

Biomarkers

Part 1: Technologies & Applications

By

Prof. K.K. Jain
MD, FRACS, FFPM
Jain PharmaBiotech
Basel, Switzerland

November 2018

A Jain PharmaBiotech Report

A U T H O R ' S B I O G R A P H Y

Professor K. K. Jain is a neurologist/neurosurgeon by training and has been working in the biotechnology/biopharmaceuticals industry for several years. He received graduate training in both Europe and USA, has held academic positions in several countries and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of UK. Currently he is a consultant at Jain PharmaBiotech. Prof. Jain's 478 publications include 30 books (6 as editor+ 24 as author) and 50 special reports, which have covered important areas in biotechnology, gene therapy and biopharmaceuticals. The following Jain PharmaBiotech reports are relevant to biomarkers: proteomics, molecular diagnostics, nanobiotechnology, and personalized medicine. Recent books include "Handbook of Nanomedicine" (Springer 2008, Chinese edition by Peking University Press 2011, 3rd ed 2017), "Textbook of Personalized Medicine" (Springer 2009; Japanese ed 2012; 2nd ed Springer 2015), "Handbook of Biomarkers" (Springer 2010; Chinese ed, Chemical Industry Press 2016, 2nd ed 2017), "Handbook of Neuroprotection" (Springer 2011, 2nd ed 2019), "Applications of Biotechnology in Cardiovascular Therapeutics" (Springer 2011), "Applications of Biotechnology in Neurology" (Springer 2013), and "Applications of Biotechnology in Oncology" (Springer 2014). He has also edited "Applied Neurogenomics" (Springer 2015).

November 2018
Copyright © 2018 by

**Jain PharmaBiotech
Bläsiring 7
CH-4057 Basel
Switzerland**

**Tel & Fax: +4161-6924461
Email: info@pharmabiotech.ch
Web site: <http://pharmabiotech.ch/>**

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, or otherwise without the prior written permission of the Publisher. This report may not be lent, resold or otherwise traded in any manner without the consent of the Publisher. While all reasonable steps have been taken to ensure the accuracy of the information presented, the Publisher cannot accept responsibility for inadvertent errors or omissions.

TABLE OF CONTENTS

0. Executive Summary	27
1. Introduction	29
Definitions	29
Historical aspects of biomarkers.....	29
Classification of biomarkers.....	30
Biomarker as a response to therapeutic intervention	31
Pharmacokinetic/pharmacodynamics biomarkers	31
Predictive biomarkers	31
Valid biomarkers.....	32
Types of biomarkers	33
Genes as biomarkers.....	33
<i>Silent gene mutations.....</i>	<i>33</i>
Epigenetic biomarkers	33
Exosomes as biomarkers	34
Proteins as biomarkers	34
<i>Proteomics.....</i>	<i>35</i>
DNA biomarkers	35
Mitochondrial DNA	35
<i>Mitochondrial mutations.....</i>	<i>35</i>
RNA biomarkers.....	36
<i>Transcriptomics</i>	<i>36</i>
<i>MicroRNAs</i>	<i>37</i>
Metabolomics	37
Glycomics	38
Single nucleotide polymorphisms	38
<i>Haplotyping.....</i>	<i>39</i>
Cell biomarkers of disease	39
Stem cell biomarkers.....	39
<i>Association of stem cell biomarkers with disease.....</i>	<i>40</i>
<i>Cancer stem cell biomarkers.....</i>	<i>40</i>
<i>Endoglin as a functional biomarker of stem cells</i>	<i>40</i>
<i>p75NTR as a biomarker to isolate adipose tissue-derived stem cells</i>	<i>40</i>
<i>Protein expression profile as biomarker of stem cells.....</i>	<i>41</i>
<i>STEMPRO® EZChek™ for analysis of biomarkers of hESCs</i>	<i>41</i>
<i>SSEA-4 as biomarker of MSCs</i>	<i>41</i>
Gaseous mediators as biomarkers of disease.....	41
Autoantibodies as biomarkers of autoimmune diseases.....	42
Variations of biomarkers with circadian rhythms.....	42
Comparison of various types of biomarkers	43
Biomarkers and systems biology	43
Systems biology approach to biomarker identification.....	44
Relation of biomarkers to other technologies and healthcare	45
Biomarkers and translational medicine.....	45
Role of biomarkers in monitoring of diseases	46
Limitations of use of biomarkers in healthcare	46
2. Technologies for Discovery of Biomarkers	48
Introduction	48
The ideal biomarker	48
Genomic technologies.....	48
Gene expression	48
<i>Whole genome expression array</i>	<i>49</i>
<i>Gene expression profiling on whole blood samples</i>	<i>50</i>
<i>Profiling gene expression patterns of white blood cells.....</i>	<i>50</i>
Tissue microarrays for study of biomarkers	50
Technologies for detection of miRNAs as biomarkers	51
Microarrays for analysis of miRNA gene expression	51
<i>Microarrays vs quantitative PCR for measuring miRNAs.....</i>	<i>52</i>
Point-of-care detection of circulating miRNAs as biomarkers.....	52
Epigenomic technologies	52
Discovery of methylation biomarkers.....	53
Detection of epigenetic biomarkers	54
Proteomic technologies	54
2D GE	55
ProteoCarta® integrated proteomics discovery platform	55
Isotope-coded affinity tags.....	56
Liquid chromatography-MS/MS	57

Lucid Proteomics System	57
Magnetics beads for protein biomarker discovery	57
MASstermind™	57
Combined analysis of protein and nucleic-acid biomarkers	58
Mass spectrometry	58
2D PAGE and mass spectrometry	59
Imaging mass spectrometry	59
MALDI mass spectrometry for biomarker discovery	60
Quantitative tandem MS	61
Single-molecule mass spectrometry using a nanopore	61
Requirements for MS-based proteomic biomarker development	61
Nucleic Acid Programmable Protein Array	62
Protein tomography	62
Protein biochips/microarrays and biomarkers	62
Antibody array/affinity proteomics-based biomarker discovery	63
Detection of biomarkers using peptide array technology	64
ProtoArray®	64
Protein nanobiochip	65
Gene expression microarray data as a source of protein biomarkers	65
Quantification of protein biomarkers	65
CyTOF for quantification of biomarkers	65
Digital protein biomarker measurement	66
Multiple reaction monitoring assays	66
Real-time PCR for quantification of protein biomarkers	67
Search for biomarkers in body fluids	67
Challenges and strategies for discovery of protein biomarkers in plasma	67
Technologies for removal of highly abundant proteins in blood	68
3D structure of CD38 as a biomarker	69
BD™ Free Flow Electrophoresis System	69
Isotope tags for relative and absolute quantification	69
Plasma protein microparticles as biomarkers	70
Proteome partitioning	70
Stable isotope tagging methods	71
Technology to measure both the identity and size of the biomarker	71
Selected reaction monitoring MS	72
Targeted MS for verification of biomarkers	72
Biomarkers in the urinary proteome	73
Peptides as biomarkers of disease	74
Analysis of peptides in bodily fluids	74
Antibody biomarker discovery via evolution of peptides	75
Selected reaction monitoring for validating peptide biomarkers	75
Serum peptidome patterns	76
SISCAPA method for quantitating proteins and peptides in plasma	76
Comparison of proteomic profiling technologies for discovery of biomarkers	76
Verification for interlaboratory reproducibility of protein biomarkers	77
Significance of similar protein biomarkers in different tissues	77
Glycomic technologies	78
Cellular glycomics for discovery of cellular biomarkers	78
Metabolomic technologies	79
Genome-wide association studies for identification of metabolic biomarkers	79
Genetic influences on human blood metabolites	80
Lipid profiling	80
Mass spectrometry for discovery of metabolic biomarkers in plasma	80
Role of metabolomics in biomarker identification and pattern recognition	81
Urinary profiling by capillary electrophoresis	81
Validation of biomarkers in large-scale human metabolomics studies	81
Lipidomics	82
Disease biomarkers in breath	82
Portable breath test for volatile organic compounds	83
Detection of breath biomarkers by sensation technology	83
Detection of breath biomarkers by nanosensors	83
Detection of breath biomarkers optical frequency comb spectroscopy	84
Detection of breath biomarkers by infrared absorption spectroscopy	84
Detection of biomarkers by electronic nose	84
Fluorescent indicators for biomarkers	84
Molecular imaging technologies	85
Computer tomography	85
Magnetic resonance imaging	85
Positron emission tomography	86
Advantages of imaging biomarkers	86
Monitoring in vivo gene expression by molecular imaging	87

