

Personalized Medicine

Part I: Scientific & Commercial Aspects

by

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

April 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 476 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. He has also written "The Textbook of Gene Therapy", which is the first book on this subject to be translated into the Chinese language in 2000. A book on gene therapy companies was published in 2000 by John Wiley & Sons and the updated version of it is incorporated in the 2013 edition of Gene Therapy published by Jain PharmaBiotech. The most recent books include "Handbook of Nanomedicine" (Humana/Springer 2008; Chinese edition, Peking University Press 2011, 2nd ed Springer 2012, 3rd ed April 2017), "Textbook of Personalized Medicine" (Springer 2009, Japanese ed 2012; 2nd ed Springer 2015), "Handbook of Biomarkers" (Springer 2010; Chinese edition, Chemical Industry Press 2016, 2nd ed Springer 2017), "Handbook of Neuroprotection" (Springer 2011, 2nd ed 2018, in preparation), "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 edited "Applied Neurogenomics" (Springer 2015).

Prof. Jain has been interested in using biotechnology to develop personalized medicine since 1997. He has also lectured and conducted several workshops on personalized medicine worldwide.

A B O U T T H I S R E P O R T

Prof. Jain wrote the first report on Personalized Medicine in 1998, which was published by Decision Resources Inc, USA. The second edition was published in 2001 by Informa Publications, London. Since 2003, the report is published and continuously updated and rewritten at Jain PharmaBiotech.

**April 2018 (first edition published in 1998 by Decision Resources Inc)
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	25
1. Basic Aspects.....	27
Definition of personalized medicine.....	27
History of medical concepts relevant to personalized medicine	28
Ayurveda as a personalized healthcare system	30
Personalized aspects of ancient oriental systems of medicine	30
Evolution of modern personalized medicine	30
Molecular biological basis of personalized medicine	31
The human genome	31
<i>ENCODE</i>	31
Chromosomes	32
Genes.....	32
<i>The genetic code</i>	33
<i>Gene expression</i>	33
<i>DNA sequences and structure</i>	33
Genetic variations in the human genome	34
<i>Single nucleotide polymorphisms</i>	34
<i>Copy number variations in the human genome</i>	35
<i>Insertions and deletions in the human genome</i>	36
<i>Large scale variation in human genome</i>	37
<i>Structural variations in the human genome</i>	38
<i>Mapping and sequencing of structural variation from human genomes</i>	38
<i>1000 Genomes Project</i>	39
<i>Role of DNA sequencing in the development of personalized medicine</i>	40
<i>Human Variome Project</i>	41
<i>Interconnected genetic and genomic patterns in human diseases</i>	41
Mitochondrial tRNA and personalized medicine.....	42
Molecular alterations in disease	42
Basics technologies for developing personalized medicine	43
Definitions of technologies relevant to personalized medicine	43
Problems with the ICH definitions of pharmacogenomics and pharmacogenetics	43
'Omics' and personalized medicine	44
Relationship of various technologies to personalized medicine	44
Conventional medicine versus personalized medicine	44
Personalized medicine and evidence-based medicine	45
Role of genetics in future approaches to healthcare	45
Genetic medicine	45
Human disease and genes.....	46
Genetic and environmental interactions in etiology of human diseases.....	46
Role of genetics in development of personalized medicines	47
<i>Genetic databases</i>	47
<i>Clinical Genomic Database</i>	47
<i>Genetic epidemiology</i>	48
<i>Limitations of medical genetics</i>	48
<i>Genetics vs. epigenetics</i>	49
Role of systems biology in personalized medicine	49
Systems pharmacology.....	50
Systems medicine.....	51
Synthetic biology and development of personalized medicines.....	52
Role of bioelectronics in development of personalized medicine	53
A personalized approach to environmental factors in disease.....	53
Reclassification of diseases	53
Translational science and personalized medicine.....	54
Personalization of multimodal therapies.....	55
2. Molecular Diagnostics in Personalized Medicine	57
Introduction	57
Molecular diagnostic technologies	57
PCR-based methods	58
<i>DirectLinear™ Analysis</i>	58
<i>Denaturing high-performance liquid chromatography</i>	59
<i>Multiplex Allele-Specific Diagnostic Assay</i>	59
<i>Representational oligonucleotide microarray analysis</i>	59
<i>Restriction fragment length polymorphism (RFLP)</i>	59
<i>Real-time PCR for detection of CNVs</i>	60
Non-PCR methods.....	60
<i>Arrayed primer extension (APEX)</i>	60

