molecular Diagnostic Technologies	73
Polymerase Chain Reaction	73
Combined PCR–ELISA	75
Non-PCR Methods	76
Transcription-Mediated Amplification	77
Rapid Analysis of Gene Expression	77
WAVE Nucleic Acid Fragment Analysis System	77

DNA Probes with Conjugated Minor Groove Binder	78
Rolling-Circle Amplification Technology	79
Circle-to-Circle Amplification	81
Biochips and Microarrays	81
Detection and Expression Profiling of miRNA	83
Real-Time PCR for Expression Profiling of miRNAs	83
Use of LNA to Explore miRNA	84
Microarrays for Analysis of miRNA Gene Expression	84
4 Biomarkers for Drug Discovery and Development	87
Introduction	87
Biomarker Technologies for Drug Discovery	88
Proteomics-Based Biomarkers for Drug Discovery	88
Chemoproteomics	89
Transcriptomics for Drug Discovery	89
Metabolomics for Drug Discovery	90
Biomarkers and Drug Safety	91
Biomarkers of Adverse Drug Reactions	91
Applications of Biomarkers in Drug Safety Studies	91
Genomic Technologies for Toxicology Biomarkers	92
Proteomic Technologies for Toxicology Biomarkers	93
Metabonomic Technologies for Toxicology Biomarkers	93
Integration of Genomic and Metabonomic Data to Develop Toxicity Biomarkers	94
Toxicology Studies Based on Biomarkers	94
Applications of Biomarkers for Drug Development	99
Application of Metabonomics/Metabolomics for Drug Development	99
Role of Pharmacokinetic/Pharmacodynamic Biomarkers in Drug Development	100
Molecular Imaging as a Biomarker in Drug Development	101
Biomarkers in Clinical Trials	105
Application of Biomarkers by the Pharmaceutical Companies	108
Drug Development in Cardiovascular Disorders	109
Drug Development in Neurological Disorders	109
Future Prospects of Biomarker-Based Drug Development	110
5 Role of Biomarkers in Health Care	115
Introduction	115
Biomarkers of Inflammation	116
Biomarkers of Oxidative Stress	116
Oxidative DNA Damage	116
Proteins as Biomarkers of Oxidative Stress in Diseases	117
1,4-Dihydroxynonane Mercapturic Acid	117
Biomarkers in Metabolic Disorders	117

Biomarkers of Acute Intermittent Porphyria	117
Liver X Receptors	118
Biomarkers of Diabetes Mellitus	118
Biomarkers of Metabolic Syndrome	122
Biomarkers in Immune Disorders	123
Biomarkers of Failure of Transplanted Organs	123
Systemic Lupus Erythematosus	126
Biomarkers of Musculoskeletal Disorders	129
Biomarkers of Rheumatoid Arthritis	129
Biomarkers of Spondylarthritis	130
Biomarkers of Osteoarthritis	131
Biomarkers of Osteoporosis	132
Dual X-Ray Absorptiometry	133
Bone Imaging with Quantitative CT and MRI	133
Assays for Detection of Biomarkers of Osteoporosis	134
Biomarkers of Infectious Diseases	134
Application of Proteomics for Discovering Biomarkers of Infections	137
Systemic Inflammatory Response Syndrome	138
Tuberculosis	138
Biomarkers of Viral Infections	141
Biomarkers in Parasitic Infections	145
Biomarkers of Liver Disease	147
Breath Biomarkers of Liver Disease	147
Biomarkers of Viral Hepatitis B and C	148
Biomarkers of Liver Injury	149
Biomarkers of Liver Cirrhosis	149
FibroMax	149
Biomarkers of Pancreatitis	150
Biomarkers of Renal Disease	150
Cystatin C as Biomarker of Glomerular Filtration Rate	151
Proteomic Biomarkers of Acute Kidney Injury	151
Biomarkers of Lupus Nephritis	152
Biomarkers of Diabetic Nephropathy	152
Biomarkers of Pulmonary Diseases	152
Biomarkers of Oxidative Stress in Lung Diseases	154
Biomarkers of Survival in Acute Respiratory Distress Syndrome	154
Pulmonary Surfactant Proteins as Biomarkers for Lung Diseases	155
Biomarkers of Chronic Obstructive Pulmonary Disease	156
Biomarkers of Asthma	158
Biomarkers for Cystic Fibrosis	161
Biomarkers of Pulmonary Embolism	162
Biomarkers in Obstetrics and Gynecology	163
Biomarkers for Preeclampsia	163
Biomarkers of Premature Birth	166