Molecular imaging in vivo as a biomarker	87
Challenges and future of molecular imaging	88
<i>Basic research in molecular imaging</i>	88
<i>Imaging intracellular NADH as a biomarker of disease</i>	88
<i>Devices for molecular imaging</i>	88
<i>Imaging biomarkers in clinical trials</i>	88
<i>Molecular imaging in clinical practice</i>	89
Nuclear magnetic resonance	89
Chemical derivatization to enhance biomarker detection by NMR	89
Fluxomics by using NMR	90
Nanobiotechnology	90
Dip Pen Nanolithography.....	90
Nanomaterials for biolabeling	91
<i>Quantum dot molecular labels</i>	92
<i>Bioconjugated QDs for multiplexed profiling of biomarkers</i>	92
<i>Magnetic nanotags for multiplex detection of biomarkers</i>	93
Nanoparticles for molecular imaging.....	93
Nanoparticles for discovering biomarkers	93
Nanoproteomics and biomarkers.....	94
<i>High-field asymmetric waveform ion mobility mass spectrometry</i>	94
Nanosensors for measuring biomarkers in blood	94
Nanobiochip sensor technique for analysis of oral cancer biomarkers.....	94
Future prospects of application of nanobiotechnology for biomarkers.....	95
Bioinformatics	95
Biomarker Workflow Guide.....	95
Analysis of microarray data for selecting useful biomarkers.....	96
Role of bioinformatics in discovery of protein biomarkers	96
Role of bioinformatics in detection of cancer biomarkers	97
Biomarker databases.....	97
Gene networks as biomarkers.....	98
Role of bioinformatics in integrating various data and biomarker discovery	98
Evaluation of biomarker studies	98
3. Biomarkers and Molecular Diagnostics	100
Introduction	100
Molecular diagnostic technologies	100
Polymerase chain reaction.....	100
<i>Amplification</i>	100
<i>Target selection</i>	101
<i>Detection of amplified DNA</i>	101
<i>Limitations of PCR</i>	101
Real-time PCR systems.....	102
<i>Limitations of real-time PCR</i>	102
<i>Future applications of real-time qPCR</i>	103
<i>Real-time qPCR for quantification of circulating mtDNA</i>	103
Combined PCR-ELISA	103
Non-PCR methods.....	104
<i>Linked Linear Amplification</i>	104
Transcription mediated amplification	104
Rapid analysis of gene expression	104
WAVE nucleic acid fragment analysis system	105
DNA probes with conjugated minor groove binder	105
Rolling circle amplification technology.....	106
<i>Gene-based diagnostics through RCAT</i>	106
<i>RCAT-immunodiagnosics</i>	107
<i>RCAT-biochips</i>	107
<i>RCAT-pharmacogenomics</i>	107
Circle-to-circle amplification	107
Biomarkers and high throughput molecular screening	108
Detection and expression profiling of miRNA	108
Real-time PCR for expression profiling of miRNAs.....	108
Use of LNA to explore miRNA.....	109
Microarrays for analysis of miRNA gene expression	109
Devices for biomarkers	109
Biochips and microarrays	109
<i>Applications of biochips/microarrays</i>	110
<i>Role of biochip/microarrays in discovery of biomarkers</i>	110
Biosensors for biomarkers.....	111
<i>Biosensor for analysis of sweat biomarkers</i>	111
4. Biomarkers for Drug Discovery & Development	114

Introduction	114
Biomarker technologies for drug discovery.....	114
Proteomics-based biomarkers for drug discovery	114
Chemoproteomics	115
<i>Activity-based chemical proteomics</i>	<i>115</i>
Transcriptomics for drug discovery	115
Metabolomics for drug discovery	116
Biomarkers and drug safety.....	116
Biomarkers of adverse drug reactions.....	116
Applications of biomarkers in drug safety studies.....	117
Genomic technologies for toxicology biomarkers	117
Proteomic technologies for toxicology biomarkers	118
Metabonomic technologies for toxicology biomarkers.....	118
Integration of genomic and metabonomic data to develop toxicity biomarkers.....	118
Toxicology studies based on biomarkers	119
<i>Biomarker of genotoxicity</i>	<i>120</i>
<i>Biomarkers of hepatotoxicity</i>	<i>120</i>
<i>Biomarkers of nephrotoxicity</i>	<i>121</i>
<i>Cardiotoxicity</i>	<i>122</i>
<i>Neurotoxicity.....</i>	<i>123</i>
Applications of biomarkers for drug development	123
Application of metabolomics/metabolomics for drug development	124
Application of biomarkers by the pharmaceutical companies.....	125
Biomarkers in clinical trials.....	126
<i>NIH recommendations on the use of biomarkers in clinical trials</i>	<i>126</i>
<i>Advantages of biomarkers for drug development</i>	<i>127</i>
<i>Limitations and problems with use of biomarkers in clinical trials</i>	<i>128</i>
Development of static and dynamic biomarkers	128
Molecular imaging as a biomarker in drug development	129
<i>Molecular imaging in preclinical studies.....</i>	<i>129</i>
<i>Molecular imaging in clinical trials</i>	<i>130</i>
<i>Prospects of molecular imaging in drug discovery and development</i>	<i>131</i>
Pharmacogenomic biomarker information in drug labels.....	131
Role of biomarkers in vaccine development	132
Role of biomarkers in relation to stage of drug discovery and development	132
Role of pharmacokinetic/pharmacodynamic biomarkers in drug development	132
Role of biomarkers for drug development in cardiovascular disorders	133
Role of biomarkers for drug development in neurological disorders.....	134
Significance of biomarkers in drug development	134
Organizations & resources for biomarker-based drug development	134
Biomarker Alliance	135
Biomarkers Consortium	135
Molecular Libraries and Imaging Roadmap of NIH	136
Rare Diseases Clinical Research Consortia	137
Future of biomarker-based drug development.....	137
5. Role of Biomarkers in Healthcare	140
Introduction	140
Biomarkers of inflammation.....	141
ESR and CRP as biomarkers of inflammation	141
Metabolic biomarkers of inflammation.....	142
YKL-40 as a biomarker inflammation and predictor of mortality	142
Biomarkers of allergic disorders	142
Biomarkers of oxidative stress	143
1,4-dihydroxynonane-mercaptopuric acid	143
Oxidized phospholipids	143
Oxidative DNA damage	144
Proteins as biomarkers of oxidative stress in diseases	144
Testing for oxidative stress	144
Biomarkers of hypoxia	145
Pathophysiology of hypoxia	145
Hypoxia inducible factor as biomarker of hypoxia and response to oxygenation	145
Identification of hypoxia biomarkers from exhaled breath	145
Metabolic biomarkers of hypoxia	146
Biomarkers of liver disease.....	146
Breath biomarkers of liver disease	146
Biomarkers of liver injury.....	146
Fibrosis and cirrhosis of liver	146
FibroMax.....	147
Hepatic encephalopathy	147
miRNA biomarkers of liver disease	147

Viral hepatitis B and C	148
<i>Biomarkers of hepatitis C</i>	148
<i>Biomarkers of hepatitis B</i>	149
Biomarkers of pancreatitis	149
Biomarkers of renal disease	150
Biomarkers of lupus nephritis	150
Biomarkers of diabetic nephropathy	151
Cystatin C as biomarker of glomerular filtration rate (GFR)	151
Estimated GFR and albuminuria as biomarkers of chronic kidney disease	151
Proteomic biomarkers of acute kidney injury	152
Symmetric dimethylarginine as biomarker of chronic kidney disease in dogs	152
Troponin-T as a biomarker for predicting end-stage renal disease	152
Biomarkers in pediatrics	152
Pediatric critical care	152
Biomarkers of acute kidney injury in children	153
Biomarkers of miscellaneous disorders	153
Biomarkers of acid-base disorders in acute care setting	153
Biomarkers of carbon monoxide poisoning	153
Biomarkers of Castleman disease	154
Biomarkers of erectile dysfunction	154
Biomarkers of fever	155
Biomarkers of heat stroke	155
Biomarkers of hyponatremia	155
Biomarkers of inflammatory bowel disease	156
Biomarkers of radiation injury	157
Biomarkers for prediction of all-cause mortality	157
Biomarkers common to multiple diseases	157
Nasal nitric oxide as a biomarker of response to rhinosinusitis therapy	158
Biomarkers of gene-environmental interactions in human disease	159
Application of biomarkers in animal health	159
6. Biomarkers in Metabolic Disorders	162
Introduction	162
Biomarkers of acute intermittent porphyria	162
Liver X receptors	162
Biomarkers of diabetes mellitus	163
β -cell function as biomarker of diabetes	164
Biomarkers of hyperglycemia	164
Biomarkers of diabetes-associated oxidative stress	164
Biomarkers of inflammation associated with diabetes	165
Biomarkers of renal complications in diabetes mellitus type 2	165
Biomarkers of diabetes	165
Biomarkers of prediabetes	165
Biomarkers of insulin resistance	166
Elevated plasma furin level	166
Glycosylated hemoglobin in diabetes mellitus	166
Glycated albumin as a biomarker of diabetes mellitus	166
Low C-peptide as a biomarker of complications of diabetes type 1	167
Personalized management of diabetes mellitus based on biomarkers	167
Biomarkers of metabolic syndrome	168
Adiponectin	168
Cystatin C	168
Human plasma lipidome	169
Neurotensin as biomarker of obesity	170
7. Biomarkers in Immune Disorders	172
Introduction	172
Biomarkers relevant to organ transplantation	172
Biomarkers of graft versus host disease	172
Biomarkers of renal allograft failure	173
Biomarkers of renal transplant tolerance	174
Biomarkers of lung transplant rejection	175
Biomarkers of GVHD following transplantation of hematopoietic cells	175
Plasma biomarkers of response to therapy of GVHD	175
Systemic lupus erythematosus	175
Adiponectin as biomarker of SLE	176
Current management and need for biomarkers of SLE	176
Role of collaborative efforts and databases of SLE biomarkers	177
C4d-bearing reticulocytes	177
CB-CAPS	177
Epigenetic biomarkers of SLE	177