<i>Enzymatic Mutation Detection (EMD)</i>	60
DNA sequencing	60
<i>Sanger-sequencing technology</i>	61
<i>ABI PRISM® 310 Genetic Analyzer</i>	62
<i>High-throughput paired end transcriptome sequencing</i>	62
Emerging sequencing technologies.....	62
<i>4300 DNA analyzer</i>	63
<i>Apollo 100</i>	63
<i>"Color blind" approach to DNA sequencing</i>	64
<i>Cyclic array sequencing</i>	64
<i>CEQ™ 8000</i>	64
<i>DeepCAGE sequencing</i>	64
<i>Electron microscope-based DNA sequencing</i>	65
<i>Genometrica™ sequencer</i>	65
<i>GS-FLEX system (Roche/454)</i>	66
<i>IBS sequencing technology</i>	67
<i>Illumina's sequencing technology</i>	67
<i>MegaBACE 500</i>	68
<i>Microdroplet-based PCR for large-scale targeted sequencing</i>	68
<i>Multiplex amplification of human DNA sequences</i>	69
<i>Nanoscale sequencing</i>	69
<i>Polonator sequencer</i>	69
<i>RainStorm™ microdroplet technology</i>	70
<i>Sequential DEXAS</i>	70
<i>SOLiD technology</i>	71
<i>Sequencing by hybridization</i>	72
<i>Whole genome sequencing</i>	72
<i>Bioinformatic tools for analysis of genomic sequencing data</i>	73
<i>Clinical Genomicist Workspace for managing NGS-based clinical tests</i>	73
<i>Detection of single molecules in real time</i>	73
<i>Direct observation of nucleotide incorporation</i>	73
<i>Molecular Combing</i>	74
<i>Nanopore sequencing</i>	74
<i>DNA sequence by use of nanoparticles</i>	74
<i>Zero-mode waveguide nanostructure arrays</i>	74
<i>Future prospects of sequencing</i>	75
<i>Role of DNA sequencing in development of personalized medicine</i>	75
<i>Role of RNA sequencing in development of personalized medicine</i>	77
Biochips and microarrays	77
Role of biochip/microarray technology in personalized medicine.....	78
Applications of biochip/microarray technology in personalized medicine	79
Standardizing the microarrays	80
Biochip technologies.....	80
<i>GeneChip</i>	80
<i>AmpliChip CYP450</i>	81
Microfluidics	82
<i>Lab-on-a-chip</i>	83
<i>Micronics' microfluidic technology</i>	83
<i>LabCD</i>	83
<i>Microfluidic automated DNA analysis using PCR</i>	83
<i>Integrated microfluidic bioassay chip</i>	84
Electronic detection of nucleic acids on microarrays.....	84
Strand displacement amplification on a biochip	85
Rolling circle amplification on DNA microarrays.....	85
Universal DNA microarray combining PCR and ligase detection reaction	85
Protein biochips	85
<i>ProteinChip</i>	86
<i>LabChip for protein analysis</i>	87
<i>TRINECTIN proteome chip</i>	87
<i>Protein expression microarrays</i>	87
<i>Microfluidic devices for proteomics-based diagnostics</i>	88
<i>New developments in protein biochips/microarrays</i>	88
<i>Protein biochips/microarrays for personalized medicine</i>	89
SNP genotyping	89
Genotyping and haplotyping.....	90
<i>Haplotype Specific Extraction</i>	91
<i>Computation of haplotypes</i>	91
<i>HapMap project</i>	91
<i>Haplotyping for whole genome sequencing</i>	92
<i>Predicting drug response with HapMap</i>	94
<i>Companies developing haplotyping technology</i>	94

Technologies for SNP analysis.....	94
Biochip and microarray-based detection of SNPs	95
<i>SNP genotyping by MassARRAY.....</i>	95
<i>BeadArray technology.....</i>	95
<i>SNP-IT primer-extension technology</i>	96
<i>Use of NanoChip for detection of SNPs.....</i>	96
Electrochemical DNA probes	96
Laboratory Multiple Analyte Profile	96
PCR-CTPP (confronting two-pair primers).....	97
TaqMan real-time PCR	97
Locked nucleic acid	98
Molecular inversion probe based assays.....	98
Pyrosequencing	98
Smart amplification process version 2	99
Zinc finger proteins	99
Mitochondrial SNPs.....	99
Limitations of SNP in genetic testing.....	100
Concluding remarks on SNP genotyping.....	100
Companies involved in developing technologies/products for SNP analysis	100
Impact of SNPs on personalized medicine	102
Detection of copy number variations	102
CNV algorithm for CNV detection.....	102
CNVnator for discovery of CNVs and genotyping	103
Study of rare variants in pinpointing disease-causing genes	103
Optical Mapping.....	104
Proteomics in molecular diagnosis.....	104
Proteomic strategies for biomarker identification.....	105
<i>Proteomic technologies for detection of biomarkers in body fluids</i>	<i>105</i>
Protein patterns.....	105
Layered Gene Scanning	106
Comparison of proteomic and genomic approaches in personalized medicine.....	106
Role of nanobiotechnology in molecular diagnostics.....	107
Cantilevers for personalized medical diagnostics	107
Role of biomarkers in personalized medicine.....	108
Role of biosensors in personalized medicine.....	110
Biomarkers for diagnostics	111
Biomarkers for drug development	111
Gene expression profiling	111
DNA microarrays.....	112
Analysis of single-cell gene expression.....	112
Gene expression profiling based on alternative RNA splicing	113
Whole genome expression array	114
Tangerine™ expression profiling	114
Gene expression analysis on biopsy samples	115
Profiling gene expression patterns of white blood cells.....	115
Serial analysis of gene expression (SAGE).....	115
Multiplexed Molecular Profiling	116
Gene expression analysis using competitive PCR and MALDI TOF MS	116
Companies involved in gene expression analysis.....	117
Monitoring in vivo gene expression by molecular imaging	118
Molecular imaging and personalized medicine.....	118
Combination of diagnostics and therapeutics	118
Use of molecular diagnostics for stratification in clinical trials	119
Companion diagnostics	119
Companies involved in companion diagnostics	120
Point-of-care diagnosis.....	122
Companies developing point-of-care diagnostic technologies	123
Point-of-care diagnosis of infections	125
Advantages versus disadvantages of point-of-care diagnosis	125
Future prospects of point-of-care diagnosis	126
Genetic testing for disease predisposition	126
Preventive genetics by early diagnosis of mitochondrial diseases	127
Direct-to-consumer genetic services.....	127
Role of diagnostics in integrated healthcare	128
Concept of integrated healthcare	128
Components of integrated healthcare	129
<i>Screening</i>	<i>129</i>
<i>Disease prediction.....</i>	<i>129</i>
<i>Early diagnosis</i>	<i>129</i>
<i>Prevention</i>	<i>130</i>
<i>Therapy based on molecular diagnosis.....</i>	<i>130</i>

Monitoring of therapy	130
Advantages and limitations of integrated healthcare.....	130
Commercially available systems for integrated healthcare.....	131
Future of molecular diagnostics in personalized medicine	131

3. Pharmacogenetics 133

Basics of pharmacogenetics..... 133

Role of molecular diagnostics in pharmacogenetics..... 134

Role of pharmacogenetics in pharmaceutical industry..... 135

 Study of the drug metabolism and pharmacological effects

 Causes of variations in drug metabolism

 Enzymes relevant to drug metabolism

 Pharmacogenetics of phase I metabolism.....