- Biomarkers of Oxidative Stress in Complicated Pregnancies 167
- Biomarkers of Premenstrual Dysphoric Disorder 167
- Biomarkers of Endometriosis 168
- Fetal Biomarkers in Maternal Blood 168
- Biomarkers for Genetic Disorders 169
 - Biomarkers for Down’s Syndrome 169
 - Biomarkers for Muscular Dystrophy 170
 - Biomarkers of Phenylketonuria 170
 - Biomarkers of Lysosomal Storage Disorders 171
- Biomarkers of Aging 173
 - Study of Biomarkers of Aging in a Genetically Homogeneous Population 174
 - Genes as Biomarkers of Aging 174
 - Role of Bioinformatics in Search for Biomarkers of Aging 176
 - Effect of Calorie Restriction on Biomarkers of Longevity 176
- Biomarkers of Miscellaneous Disorders 176
 - Biomarkers of Inflammatory Bowel Disease 176
 - Biomarkers of Erectile Dysfunction 177
 - Biomarkers of Heat Stroke 178
 - Biomarkers of Pain 179
 - Nasal Nitric Oxide as a Biomarker of Response to Rhinosinusitis Therapy 180
 - Biomarkers Common to Multiple Diseases 181
- Biomarkers and Nutrition 182
 - Biomarkers in Nutritional Epidemiology 182
 - Biomarkers of Nutritional Status 182
 - Biomarkers of Branched-Chain Amino Acid Status 183
 - Biomarkers of Caloric Restriction 183
 - Biomarkers of Malnutrition 184
 - Proteomic Biomarkers and Nutrition 184
- Biomarkers of Gene–Environmental Interactions in Human Disease 184
- Future Role of Biomarkers in Health Care 185
- Applications of Biomarkers Beyond Health Care 186
 - Combating Bioterrorism 186
 - Biomarkers for Monitoring Human Exposure to Environmental Toxins 186
 - Application of Biomarkers in Animal Health 187
- 6 Biomarkers of Cancer 189**
 - Introduction 189
 - The Ideal Biomarker for Cancer 189
 - Single Versus Multiple Biomarkers of Cancer 190
 - Types of Cancer Biomarkers 191
 - miRNAs as Biomarkers in Cancer 192
 - Biomarkers of Epigenetic Gene Silencing in Cancer 195

Immunologic Biomarkers of Cancer	196
Molecular Diagnostic Techniques for Cancer	196
Technologies for Detection of Cancer Biomarkers	197
Genomic Technologies for Cancer Biomarkers	197
Tissue Microarrays for Study of Cancer Biomarkers	202
Molecular Fingerprinting of Cancer	203
Biomarkers of Inflammation in Cancer	204
Proteomic Technologies for Detecting Biomarkers of Cancer	205
Metabolomic Biomarkers of Cancer	215
Epitomics for the Early Detection of Cancer	217
Detection of Biomarkers of DNA Methylation	217
Nanobiotechnology for Early Detection of Cancer to Improve Treatment	222
Selective Expression of Biomarkers by Cancer Compared with Normal Tissues	223
Ultrasound Radiation to Enhance Release of a Tumor Biomarker	223
In Vivo Imaging of Cancer Biomarkers	224
Kallikrein Gene Family and Cancer Biomarkers	226
Circulating Cancer Cells in Blood as Biomarkers of Cancer	226
Applications of Cancer Biomarkers	227
Use of Biomarkers for Cancer Classification	228
Use of Biomarkers for Early Detection of Cancer	228
Application of Biomarkers for Cancer Diagnosis	229
Applications of Biomarkers for Cancer Diagnosis Plus Therapy	231
Biomarkers for Assessment of Efficacy of Cancer Therapy	232
Biomarkers of Angiogenesis for Developing Antiangiogenic Therapy	234
Biomarkers of Drug Resistance in Cancer	237
Biomarkers of Radiation Exposure	238
Role of Biomarkers in Drug Development in Oncology	239
Molecular Imaging of Tumor as a Guide to Drug Development	239
Biomarkers in Plucked Hair for Assessing Cancer Therapy	241
Molecular Targets of Anticancer Drugs as Biomarkers	241
Safety Biomarkers in Oncology Studies	242
Role of Biomarkers in Phase I Clinical Trials of Anticancer Drugs	242
Biomarkers According to Location/Type of Cancer	243
Bladder Cancer Biomarkers	243
Brain Cancer Biomarkers	244
Breast Cancer Biomarkers	250
Cervical Cancer Biomarkers	268
Gastrointestinal Cancer Biomarkers	269
Head and Neck Cancer	275
Leukemia Biomarkers	276
Liver Cancer Biomarkers	281
Lung Cancer Biomarkers	282