Genetic loci of SLE	178
HMGB1	178
Biomarkers of systemic sclerosis.....	178
Biomarkers of Sjögren syndrome.....	179
8. Biomarkers of Musculoskeletal Disorders	182
Introduction	182
Muscle disorders.....	182
Biomarkers of muscle fatigue during exercise	182
Biomarkers of mitochondrial content in skeletal muscle	182
Idiopathic inflammatory myopathies.....	183
Rheumatoid arthritis.....	183
Assays for biomarkers of RA.....	184
Biomarkers for personalizing therapy of rheumatoid arthritis	184
Circulating cytokines in RA.....	185
Epigenetic biomarkers of rheumatoid arthritis.....	185
miRNA biomarkers in RA.....	185
Serum CRP in RA	186
Biomarkers of spondylarthritis	186
Biomarkers of axial spondyloarthritis.....	187
Biomarkers of psoriatic arthritis	187
Osteoarthritis	187
Molecular pathophysiology of OA	188
Biomarkers of osteoarthritis	188
Assays for biomarkers of OA.....	189
Biomarkers of OA.....	189
Concluding remarks and future prospects of biomarkers of OA.....	189
Biomarkers of osteoporosis	190
Assays for detection of biomarkers of osteoporosis.....	190
Bone imaging with quantitative CT and MRI	191
Circulating miRNAs as biomarkers of osteoporosis.....	191
Dual x-ray absorptiometry	192
Utility of biomarkers of osteoporosis.....	192
Biomarkers of osteonecrosis.....	192
Osteonecrosis in Gaucher's disease	192
9. Biomarkers of Infectious Diseases.....	194
Introduction	194
Technologies for discovery of biomarkers of infection	194
Chemokines as biomarkers of infection	194
Endotoxin as biomarker of infection.....	194
Proteomics for discovering biomarkers of infections.....	194
Soluble urokinase plasminogen activator receptor	195
Sepsis	195
Biomarkers of sepsis	196
<i>Circulating CPS-1 as biomarkers of organ damage in sepsis</i>	<i>197</i>
<i>CoQ10 level reduction in septic shock.....</i>	<i>197</i>
<i>Multibiomarker-based outcome risk stratification of septic shock.....</i>	<i>198</i>
<i>Nitric oxide as a biomarker of sepsis</i>	<i>198</i>
<i>SuPAR as a biomarker of sepsis</i>	<i>198</i>
Systemic inflammatory response syndrome.....	199
Tuberculosis	199
Conventional diagnosis of tuberculosis.....	200
Molecular diagnostics for tuberculosis	200
Biomarkers for tuberculosis.....	200
Biomarkers of pulmonary tuberculosis in the breath	201
Transcriptional signatures in active vs asymptomatic tuberculosis	201
Biomarkers of viral infections	201
Viral hepatitis	202
Biomarkers of SARS	204
Biomarkers of HIV.....	204
Biomarkers in parasitic infections.....	205
Role of biomarkers in malaria	205
Identification of biomarkers in Schistosomiasis infections.....	206
Diagnostic & therapeutic applications of biomarkers of infections.....	206
Biomarkers to discriminate bacterial from nonbacterial respiratory infections.....	206
Procalcitonin as a guide to antibiotic therapy in infections	206
10. Biomarkers of Genetic Disorders.....	208
Introduction	208
Biomarkers of Down's syndrome	208

Biomarkers of muscular dystrophy	208
Biomarkers of phenylketonuria.....	209
Genetic biomarkers of psoriasis.....	209
Biomarkers of lysosomal storage disorders	210
Biomarkers of Niemann-Pick disease	210
<i>Bile acids as biomarkers for the early diagnosis of NPD.....</i>	<i>210</i>
<i>Cholesterol oxidation products as biomarkers of NPD.....</i>	<i>210</i>
Biomarkers of mucopolysaccharidoses	211
<i>Proteomic technologies for biomarkers of MPS.....</i>	<i>211</i>
<i>Glycan-based biomarkers for MPS.....</i>	<i>212</i>
<i>Biomarkers of LSD</i>	<i>212</i>
<i>Prenatal diagnosis of LSD.....</i>	<i>212</i>
Biomarkers of Fabry's disease	212
11. Biomarkers of Aging	214
Introduction	214
Biomarkers of biological age.....	215
Gene variants as determinants of biological age.....	216
Gene expression profiles for calculating transcriptomic age	216
Biomarkers of healthy aging	216
Biomarkers of longevity.....	217
Effect of calorie restriction on biomarkers of longevity	217
Healthy aging index	217
Low serum thyroid hormone level as biomarker of longevity.....	217
Biomarkers as predictors of mortality with aging	218
Genetic biomarkers of aging.....	218
Genetic signatures of longevity	218
Metabolomic biomarkers of aging	218
Mitochondrial mutations as biomarkers of aging	219
Oxidative biomarkers of aging	219
Molecular diagnostics and biomarkers of age-related diseases.....	220
Protein biomarkers of aging	220
Carbamylated proteins as biomarkers of aging	220
Proteomic biomarkers of muscle aging.....	220
Role of humanin in age-related diseases	221
Role of bioinformatics in search for biomarkers of aging	221
Aging biomarkers in a genetically homogeneous population	221
Telomere attrition as aging biomarker.....	222
12. Nutritional Biomarkers	224
Introduction	224
Biomarkers of Nutrition for Development project	224
Biomarkers in nutritional epidemiology	224
Biomarkers of nutritional status	225
Ferritin as biomarker of nutritional status.....	225
Folate biomarkers related to nutritional health status	226
Iodine as biomarker of nutritional status.....	226
Zinc as a biomarker of nutritional status	227
Biomarkers of branched chain amino acid status.....	227
Biomarkers of caloric restriction.....	227
Biomarkers of malnutrition.....	227
Maternal nutrition during early pregnancy causes epigenetic changes.....	228
Proteomic biomarkers and nutrition	228
Vitamin deficiency as biomarker of disease	228
Vitamin A biomarkers	228
Vitamin B12 deficiency	229
Vitamin D deficiency as a biomarker of disease.....	230
Role of biomarkers in the development of personalized nutrition	230
13. Biomarkers of Cancer.....	232
Introduction	232
The ideal biomarker for cancer	232
Biomarkers and hallmarks of cancer	233
Single vs multiple biomarkers of cancer	233
Types of cancer biomarkers	234
miRNAs as biomarkers in cancer	234
<i>Diagnostic value of miRNA in cancer.....</i>	<i>236</i>
Biomarkers of epigenetic gene silencing in cancer	236
<i>5-hydroxymethylcytosine as a biomarker of cancer</i>	<i>237</i>
Carcinoembryonic antigen	237
Circulating cancer biomarkers.....	237

<i>Circulating tumor cells as cancer biomarkers</i>	237
<i>Circulating nucleic acids as potential biomarkers of cancer</i>	238
<i>Circulating exosomes and microvesicles as biomarkers of cancer</i>	238
<i>Circulating miRNAs for cancer detection</i>	239
DNA repair biomarkers	239
HER3 as biomarker of cancer.....	239
Immunologic and inflammation biomarkers of cancer	239
Metastatic cancer biomarkers	240
Molecular diagnostic techniques for cancer	240
Technologies for detection of cancer biomarkers.....	242
Genomic technologies for cancer biomarkers	242
<i>Biomarkers of PTEN tumor suppressor gene status</i>	242
<i>Cold-PCR</i>	242
<i>ddPCR for detection of cancer biomarkers in cell free plasma DNA</i>	243
<i>Digital karyotyping for cancer biomarkers</i>	243
<i>Genome analysis at the molecular level</i>	243
<i>KRAS as a biomarker of cancer</i>	244
<i>LigAmp for detection of gene mutations in cancer</i>	244
<i>Mitochondrial DNA as a cancer biomarker</i>	244
<i>Next generation sequencing for detection of cancer biomarkers</i>	245
<i>Telomerase as a biomarker of cancer</i>	246
Tissue microarrays for study of cancer biomarkers	246
Molecular fingerprinting of cancer	247
<i>NIPT for detecting biomarkers of gynecological cancers</i>	247
Proteomic technologies for detecting biomarkers of cancer	247
2D PAGE.....	248
<i>Antibody-based detection of protein biomarkers</i>	248
<i>Aptamer-based molecular probes for cancer biomarker discovery</i>	249
<i>Biomarkers of protein-drug interactions in cancer</i>	249
<i>Cancer immunomics to identify autoantibody signatures</i>	250
<i>Desorption electrospray ionization for detection of cancer biomarkers</i>	250
<i>Detection of circulating nucleosomes in serum of cancer patients</i>	250
<i>Detection of tumor biomarkers with ProteinChip technology</i>	251
<i>Glycoprotein biomarkers of cancer</i>	251
<i>HER-2/neu oncoprotein as biomarkers for cancer</i>	251
<i>Humoral proteomics</i>	252
<i>Laser capture microdissection</i>	252
<i>Membrane-type serine protease-1</i>	252
<i>Proteomic analysis of cancer cell mitochondria</i>	253
<i>Proteomic technologies for detection of autoimmune biomarkers</i>	253
SELDI-TOF MS.....	253
<i>Serum proteome analysis for early detection of cancer</i>	254
<i>Synthetic biomarker-based POC diagnostic for cancer</i>	254
<i>Triple-quadrupole MS for detection of mutant proteins</i>	254
<i>Targeted MS for validation of cancer biomarkers in plasma</i>	255
<i>Tissue proteomics for discovery of cancer biomarkers</i>	255
<i>VeraTag system for cancer biomarkers</i>	255
Metabolomic biomarkers of cancer	255
<i>Magnetic resonance for detecting metabolomics biomarkers of cancer</i>	256
<i>Choline phospholipid biomarkers of cancer</i>	256
<i>Hypoxia-inducible factor-1</i>	256
<i>Detection of drug resistance in cancer by metabolic profiling</i>	257
<i>Plasma free amino acids profiling in cancer</i>	257
<i>Urinary metabolomic biomarkers of cancer</i>	257
Epitomics for the early detection of cancer	258
Epigenetic biomarkers of cancer	258
<i>Detection of biomarkers of DNA methylation</i>	258
<i>Epigenomics Marker Machine for DNA methylation biomarkers</i>	259
<i>Histone deacetylase</i>	260
<i>MDScan™ microarray technology</i>	260
<i>Mucins as epigenetic biomarkers in epithelial cancers</i>	260
<i>PCR with bisulfite for detecting DNA methylation biomarkers in cancer</i>	261
<i>Detection of methylated DNA in serum and urine</i>	262
<i>Integrated platform for genetic and epigenetic analysis</i>	262
Nanobiotechnology for early detection of cancer to improve treatment	262
<i>Aptasensor for electrochemical detection of exosomes</i>	263
<i>Nanovesicles for detection of cancer biomarkers</i>	263
<i>Nanowire biosensors for detection of cancer biomarkers</i>	264
<i>NP-peptide complexes for detection of cancer biomarkers in urine</i>	264
Ultrasound radiation to enhance release of a tumor biomarker	264
In vivo imaging of cancer biomarkers	265