 CYP450.....

 P450 CYP 2D6 inhibition by selective serotonin reuptake inhibitors.....

 Cytochrome P450 polymorphisms and response to clopidogrel.....

 Lansoprazole and cytochrome P450.....

 Glucose-6-phosphate dehydrogenase

 Pharmacogenetics of phase II metabolism.....

 N-Acetyltransferase.....

 Uridine diphosphate-glucuronosyltransferase.....

 Measurement of CYP isoforms

 Polymorphism of drug transporters

 Genetic variation in drug targets.....

 Polymorphisms of kinase genes

 Effect of genetic polymorphisms on disease response to drugs

 Ethnic differences in drug metabolism

 Gender differences in pharmacogenetics

 Role of pharmacogenetics in drug safety

 Adverse drug reactions

 Adverse drug reactions in children

 Adverse drug reactions related to toxicity of chemotherapy.....

 Genetically determined adverse drug reactions.....

 Malignant hyperthermia

 Pharmacogenetics of clozapine-induced agranulocytosis.....

 Role of pharmacogenetics in warfarin therapy.....

 Role of pharmacogenetics in antiplatelet therapy

 Role of pharmacogenetics in carbamazepine therapy

 Role of pharmacogenetics in statin therapy

 FDA consortium linking genetic biomarkers to serious adverse events

 Therapeutic drug monitoring, phenotyping, and genotyping

 Therapeutic drug monitoring

 Phenotyping

 Genotyping

 Genotyping vs phenotyping.....

 Phenomics

 Limitations of genotype-phenotype association studies

 Molecular toxicology in relation to personalized medicines.....

 Toxicogenomics

 Biomarkers of drug toxicity

 Drug-induced mitochondrial toxicity

 Companies involved in molecular toxicology.....

 Gene expression studies

 Pharmacogenetics in clinical trials

 Postmarketing pharmacogenetics.....

Clinical implications of pharmacogenetics 160

 Application of CYP450 genotyping in clinical practice

 Genotype-based drug dose adjustment.....

 Pharmacogenomic biomarker information in drug labels.....

 Standardized terminology for clinical pharmacogenetic test results.....

 Use of pharmacogenetics in clinical pharmacology.....

 Application of CYP2C19 pharmacogenetics for personalized medicine.....

 Genotyping for identifying responders to sulfasalazine.....

 HLA alleles associated with lumiracoxib-related liver injury

 Pharmacogenetic basis of thiopurine toxicity

 Tranilast-induced hyperbilirubinemia due to gene polymorphism.....

 Linking pharmacogenetics with pharmacovigilance

 Genetic susceptibility to ADRs.....

 Linking genetic testing to postmarketing ADR surveillance

 Recommendations for the clinical use of pharmacogenetics

Limitations of pharmacogenetics 167

Pharmacoeugenomics vs pharmacogenetics in drug safety	168
Future role of pharmacogenetics in personalized medicine	168
4. Pharmacogenomics.....	169
Introduction	169
Basics of pharmacogenomics	170
Pharmacogenomics and drug discovery	170
<i>Preclinical prediction of drug efficacy</i>	<i>172</i>
Pharmacogenomics and clinical trials	172
Impact of genetic profiling on clinical studies.....	173
Limitations of the pharmacogenomic-based clinical trials.....	174
Pharmacogenomic aspects of major therapeutic areas	175
Oncogenomics	175
<i>Oncogenes</i>	<i>175</i>
<i>Tumor suppressor genes.....</i>	<i>176</i>
Cardiogenomics	177
Neuropharmacogenomics.....	179
<i>Pharmacogenomics of Alzheimer's disease</i>	<i>179</i>
<i>Pharmacogenomics of depression.....</i>	<i>180</i>
<i>Pharmacogenomics of bipolar disorder.....</i>	<i>180</i>
<i>Pharmacogenomics of schizophrenia.....</i>	<i>181</i>
<i>Companies involved in neurogenomics-based drug discovery.....</i>	<i>182</i>
Current status and future prospects of pharmacogenomics	182
5. Role of Pharmacoproteomics	183
Basics of proteomics.....	183
Proteomic approaches to the study of pathophysiology of diseases	183
Single cell proteomics for personalized medicine	184
Diseases due to misfolding of proteins	184
<i>Therapies for protein misfolding.....</i>	<i>185</i>
Significance of mitochondrial proteome in human disease	185
Proteomic technologies for drug discovery and development	186
Proteins and drug action	186
Role of reverse-phase protein microarray in drug discovery.....	186
Role of proteomics in clinical drug safety.....	186
Toxicoproteomics	187
Applications of pharmacoproteomics in personalized medicine	188
6. Role of Metabolomics in Personalized Medicine	189
Metabolomics and metabonomics	189
Metabolomics bridges the gap between genotype and phenotype	189
Metabolomics, biomarkers and personalized medicine	190
Metabolomic technologies	190
Urinary profiling by capillary electrophoresis.....	191
Lipid profiling	191
Role of metabolomics in biomarker identification and pattern recognition.....	192
Validation of biomarkers in large-scale human metabolomics studies.....	192
Pharmacometabonomics.....	193
Metabonomic technologies for toxicology studies.....	193
Metabonomics/metabolomics and personalized nutrition.....	194
7. Personalized Biological Therapies.....	195
Introduction	195
Recombinant human proteins	195
Therapeutic monoclonal antibodies	195
Cell therapy	196
Autologous tissue and cell transplants	196
Stem cells.....	196
<i>iPSCs for personalized cell therapy</i>	<i>196</i>
<i>Role of stem cells derived from unfertilized embryos</i>	<i>197</i>
Cloning and personalized cell therapy.....	197
Use of stem cells for drug testing	197
Gene therapy	197
Gene editing by CRISPR/Cas9 system.....	198
Personalized gene therapy for cancer	198
<i>Stem cell-based personalized gene therapy for cancer.....</i>	<i>199</i>
Personalized vaccines.....	199
Personalized vaccines for viral diseases	199
Personalized cancer vaccines.....	199
Antisense therapy	199