Malignant Pleural Mesothelioma	291
Melanoma Biomarkers	292
Nasopharyngeal Carcinoma Biomarkers	294
Oral Cancer Biomarkers	296
Ovarian Cancer Biomarkers	297
Pancreatic Cancer Biomarkers	302
Prostate Cancer	306
Renal Cancer Biomarkers	317
Thyroid Cancer Biomarkers	320
Role of the NCI in Biomarkers of Cancer	322
Cancer Genetic Markers of Susceptibility Project	322
Oncology Biomarker Qualification Initiative	322
Role of NCI in Cancer Biomarker Development and Validation	323
Future Prospects for Cancer Biomarkers	324
Cancer Biomarker Research at Academic Institutions	324
Future Prospects and Challenges in the Discovery of Cancer Biomarkers	325
7 Biomarkers of Disorders of the Nervous System	327
Introduction	327
Discovery of Biomarkers of Neurological Disorders	327
Biomarker Identification in the CSF Using Proteomics	328
Biomarker Identification in the CSF Using Lipidomics	329
Cerebral Microdialysis for the Study of Biomarkers of Cerebral Metabolism	329
Detection of Protein Biomarkers of CNS Disorders in the Blood	330
Brain Imaging for Detection of Biomarkers	330
Data Mining for Biomarkers of Neurological Disorders	331
Antibodies as Biomarkers in Disorders of the Nervous System	331
Biomarkers of Neural Regeneration	331
Biomarkers of Disruption of Blood–Brain Barrier	332
Biomarkers of Neurotoxicity	333
Glial Fibrillary Acidic Protein as Biomarker of Neurotoxicity	333
Single-Stranded DNA as a Biomarker of Neuronal Apoptosis	334
Biomarkers of Neurodegenerative Disorders	334
Biomarkers of Alzheimer Disease	335
Biomarkers of Parkinson Disease	354
Biomarkers of Huntington Disease	358
Biomarkers of Wilson Disease	360
Biomarkers of Amyotrophic Lateral Sclerosis	360
Biomarkers of Dementia in HIV-1-Infected Patients	364
Biomarkers of Prion Diseases	364
Biomarkers of Multiple Sclerosis	365
Antibodies in Multiple Sclerosis	366
T Cells as Biomarkers of Multiple Sclerosis	368

Matrix Metalloproteinases as Biomarkers in Multiple Sclerosis . . .	369
Gelsolin as a Biomarker of Multiple Sclerosis	369
Gene Expression Profiling of Biomarkers in Multiple Sclerosis . . .	369
Serum Proteomic Pattern Analysis in Multiple Sclerosis	370
Biomarkers of Remyelination and Repair	370
Biomarkers of Response to Therapy of Multiple Sclerosis	371
Concluding Remarks and Future Perspective of Biomarkers of Multiple Sclerosis	371
Biomarkers of Stroke	372
Biomarkers of Intracerebral Hemorrhage	374
Biomarkers of Hypoxic Brain Damage	374
Brain Natriuretic Peptide as a Biomarker of Cardioembolic Stroke . .	375
Brain Lactate and N-Acetylaspartate as Biomarkers of Stroke . . .	375
Intercellular Adhesion Molecule 1 as Biomarker of Ischemic Stroke	375
Lp-PLA2 and CRP as Biomarkers of Stroke	376
Neuroserpin Polymorphisms as a Biomarker of Stroke	376
NMDA Receptors as Biomarkers of Excitotoxicity in Stroke	376
Nucleosomes as Biomarkers of Stroke	377
PARK7 and Nucleoside Diphosphate Kinase A as Biomarkers of Stroke	377
Visinin-Like Protein 1	378
Gene Expression in Blood Following Ischemic Stroke	378
Future Prospects of Biomarkers of Stroke	379
Biomarkers of Traumatic Brain Injury	380
Technologies for Identification of Biomarkers of TBI	381
Biomarkers of TBI	383
Biomarkers of Inflicted TBI in Infants	384
Clinical Applications of Biomarkers of TBI	385
Biomarkers of CNS Infections	385
Biomarkers of CNS HIV Infection	386
Biomarkers of Bacterial Meningitis	386
Biomarkers of Epilepsy	387
Genetic Epilepsies	387
Biochemical Markers of Epilepsy	387
Imaging Biomarkers of Epilepsy	388
Biomarkers of Normal Pressure Hydrocephalus	388
Biomarkers of Retinal Disorders	389
Biomarkers of Age-Related Macular Degeneration	389
Biomarkers of Autism	390
Biomarkers of Sleep Disorders	391
Biomarker of Excessive Daytime Sleepiness	391
Biomarkers of Obstructive Sleep Apnea	392
Biomarkers of Restless Legs Syndrome	392
Biomarkers of Psychiatric Disorders	393