Computer tomography.....	265
Optical systems for in vivo molecular imaging of cancer.....	265
Positron emission tomography.....	266
Imaging of tumor oxygenation and microvascular permeability by MRI.....	266
Xenon-enhanced MRI.....	266
Kallikrein gene family and cancer biomarkers.....	266
Detection of CTCs as biomarkers of cancer.....	267
Applications of cancer biomarkers.....	268
Use of biomarkers for cancer classification.....	268
Cancer classification using microarrays.....	268
Proteomic classification of cancer.....	269
Use of biomarkers for early detection of cancer.....	269
Applications of biomarkers for cancer diagnosis.....	269
Methylated DNA sequences as cancer biomarkers.....	269
MicroRNA expression profiling for diagnosis of human cancers.....	270
MUC4 as a diagnostic biomarker in cancer.....	270
Applications of biomarkers for cancer diagnosis and therapy.....	271
ARTS as a biomarker as well as a basis of anticancer drugs.....	272
Asparagine synthetase as biomarker for therapy with L-asparaginase.....	272
Peptide-based agents for targeting cancer biomarkers.....	273
PI3K mutations as a biomarker for use as a companion diagnostic.....	273
Biomarkers for assessing efficacy of cancer therapy.....	273
ERCC1-XPF expression as a biomarker of response to chemotherapy.....	273
P53 expression level as biomarker of efficacy of cancer gene therapy.....	274
Biomarkers of angiogenesis for developing antiangiogenic therapy.....	274
Biomarkers of response to antiangiogenic agents.....	274
Circulating endothelial cells as targets for antiangiogenic drugs.....	274
Imaging biomarkers for evaluation of antiangiogenic agents.....	275
Tumor endothelial biomarkers.....	275
VEGF signaling inhibitors as biomarkers.....	276
VEGF-PET imaging for analysis of angiogenic changes within a tumor.....	276
Biomarkers of prognosis in cancer treatment.....	276
Biomarkers for monitoring cancer therapy.....	277
Biomarkers of drug resistance in cancer.....	277
A systems approach to biomarkers of innate drug resistance.....	277
Epithelial membrane protein-1 as a biomarker of gefitinib resistance.....	278
Methylation biomarkers of drug resistance in cancer.....	278
STAT3 and resistance to cisplatin.....	278
Biomarkers of radiation therapy for cancer.....	279
Role of biomarkers in drug development in oncology.....	279
Biomarker-based approval of an anticancer drug regardless of site.....	280
Biomarkers in plucked hair for assessing cancer therapy.....	280
Met receptors as targets for anticancer drugs.....	281
Molecular imaging of tumor as a guide to drug development.....	281
Use of PET and SPECT to assess response to anticancer drugs.....	281
Use of MRI to assess response to anticancer drugs.....	282
Role of biomarkers in phase I clinical trials of anticancer drugs.....	282
Safety biomarkers in oncology studies.....	283
Biomarkers according to organ/type of cancer.....	283
Bladder cancer biomarkers.....	283
Detection of FGFR3 mutations in urine for diagnosis of bladder cancer.....	283
NMP22 BladderChek.....	284
Urinary telomerase as biomarker for detection of bladder cancer.....	284
Concluding remarks about biomarkers of urinary cancer.....	284
Brain tumor biomarkers.....	284
14-3-3zeta expression as prognostic biomarker for glioblastoma.....	285
ALDH1A3 as a biomarker of glioblastoma.....	285
Biomarkers to predict response to EGFR inhibitors.....	285
Biomarkers for predicting recurrence of meningiomas.....	286
CD133 as biomarker of resistance to radiotherapy.....	286
Circulating microvesicles as biomarkers.....	286
CSF attractin as a biomarker of malignant astrocytoma.....	286
ELTD1 as a biomarker of gliomas.....	287
Methylation profiling of brain tumors.....	287
Metabolite biomarkers of brain tumors.....	288
miRNAs as biomarkers of brain tumors.....	289
MRI biomarker for response of brain tumor to therapy.....	289
Multigene predictor of outcome in glioblastoma.....	289
Neuroimaging biomarkers combined with DNA microarray analysis.....	290
Proteomic analysis of CSF for identification of biomarkers for gliomas.....	290
Receptor protein tyrosine phosphatase β as biomarker of gliomas.....	290

Serum protein fingerprinting	291
VEGF-R2 as biomarker of angiogenesis in brain tumors.....	291
Future prospects of biomarkers of malignant gliomas	291
Bone tumor biomarkers	291
Cytogenetics for the study of bone and soft tissue tumors.....	291
Biomarkers of Ewing's tumors.....	292
Role of biomarkers in the diagnosis of bone tumors.....	292
Breast cancer biomarkers	292
Autoantibody biomarkers of breast cancer.....	294
Biomarkers of breast cancer in breath	294
Biomarkers for breast cancer in nipple aspiration fluid	295
Circulating tumor DNA as biomarker of breast cancer	295
Circulating exosomes as biomarkers of breast cancer	295
Proteomic biomarkers of breast cancer	295
Quantification of biomarker expression patterns by flow cytometry	296
Quantitative realtime PCR assays for biomarker validation	296
Cdk6 as a biomarker of breast cancer.....	297
Centromere protein-F.....	297
Carbonic anhydrase IX.....	297
COX-2 as a biomarker of breast cancer.....	297
G88 as a biomarker of progression of ER+ breast cancer	298
Glycomic biomarkers of breast cancer.....	298
HER-2/neu oncoprotein.....	298
High mobility group protein A2	299
Hypermethylated genes as biomarkers of metastatic breast cancer	300
Lipocalin 2 as biomarker of breast cancer progression	300
Long intervening non-coding RNAs	300
Mammaglobin.....	301
miRNA biomarkers of breast cancer.....	301
p27 expression as biomarker for survival after chemotherapy.....	302
Podocalyxin.....	302
Proneurotensin and Proenkephalin	302
Proliferating cell nuclear antigen	303
Protein kinase C as a predictive biomarker of metastatic breast cancer.....	303
Retinoblastoma tumor suppressor gene as a biomarker	303
Riboflavin carrier protein.....	304
Risk of invasive cancer after diagnosis of ductal carcinoma in situ	304
Serum CA 15-3 as biomarker of prognosis in advanced breast cancer.....	304
Stage-specific embryonic antigen-3.....	305
Suppressor of deltex protein.....	305
Tumor microenvironment as biomarker of metastasis in breast cancer.....	305
Type III TGF- β receptor as regulator of cancer progression	305
Diagnostic tests based on breast cancer genes	306
Prognostic role of breast cancer genes.....	307
Protein biomarkers for breast cancer prevention	307
Biomarkers to evaluate efficacy of chemoprevention	307
Biomarkers of response to chemotherapy of breast cancer	308
Biomarker-guided decisions for breast cancer therapy	308
Concluding remarks and future prospects of breast cancer biomarkers	309
Cervical cancer biomarkers	309
Gastrointestinal cancer biomarkers	310
Esophageal cancer biomarkers.....	310
Gastric cancer biomarkers.....	310
Colorectal cancer biomarkers.....	311
Head and neck cancer	317
Leukemia biomarkers	319
Chromosome translocations in leukemias.....	319
DNA methylation biomarkers in leukemia.....	320
Gene mutations as biomarkers in leukemia	320
Molecular diagnostic techniques for leukemia.....	320
Proteomic technologies for discovering biomarkers of leukemia.....	321
Biomarkers of chronic lymphocytic leukemia.....	321
Biomarkers of chronic myeloid leukemia	322
Biomarkers of drug resistance in leukemia	322
Biomarkers of myelodysplastic syndromes.....	323
Lymphoma biomarkers	323
Liver cancer biomarkers.....	323
Biomarkers indicating lower risk of HCC in coffee drinkers.....	324
Metabonomic profiles discriminate HCC from liver cirrhosis	324
Urinary biomarkers of HCC.....	325
Lung cancer biomarkers.....	325