RNA interference.....	200
MicroRNAs	201
8. Personalized Non-pharmacological Therapies.....	203
Introduction	203
Acupuncture	203
Personalized acupuncture therapy.....	203
Personalized hyperbaric oxygen therapy	204
Personalized nutrition.....	204
Nutrigenomics	205
<i>Evolutionary basis of nutrigenomics</i>	<i>206</i>
<i>Genomics of vitamin D and calcium supplementation.....</i>	<i>206</i>
<i>Nutrigenomics and functional foods</i>	<i>207</i>
<i>Nutrigenomics and personalized medicine</i>	<i>207</i>
<i>Nutriproteomics</i>	<i>207</i>
Nutrigenetics and personalized medicine.....	208
Personalized diet prescription	208
<i>Personalized nutrition and aging</i>	<i>209</i>
<i>Personalized diet for diabetics.....</i>	<i>210</i>
Role of systems medicine in personalized nutrition.....	210
Companies involved in personalized nutrition	210
Personalized physical exercise	210
Variations in response to aerobic exercise	211
Variations in exercise-induced muscle hypertrophy and strength.....	211
Personalized surgery	211
9. Personalized Medicine in Major Therapeutic Areas	213
Introduction	213
Personalized management of infections	214
Genetic susceptibility to infections.....	214
Management of HIV	214
<i>CD4 counts as a guide to drug therapy for AIDS</i>	<i>214</i>
<i>Drug-resistance in HIV</i>	<i>214</i>
<i>Genetics of human susceptibility to HIV infection</i>	<i>216</i>
<i>Measurement of Replication Capacity.....</i>	<i>216</i>
<i>Personalized vaccine for HIV.....</i>	<i>217</i>
<i>Prevention of adverse reactions to antiviral drugs</i>	<i>217</i>
<i>Pharmacogenetics and HIV drug safety.....</i>	<i>218</i>
<i>Pharmacogenomics of antiretroviral agents</i>	<i>218</i>
<i>Role of diagnostic testing in management of HIV</i>	<i>218</i>
<i>Role of genetic variations in susceptibility to HIV-1</i>	<i>219</i>
<i>Role of personalized HIV therapy in controlling drug resistance.....</i>	<i>219</i>
<i>PhenoSense® to test HIV drug resistance.....</i>	<i>220</i>
<i>Sequencing for detecting mutations to personalize HIV therapy</i>	<i>220</i>
Personalized treatment of hepatitis B	221
Personalized treatment of hepatitis C	221
<i>Responders vs non-responders to treatment for hepatitis C.....</i>	<i>222</i>
<i>Drug resistance in hepatitis C.....</i>	<i>223</i>
<i>Challenges for personalized management of hepatitis C.....</i>	<i>223</i>
Personalized management of tuberculosis	223
Personalized management of fungal infections.....	224
Psychiatric disorders	224
Psychopharmacogenetics/psychopharmacodynamics	225
<i>Serotonin genes.....</i>	<i>225</i>
<i>Calcium channel gene.....</i>	<i>225</i>
<i>Dopamine receptor genes</i>	<i>226</i>
<i>COMT genotype and response to amphetamine.....</i>	<i>226</i>
<i>Methylenetetrahydrofolate reductase.....</i>	<i>226</i>
<i>Genetic loci associated with risk of major depressive disorder.....</i>	<i>226</i>
<i>Role of gene mutations in ADHD</i>	<i>227</i>
<i>Genotype and response to methylphenidate in children with ADHD</i>	<i>227</i>
<i>GeneSight tests for individualized therapy of psychiatric disorders</i>	<i>227</i>
Personalized antipsychotic therapy.....	228
Personalized antidepressant therapy	230
<i>Biomarkers of response to antidepressant treatment</i>	<i>231</i>
<i>EEG to predict adverse effects and evaluate antidepressant efficacy.....</i>	<i>231</i>
<i>GeneSight pharmacogenomic test</i>	<i>232</i>
<i>Individualization of SSRI treatment</i>	<i>232</i>
<i>Role of protein sFRP3 in predicting response to antidepressants.....</i>	<i>233</i>
<i>Treatment resistant depression.....</i>	<i>234</i>
<i>Vilazodone with a test for personalized treatment of depression.....</i>	<i>234</i>