Biomarkers of Depression 393

Biomarkers of Psychosis 394

Biomarkers of Schizophrenia 394

8 Biomarkers of Cardiovascular Disorders 397

Introduction 397

 Epidemiology of Cardiovascular Disease 397

Biomarkers of Cardiovascular Diseases 398

 Genetic Biomarkers of Cardiovascular Disorders 399

Methods for Identification of Cardiovascular Biomarkers 401

 Application of Proteomics for Biomarkers of Cardiovascular Disease 401

 Detection of Biomarkers of Myocardial Infarction in Saliva by a Nanobiochip 402

 Metabolomic Technologies for Biomarkers of Myocardial Ischemia 402

 Imaging Biomarkers of Cardiovascular Disease 403

Applications of Biomarkers of Cardiovascular Disease 404

 Biomarkers for Ischemic Heart Disease and Myocardial Infarction 404

 Biomarkers of Congestive Heart Failure 409

 Biomarkers for Atherosclerosis 413

 Biomarkers of Risk Factors for Coronary Heart Disease 416

 Biomarkers for Pulmonary Arterial Hypertension 419

 Genetic Biomarkers for Cardiovascular Disease 420

 Multiple Biomarkers for Prediction of Death from Cardiovascular Disease 425

Role of Biomarkers in the Management of Cardiovascular Disease 426

 Role of Biomarkers in the Diagnosis of Myocardial Infarction 426

 Role of Biomarkers in the Prevention of Cardiovascular Disease 426

 Molecular Signature Analysis in Management of Cardiovascular Diseases 427

 C-Reactive Protein as Biomarker of Response to Statin Therapy 427

 Role of Circulating Biomarkers and Mediators of Cardiovascular Dysfunction 428

 Use of Biomarkers in the Management of Peripheral Arterial Disease 429

 Use of Biomarkers in the Management of Hypertension 429

 Use of Protein Biomarkers for Monitoring Acute Coronary Syndromes 429

 Use of Multiple Biomarkers for Monitoring of Cardiovascular Disease 430

Future Prospects for Cardiovascular Biomarkers 431

 Cardiovascular Biomarker Consortium 431

 Systems Approach to Biomarker Research in Cardiovascular Disease 432

9	Biomarkers and Personalized Medicine	433
	Introduction	433
	Pharmacogenetics	434
	Biomarkers and Pharmacogenetics	434
	Pharmacogenomics	436
	Pharmacoproteomics	436
	Single-Cell Proteomics for Personalized Medicine	437
	Role of Biomarkers in Development of Personalized Drugs	438
	Use of Biomarkers for Developing MAb Therapy in Oncology	438
	Biobanking, Biomarkers, and Personalized Medicine in EU	438
	Expression Signatures as Diagnostic/Prognostic Tools	440
	Biomarkers for Monitoring Response to Therapy	440
	Drug Rescue by Biomarker-Based Personalized Medicine	441
	Future Role of Biomarkers in Personalized Medicine	442
10	Regulatory Issues	443
	Introduction	443
	Biomarker Validation	443
	FDA Criteria for a Valid Biomarker	444
	Role of NIST in Validation of Cancer Biomarkers	445
	Quality Specifications for BNP and NT-proBNP as Cardiac Biomarker Assays	446
	FDA Perspective of Biomarkers in Clinical Trials	447
	FDA and Predictive Medicine	449
	Biomarkers and FDA’s Voluntary Genomic Data Submission	449
	Role of Imaging Biomarkers in Approval of Drugs	450
	FDA Critical Path Initiative and Biomarker R&D	451
	FDA Consortium Linking Genetic Biomarkers to Serious Adverse Events	451
	Oncology Biomarker Qualification Initiative	452
	Critical Path Initiative	453
	From Validated Biomarker Assay to a Clinical Laboratory Diagnostic	456
	Fast Path Programs	456
	Need for a Single Federal Agency to Oversee Biomarker Field	457
	References	459
	Subject Index	487



<http://www.springer.com/978-1-60761-684-9>

The Handbook of Biomarkers

Jain, K.K.

2010, XX, 492 p., Hardcover

ISBN: 978-1-60761-684-9

A product of Humana Press