<i>Autoantibodies as biomarkers in lung cancer</i>	326
<i>Biomarkers associated with neuroendocrine differentiation in NSCLC</i>	327
<i>Biomarkers of chronic inflammation in lung cancer</i>	327
<i>Biomarkers for predicting sensitivity to chemotherapy in lung cancer</i>	327
<i>Biomarkers for prediction of sensitivity to EGFR inhibitors</i>	328
<i>CTCs as biomarkers of lung cancer</i>	329
<i>Genomic biomarkers of lung cancer</i>	329
<i>Methylation biomarkers of lung cancer</i>	330
<i>miRNA biomarkers in lung cancer</i>	330
<i>Noninvasive detection of lung cancer using exhaled breath</i>	331
<i>Serum protein biomarkers of lung cancer</i>	331
<i>tNOX as biomarker of lung cancer</i>	333
<i>Tumor-derived DNA and RNA markers in blood</i>	333
<i>Volatile organic compounds in the exhaled breath</i>	333
Malignant pleural mesothelioma	333
Melanoma biomarkers	334
Nasopharyngeal carcinoma biomarkers	335
<i>Proteomic biomarkers of nasopharyngeal cancer</i>	336
<i>miRNA biomarkers of nasopharyngeal carcinoma</i>	337
Oral cancer biomarkers	337
Ovarian cancer biomarkers	337
<i>3D microfluidic platform to assess multiple ovarian cancer biomarkers</i>	338
<i>CA125 as biomarker of ovarian cancer</i>	339
<i>Epitomics approach for ovarian cancer biomarkers in serum</i>	339
<i>FGF18 as a biomarker in ovarian cancer</i>	339
<i>Gene expression studies in ovarian cancer</i>	340
<i>HE4 protein in urine as a biomarker for ovarian cancer</i>	340
<i>Hematogenous metastasis of ovarian cancer</i>	340
<i>HtrA1 as a biomarker of response to chemotherapy in ovarian cancer</i>	341
<i>Mutation of genes in ovarian cancer</i>	341
<i>Serum biomarkers of ovarian cancer prognosis</i>	341
<i>TIM-3 as a biomarker of ovarian cancer</i>	342
<i>Multiplex assays for biomarkers of ovarian cancer</i>	342
<i>Concluding remarks on biomarker-based tests of ovarian cancer</i>	343
Pancreatic cancer biomarkers	343
<i>Discovery and validation of pancreatic cancer biomarkers</i>	344
<i>Cancer stem cells as biomarkers of pancreatic cancer</i>	344
<i>Circulating exosomes as biomarkers of pancreatic cancer</i>	344
<i>Histone modifications used as biomarkers in pancreatic cancer</i>	344
<i>miRNA biomarkers of pancreatic cancer</i>	345
<i>Macrophage inhibitory cytokine-1 as biomarker of pancreatic cancer</i>	346
<i>Proteomic biomarkers of pancreatic cancer</i>	346
<i>Concluding remarks on biomarkers of pancreatic cancer</i>	347
Parathyroid cancer biomarkers	347
Peripheral nerve tumors	347
<i>Biomarkers of neurofibromatosis</i>	347
Prostate cancer	348
<i>Adipose tissue-derived biomarkers of obesity-related prostate cancer</i>	349
<i>B7-H3 as biomarker of prostate cancer</i>	349
<i>Cancer genetics-guided biomarker signatures of prostate cancer</i>	349
<i>Detection of prostate cancer biomarkers in urine</i>	349
<i>Detection of prostatic intraepithelial neoplasia</i>	350
<i>Epigenetic biomarkers of prostate cancer</i>	351
<i>Exosomes as biomarkers of prostate cancer</i>	351
<i>Gene expression analysis of prostate cancer</i>	352
<i>Genetic biomarkers of prostate cancer</i>	352
<i>Identification of prostate cancer mRNA biomarkers</i>	352
<i>Kallikreins as biomarkers of prostate cancer</i>	353
<i>LCM for diagnosis of prostate cancer</i>	353
<i>Microarray for diagnosis of prostate cancer</i>	354
<i>miRNA biomarkers of prostate cancer</i>	354
<i>Prostate cancer biomarkers in semen</i>	355
<i>PSA as biomarker of prostate cancer</i>	356
<i>ProPSA as biomarker of prostate cancer</i>	356
<i>Prostate Health Index</i>	356
<i>Prostasomes in blood as biomarker of prostate cancer</i>	356
<i>PSMA as biomarker of prostate cancer</i>	357
<i>Sarcosine as a metabolic biomarker of prostate cancer</i>	357
<i>Silenced CDH13 gene as a biomarker of cancer</i>	357
<i>Serum-protein fingerprinting</i>	357
<i>Concluding remarks on biomarkers of prostate cancer</i>	358

Renal cancer biomarkers.....	358
<i>Gene expression profile of RCC for biomarkers</i>	358
<i>KIM-1 as a plasma biomarker of RCC</i>	359
<i>miRNA biomarkers of renal cancer</i>	359
<i>Use of proteomics for detection of RCC biomarkers</i>	359
<i>Use of RCC biomarkers for prognosis and therapy</i>	359
Thyroid cancer biomarkers.....	360
<i>Detection of BRAF mutation</i>	361
<i>Gene expression biomarkers of thyroid cancer</i>	361
<i>miRNA biomarkers of thyroid cancer</i>	361
<i>Multiple endocrine neoplasia type 2B as risk factor for thyroid cancer</i>	361
Role of the NCI in cancer biomarkers.....	362
Future prospects for cancer biomarkers	363
Cancer biomarker research at academic institutions	363
Future challenges in the discovery of cancer biomarkers	364
14. Biomarkers of Disorders of the Nervous System	365
Introduction	365
Discovery of biomarkers for neurological disorders.....	365
Antibodies as biomarkers in disorders of the nervous system	366
Biomarker identification in the CSF using proteomics.....	367
Biomarker identification in the CSF using lipidomics	367
Cerebral microdialysis for the study of biomarkers of cerebral metabolism	367
Brain imaging for detection of biomarkers	368
Data mining for biomarkers of neurological disorders	368
Detection of protein biomarkers of CNS disorders in the blood	369
Genomic technologies for study of biomarkers of neurological disorders.....	369
Biomarkers of neuroinflammation	369
Biomarkers of neural regeneration	370
Biomarkers of disruption of blood-brain barrier.....	370
Biomarkers of neurotoxicity.....	371
Glial fibrillary acidic protein as biomarker of neurotoxicity	371
Single-stranded DNA as a biomarker of neuronal apoptosis	372
Biomarkers of neurogenetic disorders	372
Charcot-Marie Tooth disease	372
Duchenne and Becker muscular dystrophy	373
Early-onset torsion dystonia	374
Fragile X syndrome	374
Genetic neurotransmitter disorders	375
Hereditary neuropathy with liability to pressure palsies.....	375
Hereditary metabolic storage disorders with neurologic manifestations	375
<i>Gaucher disease</i>	375
<i>Pompe's disease</i>	376
Mitochondrial disorders affecting the nervous system	376
Spinal muscular atrophy	376
<i>Biomarkers of SMA</i>	377
Biomarkers of the aging brain	377
Cellular biomarker of aging of the brain	377
CSF F2-isoprostanes as biomarker of aging brain	377
IL-6 as a biomarker of cognitive impairment with aging	378
MRI transverse relaxation rate alteration as biomarker of aging brain.....	378
Protein aggregation as a biomarker of aging brain.....	378
Telomere shortening as a biomarker of aging brain and dementia	378
Biomarkers of neurodegenerative disorders	379
Biomarkers of dementia.....	379
Biomarkers of vascular dementia	380
Biomarkers of Alzheimer's disease	380
The ideal biomarker for AD.....	382
Methods for determining biomarkers of AD.....	382
<i>Gene expression patterns in AD</i>	382
<i>Magnetic resonance spectroscopy in AD</i>	383
<i>MicroRNAs as biomarkers of neurodegenerative disorders</i>	383
<i>MRI for biomarkers of AD</i>	384
<i>Nanotechnology to measure Aβ-derived diffusible ligands</i>	385
<i>PET scanning for biomarkers of AD</i>	385
<i>Simultaneous measurement of several biomarkers for AD</i>	387
<i>Targeting of chemokine receptor as biomarker for brain imaging</i>	387
Biomarkers of AD in CSF	388
<i>CSF sulfatide as a biomarker for AD</i>	388
<i>CSF Reelin as biomarker of AD</i>	388
<i>Monitoring of synthesis and clearance rates of Aβ in the CSF</i>	388