Neurological disorders	234
Introduction to personalized neurology	234
Personalized management of Alzheimer's disease	235
Personalized management of Parkinson's disease.....	237
<i>Direct-to-consumer genetic testing in PD</i>	237
<i>Discovery of subgroup-selective drug targets in PD</i>	237
<i>Personalized cell therapy for PD</i>	238
<i>Use of wearable sensors to monitor PD response to levodopa therapy</i>	238
Personalized management of amyotrophic lateral sclerosis	239
Personalized management of epilepsy	239
<i>Adverse effects of AEDs</i>	239
<i>An algorithm for personalized management of epilepsy</i>	240
<i>Biomarkers of epilepsy</i>	241
<i>Drug resistance in epilepsy</i>	243
<i>Genetics/genomics of epilepsy</i>	244
<i>Pharmacogenomics of epilepsy</i>	245
<i>Selection of the right AED</i>	246
<i>Future of management of epilepsy</i>	247
Personalized management of migraine.....	247
<i>Individualization of use of triptans for migraine</i>	248
<i>Multitarget therapeutics for personalized treatment of headache</i>	248
<i>Personalized strategy for prevention of migraine attacks</i>	248
Personalized management of intracranial aneurysms	249
<i>Personalized management of cerebral vasospasm following SAH</i>	250
Personalized management of stroke	250
<i>Anticoagulation for stroke prevention</i>	250
<i>Application of proteomics for personalizing stroke management</i>	252
<i>Brain imaging in trials of restorative therapies for stroke</i>	252
<i>Personalized management of intracerebral hemorrhage</i>	252
<i>Revascularization procedures in chronic post-stroke stage</i>	253
<i>Personalized cell therapy for management of stroke</i>	253
<i>Management of stroke according to stage</i>	254
Personalized treatment of multiple sclerosis	254
<i>Autologous bone marrow stem cell therapy for multiple sclerosis</i>	255
<i>Fusokine method of personalized cell therapy of multiple sclerosis</i>	256
<i>Immunopathological patterns of demyelination for assessing therapy</i>	256
<i>Personalizing mitoxantrone therapy of multiple sclerosis</i>	256
<i>Pharmacogenomics of IFN-β therapy in multiple sclerosis</i>	257
<i>Preclinical detection of multiple sclerosis in children</i>	258
<i>Predictive models of individual treatment response in MS</i>	258
<i>T cell-based personalized vaccine for MS</i>	259
<i>Targeting MS therapy to cell type of lesion</i>	259
Personalized management of traumatic brain injury	260
<i>Biomarkers of TBI</i>	260
<i>Comparative effectiveness research for management of TBI</i>	261
<i>CT scores for prognosis and risk stratification of TBI</i>	261
Personalized management of myasthenia gravis	261
Personalized management of pain	262
<i>Genetic factors in response to pain</i>	262
<i>Genetic mutations with loss of pain</i>	263
<i>Genetic mutations and painful conditions</i>	263
<i>Pharmacogenetics/pharmacogenomics of pain</i>	263
<i>Personalized management of pain with opioids</i>	264
<i>Pharmacogenetics of NSAIDs</i>	265
<i>Mechanism-specific management of pain</i>	266
<i>Preoperative testing to tailor postoperative analgesic requirements</i>	266
<i>Personalized analgesics</i>	266
<i>Signature of pain on brain imaging</i>	267
<i>Concluding remarks on personalized management of pain</i>	267
Personalized management of sleep disorders	268
<i>Personalized therapy of insomnia</i>	268
Future of personalized neurology	269
Personalized management of ophthalmic disorders	269
Proteomics-based personalized management of uveitis	269
Combining cell and gene therapies for retinal disorders	269
Cardiovascular disorders	270
Role of diagnostics in personalized management of cardiovascular disease.....	270
<i>Cardiovascular disorders with a genetic component</i>	270
<i>Gene mutations associated with risk of coronary heart disease</i>	271
<i>Gene variant as a risk factor for sudden cardiac death</i>	272
<i>KIF6 gene test as a guide to management of heart disease</i>	273

<i>NGS sequencing for management of cardiovascular disorders</i>	273
<i>Personalized antiplatelet therapy after PCI</i>	273
Assessing patients with coronary heart disease.....	274
Assessing coronary artery disease for percutaneous coronary interventions.....	275
Companion diagnostics for therapy of cardiovascular disorders.....	276
Biomarkers and personalized management of cardiovascular disorders.....	277
Pharmacogenomics of cardiovascular disorders.....	277
Nanotechnology-based personalized therapy of cardiovascular diseases.....	277
Personalized management of chronic myocardial ischemia.....	278
<i>Management of chronic angina pectoris</i>	278
Personalized management of myocardial infarction.....	279
Management of heart failure.....	279
<i>β-blockers</i>	279
<i>Bucindolol</i>	280
<i>BiDil</i>	280
Management of atrial fibrillation.....	281
Management of hypertension.....	282
<i>Adjusting therapy of hypertension to fluctuations of blood pressure</i>	283
<i>Choice of drugs for hypertension</i>	284
<i>Control of blood pressure with vagal nerve stimulation</i>	284
<i>Correction of causes and risk factors of hypertension</i>	285
<i>Genes and hypertension</i>	285
<i>Guideline for management of HPN</i>	285
<i>Improving management of HPN by targeting new pathways</i>	286
<i>Individualized therapy of HPN based on risk factors of heart disease</i>	287
<i>Personalized management of hypertensive patients with albuminuria</i>	287
<i>Personalized management of hypertension in the elderly</i>	288
<i>Personalized management of hypertension in women</i>	288
<i>Pharmacogenomics of diuretic drugs</i>	288
<i>Pharmacogenomics of ACE inhibitors</i>	289
<i>Prediction of antihypertensive activity of rosfuroxin</i>	289
<i>Role of pharmacogenetics in management of hypertension</i>	290
<i>Scheme for management of hypertension by personalized approach</i>	291
Personalized lipid-lowering therapies.....	291
<i>NIR spectroscopy of plaques to guide cholesterol-lowering therapy</i>	291
<i>Polymorphisms in genes involved in cholesterol metabolism</i>	292
<i>Role of eNOS gene polymorphisms</i>	292
<i>Prediction of response to statins</i>	293
<i>Personalized management of women with hyperlipidemia</i>	293
<i>Therapeutic alternatives in patients with statin intolerance</i>	294
<i>Treatment of familial hypercholesterolemia</i>	294
<i>PCSK9 inhibitors</i>	294
Thrombotic disorders.....	295
<i>Factor V Leiden mutation</i>	295
<i>Anticoagulant therapy</i>	296
<i>Antiplatelet therapy</i>	297
Personalized management of aortic aneurysms.....	298
Clinical trials of personalized therapy of cardiovascular diseases.....	298
Project euHeart for personalized management of heart disease.....	299
Modification of life style factors in management of cardiovascular disorders.....	299
Multimorbidity in patients with cardiovascular disease.....	300
Systems biology approach to personalized cardiology.....	300
Concluding remarks on personalized management of cardiovascular diseases.....	300
Personalized management of pulmonary disorders.....	301
Role of genetic ancestry in lung function.....	301
Targeted drug delivery for personalized management of pulmonary disorders.....	301
Personalized therapy of asthma.....	302
<i>Asthma phenotyping for improving therapeutic precision</i>	302
<i>Biomarkers for predicting response to corticosteroid therapy</i>	303
<i>Genetic polymorphism and response to β_2-adrenergic agonists</i>	303
<i>Genotyping in asthma</i>	303
<i>IgE as guide to dosing of omalizumab for asthma</i>	304
<i>Lebrikizumab for personalised treatment of asthma</i>	304
Personalized management of chronic obstructive pulmonary disease.....	305
Personalized management of idiopathic pulmonary fibrosis.....	305
Personalized management of skin disorders.....	306
Genetic testing for personalized skin care.....	307
Management of hair loss based on genetic testing.....	307
Personalized urology.....	307
Personalized approaches in immunology.....	308
<i>Immunological tests in personalized medicine</i>	308