<i>Protein biomarkers of AD in CSF</i>	389
<i>Tau proteins in CSF</i>	390
<i>Tests for the detection of Aβ in CSF</i>	390
<i>Tests combining CSF tau and Aβ</i>	391
Blood biomarkers of AD	392
<i>A serum protein-based algorithm for the detection of AD</i>	392
<i>Amyloid precursor protein</i>	392
<i>Detection of aggregated misfolded proteins in the blood</i>	392
<i>Lipid biomarkers for preclinical detection of AD</i>	393
<i>Lymphocyte Proliferation Test</i>	393
<i>Metabolomic biomarker profiling</i>	393
<i>Plasma protein biomarkers of AD</i>	393
<i>Protein kinase C in red blood cells</i>	394
Urinary biomarkers of AD	394
A biomarker-based skin test for AD	395
Salivary biomarkers of AD	395
Applications of biomarkers of AD	395
<i>Biomarker changes in autosomal dominantly inherited AD</i>	395
<i>Correlation of imaging biomarkers with CSF biomarkers of AD</i>	396
<i>Genetic tests for AD</i>	396
<i>Humanin as a biomarker as well as neuroprotective in AD</i>	397
<i>Plasma biomarkers of drug response in AD</i>	397
<i>PredictAD project</i>	397
<i>TOMM40 gene and risk of AD</i>	398
<i>Use of biomarkers to predict AD in patients with MCI</i>	398
Concluding remarks about biomarkers for AD and future prospects	399
Biomarkers of Parkinson's disease	400
Autoantibodies as biomarkers of PD	401
Biomarkers of PD based on gene expression in blood	401
Cardiac denervation as a biomarker of PD	401
Caffeine levels in blood	402
Genetic biomarkers of PD	402
Imaging biomarkers of PD	402
Metabolic brain networks as biomarkers	403
Metabonomic biomarker profile for diagnosis and monitoring of PD	403
Protein biomarkers of PD	404
<i>P11 protein as a biomarker of depression in PD</i>	404
Serum vitamin D as a biomarker of PD	405
Biomarkers of prodromal PD	405
Future needs for biomarkers of PD	405
Biomarkers of Huntington's disease	406
Genetic biomarker of HD progression	407
Quantitative MRI measurement of brain atrophy as biomarker of HD	407
Metabolic networks as biomarkers of preclinical Huntington disease	408
Biomarkers of Wilson's disease	408
Biomarkers of amyotrophic lateral sclerosis	408
ALS biomarker detection in blood vs CSF	409
Biomarkers of neuroinflammation in ALS	410
Genetic biomarkers of ALS	410
Epigenetic biomarkers of ALS	410
Imaging biomarkers of ALS	411
Metabolomic biomarkers of ALS	411
Proteomic biomarkers of ALS	411
Ideal biomarker of ALS	412
Future of biomarkers of ALS	412
HIV-1-associated neurocognitive disorders	412
Biomarkers of dementia in HIV-1-infected patients	413
Biomarkers of autoimmune encephalitis	413
Biomarkers of prion diseases	413
14-3-3 protein and tTau/P-Tau ratio	413
Bioluminescence imaging as a surrogate biomarker of prion infectivity	414
miRNAs as biomarkers of prion-induced neurodegeneration	414
MRI biomarker of CJD	414
Prion protein detection by real-time quaking-induced conversion	415
Prions in the urine of patients with variant CJD	415
Biomarkers of multiple sclerosis	415
Antibodies in multiple sclerosis	417
<i>Antibodies to galactocerebroside</i>	417
<i>Antibodies to myelin oligodendrocyte glycoprotein</i>	417
Brain N-acetylaspartylglutamate as biomarker of cognitive function in MS	417
Brain imaging biomarkers of multiple sclerosis	418

MRI biomarkers of multiple sclerosis.....	418
Molecular imaging	418
Biomarkers of response to therapy of multiple sclerosis	419
Biomarkers of response to of interferon β -1a.....	419
DNA motifs in the blood as biomarkers of response to treatment	419
Gene expression	419
Lymphocyte subsets as biomarkers of therapeutic response	420
Neurofilaments	421
Vitamin D as predictor of activity and progression of MS	421
CSF biomarkers in multiple sclerosis.....	421
CSF Cystatin C as a biomarker of multiple sclerosis	421
Detecting autoantibodies in multiple sclerosis	421
Switch-associated protein 70 antibodies in multiple sclerosis	422
Gelsolin as a biomarker of multiple sclerosis.....	422
Matrix metalloproteinases as biomarkers in multiple sclerosis	422
Oligoclonal bands as biomarkers of MS	423
Serum proteomic pattern analysis in multiple sclerosis	423
T cells as biomarkers of multiple sclerosis	423
Concluding remarks and future perspective for biomarkers of multiple sclerosis.....	423
Biomarkers of cerebrovascular disorders.....	424
Biomarkers of stroke	424
Etiological biomarkers of ischemic stroke	426
Brain natriuretic peptide as a biomarker for cardioembolic stroke.....	427
Brain lactate and N-acetylaspartate as biomarkers of stroke.....	427
CCL23 for prediction of stroke patient outcome.....	427
CRP as biomarker of risk of stroke	427
CSF biomarkers in acute stroke	428
Gene expression in blood following ischemic stroke.....	428
Glutathione S-Transferase-n.....	428
Intercellular adhesion molecule 1 as biomarker of ischemic stroke	429
Lp-PLA2 and CRP as biomarkers for stroke	429
Matrix metalloproteinase-9.....	429
miRNAs as biomarkers of stroke	429
Neuroserpin polymorphisms as a biomarker of stroke	429
NMDA receptors as biomarkers of excitotoxicity in stroke.....	430
Nucleosomes as biomarkers of stroke	430
PARK7 and nucleoside diphosphate kinase A as biomarkers of stroke.....	430
Visinin-like protein 1.....	431
Biomarker panels for stroke	431
Future prospects for biomarkers of stroke	431
Biomarkers of cerebral vasospasm	432
Biomarkers of intracerebral hemorrhage	432
Biomarkers of hypoxic brain damage.....	433
Biomarkers of ischemic brain damage.....	433
D-dimer as a biomarker of cerebral venous thrombosis.....	433
Biomarkers of traumatic brain injury	434
Technologies for identification of biomarkers of TBI.....	434
Cerebral microdialysis for study of biomarkers of TBI	434
Proteomic technologies for biomarkers of TBI.....	435
Systems biology approach for discovery of biomarkers of TBI.....	436
Biomarkers of TBI	436
A β as a biomarker of TBI	436
CCL11 as a biomarker of chronic traumatic encephalopathy	437
Diffusion tensor imaging in TBI.....	437
Glial fibrillary acidic protein as biomarker of TBI	437
Hyperphosphorylated axonal neurofilament protein	437
IL-6 and nerve growth factor as biomarkers of TBI.....	438
Myelin basic protein	438
Neural exosome cargo	438
Neurofilament heavy chain.....	438
Serum S100 β as biomarker of TBI.....	439
SNTF as a biomarker for predicting cognitive decline after mild TBI.....	439
Tau as biomarker of TBI	440
Ubiquitin C-terminal Hydrolase-L1.....	440
Biomarkers of inflicted TBI in infants	441
Biomarkers of concussion.....	441
Clinical applications of biomarkers of TBI	441
Biomarkers of CNS infections.....	442
Biomarkers of bacterial meningitis	442
Biomarkers of viral infections of CNS.....	442
Biomarkers of CNS HIV infection	442

<i>CSF kynurenic acid level as a biomarker of tick-borne encephalitis</i>	443
<i>Serum uric acid levels as biomarker of acute CNS viral infections</i>	443
Biomarkers of epilepsy	443
Biochemical markers of epilepsy	444
Biomarkers of temporal lobe epilepsy	445
Biomarkers of drug-resistant epilepsy	445
Genetic epilepsies	445
Electrophysiological biomarkers of epilepsy	445
Imaging biomarkers of epilepsy	445
Protein biomarkers of inflammation in epilepsy	446
Biomarkers of normal pressure hydrocephalus	446
Biomarkers of pseudotumor cerebri	447
Biomarkers of retinal disorders	447
Biomarkers of age-related macular degeneration	447
Biomarkers of sleep disorders	448
Biomarker of excessive daytime sleepiness	448
Biomarkers of obstructive sleep apnea	448
Biomarkers of restless legs syndrome	449
Biomarkers of pain	450
Biomarkers of disorders with musculoskeletal pain	450
Biomarkers of neuropathic pain	450
Brain insular glutamate as biomarker of fibromyalgia	450
Biomarkers of visceral pain	451
Biomarkers of migraine	451
Biomarkers of myalgic encephalomyelitis/chronic fatigue syndrome	452
Biomarkers of psychiatric disorders	453
Anorexia nervosa	453
Attention-deficit hyperactivity disorder	453
Biomarkers of autism	453
<i>Epigenetics of ASD</i>	454
<i>Gastrointestinal microbiota disturbances and ASD</i>	454
<i>Genetic factors in ASD</i>	454
<i>Immune biomarkers of ASD</i>	455
<i>Metabolic disturbances in autism</i>	455
<i>Neurophysiological biomarkers</i>	456
<i>Role of oxidative stress in autism</i>	456
<i>Test for ASD based on a 55-gene expression panel</i>	456
<i>Umbilical cord biomarkers</i>	456
Biomarkers of bipolar disorder	456
Biomarkers of depression	457
<i>Biochemical biomarkers of depression</i>	458
<i>Biomarkers and response to antidepressant treatment</i>	458
<i>Cingulate cortex activity and response to antidepressants</i>	459
<i>Genetic biomarkers of response to antidepressants</i>	459
<i>Inflammatory biomarkers of depression and psychosis</i>	459
<i>P11 as a biomarker of depression</i>	459
<i>Panels of blood-based biomarkers for diagnosis of MDD</i>	460
<i>Plasma metabolomics for diagnosis of MDD</i>	460
<i>Post-partum depression</i>	460
Biomarkers of posttraumatic stress disorder	461
Biomarkers of psychosis	462
Biomarkers of schizophrenia	462
<i>Biomarkers of abnormalities of visual information processing</i>	463
<i>Genetic biomarkers of schizophrenia</i>	463
<i>Gene expression analysis of blood for biomarkers of schizophrenia</i>	463
<i>Metabolic biomarkers of schizophrenia</i>	464
<i>Proteomic studies for biomarkers of schizophrenia</i>	464
Biomarkers of suicide	464
15. Biomarkers of Cardiovascular Disorders	467
Epidemiology of cardiovascular disease	467
Biomarkers of cardiovascular diseases	467
Biomarkers of acute myocardial infarction	469
Genetic biomarkers of cardiovascular disorders	469
Methods for identification of cardiovascular biomarkers	471
Application of proteomics for biomarkers of cardiovascular disease	471
<i>Targeted MS-based pipeline approach</i>	471
<i>Cardiovascular disease biomarker panel</i>	472
Detection of biomarkers of myocardial infarction in saliva by a nanobiochip	472
Metabolomic technologies for biomarkers of myocardial ischemia	472
Imaging biomarkers of cardiovascular disease	472

Annexin A5 as an imaging biomarker of cardiovascular disease.....	473
Cardiovascular MRI	473
Cardiovascular hybrid imaging.....	473
Myocardial perfusion imaging	473
Implantable magnetic biosensors for detecting cardiac biomarkers.....	474
Applications of biomarkers of cardiovascular disease.....	474
Biomarkers for ischemic heart disease and myocardial infarction	474
Troponin	475
Natriuretic peptide	476
Copeptin	477
Creatine kinase muscle brain.....	478
miRNAs as biomarkers of acute coronary syndrome	478
Myoglobin	478
Fatty acid binding protein.....	478
Growth Differentiation Factor-15.....	479
High density lipoprotein 2	479
Cripto-1 as a biomarker of myocardial infarction	479
Cataract as a biomarker of ischemic heart disease	479
Plasma CD93 as a biomarker for coronary artery disease	480
Plasma fetuin-A levels and the risk of myocardial infarction.....	480
YKL-40 as an inflammatory biomarker in ischemic heart disease.....	480
Biomarkers of cardiomyopathy	480
miRNA biomarkers of peripartum cardiomyopathy.....	480
Takotsubo cardiomyopathy	481
Troponin T levels in hypertrophic cardiomyopathy	481
Biomarkers of heart failure.....	481
Annexin A5 for prognosis of heart failure	481
Angiogenesis biomarkers	482
β -2a protein as a biomarker of heart failure	482
Desmin.....	482
Galectin-3 as biomarker of acute heart failure	482
G protein-coupled receptor kinase-2 as biomarker of CHF	483
KIF6 gene as biomarker of heart failure.....	483
Metabolic biomarkers of heart failure.....	484
miRNA biomarkers of heart failure.....	484
Natriuretic peptide as biomarker of heart failure	484
Oxidative stress as biomarker of heart failure.....	485
Soluble source of tumorigenicity 2	485
Future prospects for biomarkers of heart failure.....	485
Biomarkers for atherosclerosis.....	486
9p21-3 locus and coronary atherosclerosis.....	486
Adipocyte enhancer-binding protein 1.....	486
Gene signatures on leucocytes as biomarkers of atherosclerosis	486
Ghrelin as a biomarker of atherosclerosis.....	487
Imaging biomarkers of hypercholesterolemia/atherosclerosis	487
Inflammatory biomarkers of atherosclerosis	487
Lipid-modified proteins as biomarkers of atherosclerosis.....	488
Lp-PLA2 as biomarker of atherosclerotic heart disease.....	488
Metabolomic profile in hypercholesterolemia.....	488
Nitric oxide impairment and atherosclerosis	488
Oxygen free radicals as biomarkers of atherosclerosis	488
Proteomic profiles of serum inflammatory biomarkers of atherosclerosis	489
Biomarkers of coronary heart disease.....	489
Apolipoproteins as risk factors for coronary heart disease	489
CRP as biomarker of risk for coronary heart disease	490
High level of blood ceramides as a biomarker of CHD	490
Impairment of EPCs by oxidative stress as a biomarker of disease	490
Role of TNF in acute coronary syndromes.....	491
Serum parathyroid hormone as biomarker of CHD.....	491
Serum stem cell factor as a biomarker of CHD.....	491
VILCAD biomarker score for prediction of long-term mortality in CHD.....	492
Biomarkers for pulmonary arterial hypertension.....	492
Biomarkers of abdominal aortic aneurysm.....	493
Biomarkers of thrombotic disorders	494
Biomarkers of arterial thromboembolism.....	494
Nanoparticles as synthetic biomarkers of thrombus formation	494
Biomarkers of venous thromboembolism.....	494
BNP and cTnT as biomarkers of outcome in pulmonary embolism.....	495
D-dimer as biomarker of venous thromboembolism.....	495
Molecular biomarkers of venous thromboembolism.....	495
Genetic biomarkers for cardiovascular disease.....	495

<i>Biomarkers of inherited cardiomyopathies</i>	495
<i>Gene mutations in pulmonary arterial hypertension</i>	496
<i>Gene variant as a risk factor for sudden cardiac death</i>	496
<i>Genetic biomarkers of early onset myocardial infarction</i>	497
<i>Genetic biomarkers of atherosclerosis</i>	497
<i>IL-1 gene polymorphism as biomarker of cardiovascular disease</i>	497
<i>IL-6R signaling pathway and coronary heart disease</i>	497
<i>Kallikrein gene mutations in cardiovascular disease</i>	498
<i>Kallikrein gene and essential hypertension</i>	498
<i>Mutations in the low density lipoprotein receptor gene</i>	498
<i>Mutations within several genes that code for ion channel</i>	499
<i>Polymorphisms of the eNOS gene and angina pectoris</i>	499
<i>Lipoprotein (a) genetics</i>	499
<i>Polymorphisms in the apolipoprotein C gene</i>	499
<i>Polymorphisms in the apolipoprotein E gene</i>	500
<i>Polymorphism in the angiotensinogen gene</i>	500
Multiple biomarkers for prediction of death from cardiovascular disease	501
Role of biomarkers in the management of cardiovascular disease	501
Biomarkers in the diagnosis/prognosis of myocardial infarction	501
Biomarkers for prevention of cardiovascular disease	501
C reactive protein as biomarker of response to statin therapy	503
C125 as biomarker for stratification in heart disease	504
HSP72 and eNOS as biomarkers of cardioprotective effect of HBO	504
Multimarker panel for prognosis in chronic heart failure	504
Molecular signature analysis in management of cardiovascular diseases	504
Presage ST2 Assay	505
Role of circulating biomarkers and mediators of cardiovascular dysfunction	505
Use of protein biomarkers for monitoring acute coronary syndromes	505
Use of biomarkers for prognosis of recurrent atrial fibrillation	506
Use of multiple biomarkers for monitoring of cardiovascular disease	506
Use of biomarkers in the management of peripheral arterial disease	507
Use of biomarkers in the management of hypertension	507
Systems approach to cardiovascular biomarker research	507
16. Biomarkers of Pulmonary Diseases	509
Introduction	509
Association of biomarkers of inflammation with lung function in the elderly	509
Biomarkers of oxidative stress in lung diseases	510
Biomarkers of community-acquired pneumonia	510
Biomarkers of acute lung injury and respiratory distress syndrome	510
<i>Cytokine/chemokine biomarkers of SARS</i>	510
<i>Plasma biomarkers related to inflammation</i>	511
<i>Urinary NO as biomarker</i>	511
Biomarkers of interstitial lung disease	511
<i>Pulmonary surfactant proteins as biomarkers for lung diseases</i>	511
<i>Serum KL-6 as biomarker of interstitial lung disease</i>	512
Biomarkers of chronic obstructive pulmonary disease	512
<i>Alpha1-antitrypsin gene polymorphisms predisposing to emphysema</i>	512
<i>Biomarkers of extracellular matrix turnover in COPD</i>	513
<i>Biomarkers of lung failure in COPD</i>	513
<i>BNP as a biomarker of chronic pulmonary disease</i>	513
<i>Chromagranin A (CgA) as biomarker of airway obstruction in smokers</i>	513
<i>C-reactive protein as a biomarker of COPD</i>	514
<i>Gene expression profile in peripheral blood of patients with COPD</i>	514
<i>Hyperuricemia as a biomarker of early mortality in COPD</i>	514
<i>Increased expression of PIGF as a biomarker of COPD</i>	514
Biomarkers of asthma	515
<i>Biomarker for rhinovirus-induced asthma exacerbation</i>	515
<i>Biomarkers for predicting response to corticosteroid therapy</i>	515
<i>Comparison of biomarkers of asthma and COPD</i>	515
<i>Cytokines as biomarkers of asthma severity</i>	516
<i>Exhaled NO as a biomarker of asthma</i>	516
<i>Endothelin-1 in exhaled breath as biomarker of asthma</i>	517
<i>IgE as guide to dosing of omalizumab for asthma</i>	517
<i>Periostin as a biomarker for treatment of asthma with lebrikizumab</i>	517
Biomarkers of cystic fibrosis	518
17. Biomarkers in Gynecology and Obstetrics	519
Introduction	519
Biomarkers of menopause	519
Biomarkers of premenstrual dysphoric disorder	519