<i>Antibody profiles</i>	308
<i>Role of Mannose-binding lectin testing in personalized medicine</i>	308
Pharmacogenetics and pharmacogenomics of immunosuppressive agents	309
Personalized management of patients with lupus erythematosus.....	309
Personalized therapy of rheumatoid arthritis	310
Biomarkers for personalizing therapy of rheumatoid arthritis	310
DIATSTAT™ anti-cyclic citrullinated peptides in rheumatoid arthritis	311
Genetics and epigenetic aspects of rheumatoid arthritis	311
Personalization of COX-2 inhibitor therapy	311
Personalized biological therapy of RA.....	312
Personalization of infliximab therapy	312
Personalized therapy of RA guided by anti-citrullinated protein antibodies.....	312
Variations in the effectiveness of therapies for RA	313
Personalized management of obesity	313
Basics of obesity	313
Genetics of obesity as a basis for personalized management	314
Limitations of personalized approach to management of obesity	314
Personalized management of diabetes	315
<i>Biomarkers in the management of diabetes</i>	315
<i>Personalized management of monogenic diabetes</i>	315
<i>Selection from multiple options for treatment of T2DM</i>	316
<i>Stratification of diabetes into 5 subgroups and personalized medicine</i>	316
Management of genetic disorders	316
Personalized treatment of cystic fibrosis	317
Personalized management of Prader-Willi syndrome.....	318
Personalized management of gastrointestinal disorders	319
Role of microbiome in personalized management of gastrointestinal disorders	319
Personalized therapy of inflammatory bowel disease	319
Personalized management of lactose intolerance.....	320
Personalized approaches to improve organ transplantation	320
Personalization of kidney transplantation	321
<i>Cell-based bioengineered kidney transplant</i>	321
Personalization of cardiac transplantation.....	321
<i>Cell-based regeneration of heart for personalized transplantation</i>	322
Prediction of rejection for personalized anti-rejection treatment.....	322
Personalized immunosuppressant therapy in organ transplants.....	323
Role of immunological biomarkers in monitoring grafted patients	324
Improved matching of blood transfusion	325
Personalized approaches to addiction.....	325
Reversal of cocaine-evoked synaptic plasticity	325
Pharmacogenetics of drug addiction	326
Genetic polymorphism and management of alcoholism	326
Personalized therapy for smoking cessation.....	327
<i>Antidepressant therapy for smoking cessation</i>	327
<i>Effectiveness of nicotine patches in relation to genotype</i>	328
Personalized geriatrics	328
Chronological vs biological age	328
Pharmacogenetics and adverse drug reactions.....	328
Systems pharmacology approach to disorders of aging	329
Personalized pediatrics.....	329
WGS for personalized management of genetic disorders in critically ill infants.....	329
Personalized nephrology.....	329
Personalized management of chronic kidney disease	329
<i>Genes and chronic kidney disease</i>	329
<i>MicroRNAs and chronic kidney disease</i>	330
<i>Metabolomics and chronic kidney disease</i>	330
<i>TGF-β1 as a target for therapy of chronic kidney disease</i>	330
<i>Proteomics and chronic kidney disease</i>	331
Personalized management of renal disease associated with hypertension.....	331
<i>ACE inhibitors as renoprotective agents in hypertension</i>	331
<i>Gene associated with end-stage renal disease and hypertension</i>	331
Personalized approach to type I primary hyperoxaluria	332
Personalized approaches to miscellaneous problems	332
Female sexual dysfunction	332
<i>Hormone replacement therapy in women</i>	332
Personalized treatment of malaria.....	333
Personalized management of osteoporosis	333
Personalized care of trauma patients	334
Personalized medical care of astronauts during space flights	334
Personalized management of motion sickness.....	335
Personalized treatment of rare diseases.....	335