Biomarkers of endometriosis	520
Biomarkers for preeclampsia	520
Pathogenesis of preeclampsia	520
Metabolomic biomarkers in urine in preeclampsia.....	521
Protein biomarker of preeclampsia in urine.....	521
Protein biomarkers of preeclampsia in CSF.....	522
Protein HtrA1 as a biomarker for preeclampsia	522
Placental growth factor as a biomarker for preeclampsia	523
sFlt1 and soluble endoglin as biomarkers of preeclampsia	523
RNA biomarkers.....	523
Genes associated with preeclampsia.....	524
Biomarkers of premature birth	524
Proteomic biomarkers of premature birth	524
Biomarkers of oxidative stress in complicated pregnancies	525
Fetal biomarkers in maternal blood	525
Metabolic biomarkers of prenatal disorders in the mother.....	526
18. Biomarkers & Personalized Medicine	527
Introduction	527
Pharmacogenetics	527
Biomarkers and pharmacogenetics.....	528
Pharmacogenomics.....	529
Pharmacoproteomics	530
Single cell proteomics for personalized medicine	530
Role of biomarkers in development of personalized drugs.....	531
Metabolomic biomarker-based drug discovery	531
Use of biomarkers for developing MAb therapy in oncology	531
Biomarker tests for molecularly targeted therapies.....	532
Biobanking, biomarkers and personalized medicine in EU	533
Bioinformatics to sort biomarker data for personalized medicine	534
Biomarkers for monitoring response to therapy	535
Drug rescue by biomarker-based personalized medicine	535
Future role of biomarkers in personalized medicine	536
19. Biomarkers and Regulatory issues.....	537
Introduction	537
Biomarker validation	537
FDA criteria for a valid biomarker.....	537
FDA letter of support for biomarkers	539
Role of NIST in validation of cancer biomarkers	540
Quality specifications for BNP and NT-proBNP as cardiac biomarker assays	540
National Biomarker Development Alliance	540
FDA perspective of biomarkers in clinical trials	541
FDA and predictive medicine.....	542
Biomarkers and FDA's Voluntary Genomic Data Submission	543
Role of imaging biomarkers in approval of drugs.....	543
Regulatory oversight of biomarker tests for targeted therapies	544
FDA and biomarkers	544
FDA consortium linking genetic biomarkers to serious adverse events	544
Oncology Biomarker Qualification Initiative	544
Critical Path Initiative	545
Predictive Safety Testing Consortium.....	546
The 21st Century Cures Act and biomarkers	547
From validated biomarker assay to a clinical laboratory diagnostic	548
Fast Path programs.....	548
Regulatory challenges in the biomarker field	549
FDA requirements of biomarkers and companion diagnostics	550
20. References.....	551

Tables

Table 1-1: Historical landmarks in discovery and development of biomarkers	30
Table 1-2: Classification of biomarkers	30
Table 1-3: Terminology of clinically relevant biomarkers of disease	32
Table 1-4: Autoimmune disorders under study for autoantibodies as predictors	42
Table 1-5: Comparison of various types of biomarkers	43
Table 1-6: Various "omics" technologies for discovery of biomarkers	44
Table 1-7: Role of biomarkers in translational medicine	45

Table 2-1: Classification of methods of gene expression analysis	49
Table 2-2: Comparison of proteomic profiling technologies for discovery of biomarkers	76
Table 2-3: Companies involved in developing molecular imaging	87
Table 3-1: Applications of biochip/microarray technology in relation to biomarkers	110
Table 4-1: Companies using metabolomics for drug discovery	124
Table 4-2: Biomarker-based drug development at major pharmaceutical companies	125
Table 4-3: Causes of failures in clinical trials and their reduction by use of biomarkers	128
Table 5-1: Metabolic biomarkers of inflammatory diseases.....	142
Table 5-2: Oxidized phospholipids as biomarkers of various diseases	143
Table 5-3: Examples of biomarkers common to multiple diseases	157
Table 5-4: Examples of use of biomarkers in animal health	159
Table 6-1: Biomarkers of diabetes mellitus	163
Table 7-1: Biomarkers of Sjögren syndrome	179
Table 8-1: miRNAs deregulated in rheumatoid arthritic tissues	185
Table 8-2: Classification of inflammatory biomarkers in osteoarthritis.....	188
Table 9-1: Biomarkers of sepsis.....	197
Table 11-1: Biomarkers of aging.....	214
Table 12-1: Nutritional biomarkers.....	225
Table 13-1: Desirable characteristics of biomarkers for cancer	232
Table 13-2: Types of cancer biomarkers	234
Table 13-3: A classification of molecular diagnostic methods in cancer	241
Table 13-4: Cancer biomarkers used for diagnosis and therapy	271
Table 13-5: Novel biomarkers of prognosis in cancer treatment.....	276
Table 13-6: Biomarkers of brain tumors	284
Table 13-7: Biomarkers of breast cancer	292
Table 13-8: miRNA associated with breast cancer	301
Table 13-9: Biomarkers of colorectal cancer.....	311
Table 13-10: Biomarkers of lung cancer	325
Table 13-11: Classification of biomarkers of melanoma	334
Table 13-12: Biomarkers of nasopharyngeal carcinoma and potential applications	336
Table 13-13: Biomarkers of ovarian cancer	338
Table 13-14: Classification of biomarkers of pancreatic cancer	343
Table 13-15: Biomarkers of prostate cancer.....	348
Table 14-1: Biomarkers of cerebral metabolism	367
Table 14-2: Classification of biomarkers of Alzheimer disease in blood and CSF	380
Table 14-3: Characteristics of an ideal biomarker for Alzheimer disease	382
Table 14-4: miRNA expression in neurodegenerative diseases	383
Table 14-5: Biomarkers of Parkinson disease	400
Table 14-6: Biomarkers of Huntington disease	406
Table 14-7: Classification of biomarkers of amyotrophic lateral sclerosis.....	409
Table 14-8: Biomarkers of multiple sclerosis	416
Table 14-9: Gene expression as biomarker of response to interferon- β in multiple sclerosis	420
Table 14-10: Biomarkers of stroke.....	425
Table 14-11: Etiological blood biomarkers of ischemic strokes due to large artery atherosclerosis.....	426
Table 14-12: Biomarkers of traumatic brain injury	436
Table 14-13: Biomarkers of epilepsy	444
Table 14-14: Biomarkers of autism spectrum disorder.....	454
Table 14-15: Biomarkers of response to antidepressant treatment.....	458
Table 14-16: Biomarkers of posttraumatic stress disorder.....	461
Table 15-1: Classification of biomarkers for cardiovascular diseases.....	468
Table 15-2: Genes that cause cardiovascular diseases.....	470
Table 15-3: Biomarkers of abdominal aortic aneurysm	493
Table 15-4: Biomarkers for cardiovascular disease risk prediction	502
Table 16-1: Biomarkers of pulmonary diseases.....	509
Table 18-1: Pharmacogenetic vs. pharmacogenomic studies	528
Table 18-2: Applications of pharmacoproteomic biomarkers in personalized medicine.....	530
Table 19-1: Issued letters of support for biomarkers by the FDA.....	539
Table 19-2: Drugs requiring biomarker/companion diagnostic information in the label.....	550

Figures

Figure 1-1: Relation of biomarkers to other technologies and healthcare	45
Figure 1-2: Role of biomarkers in monitoring of diseases	46
Figure 2-1: The central role of spectrometry in proteomics	59
Figure 2-2: Selected reaction monitoring workflow for verification of biomarkers	73
Figure 4-1: Role of biomarkers in drug discovery and development process	114
Figure 4-2: Onion-peel model of biomarker development.....	129
Figure 5-1: Diseases associated with myositis autoantibodies.....	158
Figure 6-1: Plasma lipids in metabolic syndrome.....	169
Figure 8-1: β -CrossLaps bone resorption biomarker assay	191

Figure 13-1: Role of proteomics in the discovery of cancer biomarkers	248
Figure 13-2: Nanovesicles for detection of cancer biomarkers	263
Figure 13-3: Nanowire biosensor for cancer diagnosis	264
Figure 13-4: Cancer biomarker development and validation	363
Figure 14-1: Discovery and application of biomarkers in neurological diseases	365
Figure 14-2: MRI in Creutzfeld-Jakob disease	415
Figure 14-3: A scheme of pathogenesis of MDD with relevant biomarkers	457
Figure 15-1: Biomarkers of acute myocardial infarction related to pathophysiology	469
Figure 18-1: Role of pharmacogenetic biomarkers in personalized medicine	529
Figure 18-2: Workflow for developing metabolomics-based biomarkers for personalized treatment	531
Figure 18-3: Impact of biomarkers on personalized medicine	536
Figure 19-1: Stages and timelines of biomarker discovery, development and marketing	537
Figure 19-2: Biomarker qualification pilot process at the FDA	539
Figure 19-3: From a validated biomarker assay to a clinical laboratory diagnostic	548