Personalized management of DNA repair disorders	336
Personalized preventive medicine	336
10. Personalized Therapy of Cancer	337
Introduction	337
Challenges of cancer classification.....	337
Molecular biology of cancer as basis for personalized management	338
<i>Cancer epigenetics/epigenomics and personalized therapy</i>	<i>339</i>
<i>Cell division and mitotic spindles.....</i>	<i>339</i>
<i>Chromosomes and cancer</i>	<i>339</i>
<i>Chromosomal instability.....</i>	<i>340</i>
<i>DNA damage, repair and cancer.....</i>	<i>340</i>
<i>Gene mutations and cancer.....</i>	<i>341</i>
<i>Telomeres and cancer.....</i>	<i>342</i>
Systems biology of cancer.....	342
Relationships of technologies for personalized management of cancer	342
Impact of molecular diagnostics on the management of cancer	343
A universal NGS-based oncology test system	344
Analysis of RNA splicing events in cancer	344
Analysis of chromosomal alterations in cancer cells	345
Cancer classification using microarrays	345
Cancer gene panel for detection of genetic alterations	346
Companion diagnostics for cancer	346
Circulating tumor cells isolation and characterization	346
Circulating cell-free DNA for monitoring personalized cancer therapy.....	347
Detection of loss of heterozygosity	347
Diagnostics for detection of minimal residual disease.....	348
DNA repair biomarkers	348
Fluorescent in situ hybridization.....	348
Gene expression profiling.....	349
<i>Gene expression profiles predict chromosomal instability in tumors.....</i>	<i>350</i>
<i>OnkoMatch tumor genotyping.....</i>	<i>350</i>
<i>Synthetic dosage lethality predicts tumor growth and patient survival</i>	<i>350</i>
GPS Cancer test.....	351
Modulation of CYP450 activity for cancer therapy	351
NanoFlares for detection of CTCs	351
Pathway-based analysis of cancer	351
<i>Conversion of gene-level information into pathway-level information.....</i>	<i>351</i>
<i>Personalized therapies based on oncogenic pathways signatures.....</i>	<i>352</i>
Quantum dot-based test for DNA methylation.....	352
Role of molecular imaging in personalized therapy of cancer	353
<i>Functional diffusion MRI.....</i>	<i>353</i>
<i>FDG-PET/CT for personalizing cancer treatment.....</i>	<i>354</i>
<i>Image-guided personalized drug delivery in cancer</i>	<i>354</i>
<i>Optoacoustic imaging and nanoparticles in cancer management</i>	<i>354</i>
<i>Tumor imaging and elimination by targeted gallium corrole.....</i>	<i>355</i>
<i>Future prospects of molecular imaging in management of cancer.....</i>	<i>355</i>
Unraveling the genetic code of cancer	356
Cancer prognosis	356
Personalized cancer prevention	356
Detection of mutations for cancer risk assessment and prevention	357
Impact of biomarkers on management of cancer.....	358
HER-2/neu oncogene as a biomarker for cancer.....	358
L-asparaginase treatment of cancer guided by a biomarker	358
miRNA biomarkers for personalized management of cancer	359
Oncogene GOLPH3 as a cancer biomarker	359
Predictive biomarkers for efficacy of anticancer therapy	359
Sequencing to discover biomarkers to personalize cancer treatment.....	359
VeraTag™ assay system for cancer biomarkers.....	360
Determination of response to therapy	360
Biomarker-based assays for predicting response to anticancer therapeutics	361
Ex vivo testing of tumor biopsy for chemotherapy sensitivity	361
Genomic approaches to predict response to anticancer agents.....	362
<i>Gene expression patterns to predict response of cancer to therapy</i>	<i>362</i>
<i>Genomic analysis of tumor biopsies.....</i>	<i>362</i>
<i>Genotype-dependent efficacy of pathway inhibition in cancer</i>	<i>362</i>
<i>Mutation detection at molecular level</i>	<i>363</i>
<i>RNA Disruption Assay™</i>	<i>363</i>
<i>Role of genetic variations in susceptibility to anticancer drugs</i>	<i>363</i>
Non-genetic factors for variations in response of cancer cells to drugs	363
Profiling of cancer therapy in zebrafish xenografts to predict response.....	364

Proteomic analysis of tumor biopsies to predict response to treatment	364
Real-time apoptosis monitoring	364
Serum nucleosomes as indicators of sensitivity to chemotherapy	365
Targeted microbubbles to tumors for monitoring anticancer therapy.....	365
PET imaging for determining response to chemotherapy	366
<i>PET imaging with tyrosine kinase inhibitors</i>	366
Concluding remarks about predicting response to anticancer therapy	366
Molecular diagnostics combined with cancer therapeutics.....	367
Aptamers for combined diagnosis and therapeutics of cancer	367
Combining diagnosis and therapy of metastatic cancer	367
Detection and destruction of CTCs with nanoparticles and X-rays.....	368
Molecular profiling of cancer.....	369
Targeted cancer therapies	369
Targeting glycoproteins on cell surface	369
Targeting pathways in cancer	369
Targeted personalized anticancer medicines in clinical use	369
Immunotherapy of cancer	370
Monoclonal antibodies for personalized management of cancer	370
Targeted MAb-based immune therapy of cancer.....	372
<i>MAbs targeted to alpha fetaprotein receptor</i>	372
<i>MAbs targeted to tumor blood vessels</i>	372
<i>MAbs that selectively target cancer</i>	372
<i>Velociximab</i>	373
MAbs for immune activation	373
Functional MAb-based therapies.....	373
Immunotherapy of dormant cancer	374
Combined use of MAbs and cytokines	375
Combining diagnostics with therapeutics based on MAbs.....	375
<i>Radiolabeled antibodies for detection and targeted therapy of cancer</i>	375
Cancer immunotherapy based on suppression of enzymes	377
Personalized cancer vaccines.....	377
Antigen-specific vaccines	377
<i>Active immunotherapy based on antigen specific to the tumor</i>	377
Tumor-derived vaccines.....	378
<i>FANG vaccine</i>	379
<i>MyVax</i>	379
<i>OncoVAX</i>	380
<i>Tumor cells treated with dinitrophenyl</i>	380
<i>Prophage</i>	380
<i>Melacine</i>	380
Patient-specific cell-based vaccines	381
<i>Dendritic cell-based vaccines</i>	381
Adoptive cell therapy.....	383
<i>Combination of antiangiogenic agents with ACT</i>	384
<i>Genetically targeted T cells for treating B cell malignancies</i>	384
<i>Genetic engineering of tumor cells</i>	385
<i>Hybrid cell vaccination</i>	385
Personalized peptide cancer vaccines.....	385
Targeting core mutations in cancer	386
Current status and future prospects of personalized cancer vaccines	386
Personalized radiation therapy	387
Peptide receptor radionuclide therapy.....	388
Use of radiation sensitivity biomarkers to personalized radiotherapy	389
Use of imaging to monitor radioimmunotherapy of non-Hodgkin lymphoma.....	389
Role of nanobiotechnology in personalized management of cancer	390
Design of future personalized cancer therapies	390
Personalized therapy of cancer based on cancer stem cells.....	391
Role of CRISPR-Cas9 in personalized cancer gene therapy	391
Role of epigenetics in development of personalized cancer therapies	392
<i>Cancer epigenetics and immunotherapy</i>	392
Selective destruction of cancer cells while sparing normal cells	393
<i>Sphingolipids</i>	393
<i>Hyperbaric oxygen as adjunct to radiotherapy</i>	393
<i>Targeting response to transformation-induced oxidative stress</i>	394
<i>Targeting enzymes to prevent proliferation of cancer cells</i>	394
Tissue systems biology approach to personalized management of cancer.....	394
Role of oncoproteomics in personalized therapy of cancer	394
Cancer tissue proteomics	395
Proteomics technologies to guide targeted drug selection for cancer.....	395
<i>LC-MS/MS proteomics as a companion diagnostic</i>	395
<i>Personalized cancer therapy based on targeted proteomics</i>	396

Role of metabolomics in personalized therapy of cancer	397
Role of sequencing in personalized therapy of cancer	398
Pharmacogenomic-based chemotherapy	399
Whole genome technology to predict drug resistance	399
Anticancer drug selection based on molecular characteristics of tumor.....	399
Testing microsatellite-instability for response to chemotherapy.....	399
Pharmacogenetics of cancer chemotherapy.....	400
CYP 1A2	401
Thiopurine methyltransferase	401
Dihydropyrimidine dehydrogenase	401
UGT1A1 test as guide to irinotecan therapy.....	402
Role of computational models in personalized anticancer therapy.....	402
A computational model of kinetically tailored treatment	402
Mathematical modeling of tumor microenvironments.....	403
Modeling signaling pathways to reposition anticancer drugs	403
Therapy resistance in cancer	404
Mechanism of therapy resistance in cancer.....	404
<i>Cancer stem cells and radioresistance</i>	<i>404</i>
<i>Expression of P-glycoprotein gene by tumor.....</i>	<i>405</i>
<i>Overexpression of multidrug resistance gene.....</i>	<i>405</i>
<i>P53 mutations</i>	<i>405</i>
<i>Role of splice variants in resistance to cancer therapy</i>	<i>405</i>
Detection of drug resistance.....	406
<i>Anaplastic lymphoma kinase.....</i>	<i>406</i>
<i>CRISPR for studying mechanism of drug-resistance in cancer</i>	<i>406</i>
<i>Metabolic profiling of cancer</i>	<i>406</i>
Management of drug resistance in cancer	407
<i>Chemogenomic approach to drug resistance.....</i>	<i>407</i>
<i>Determination of chemotherapy response by topoisomerase levels.....</i>	<i>407</i>
<i>Management of drug resistance in leukemia</i>	<i>407</i>
<i>Patient-derived xenograft mouse models in drug resistant cancer</i>	<i>408</i>
<i>Resistance to vaccines in cancer recurrence after surgery</i>	<i>409</i>
<i>Systems biology approach to drug-resistant cancer.....</i>	<i>409</i>
Personalized therapy of cancer metastases	409
Technologies for analysis of CTCs.....	409
<i>Microfluidic technologies</i>	<i>410</i>
<i>BEAMing technology for analysis of circulating tumor DNA.....</i>	<i>410</i>
<i>Technologies for detection of interplay of environments and CTCs.....</i>	<i>411</i>
Systemic antitumor effect of localized radiotherapy for cancer metastases	411
Diagnosis of cancer of an unknown primary.....	412
Personalized management of cancers of various organs/systems	412
Personalized management of bladder tumors	412
Personalized management of brain tumors.....	413
<i>Aptamers for selective targeting of tumor initiating cells in GBM</i>	<i>413</i>
<i>Bioinformatic approach to personalizing treatment of GBM</i>	<i>413</i>
<i>Biosimulation approach to personalizing treatment of brain cancer.....</i>	<i>414</i>
<i>Brain cancer chip for personalized drug screening</i>	<i>414</i>
<i>Combination of gene therapy and CAR-T cell therapy for GBM</i>	<i>414</i>
<i>Drug resistance in GBM.....</i>	<i>415</i>
<i>Genetics and genomics of GBM</i>	<i>415</i>
<i>Genomic analysis as a guide to personalized therapy of GBM.....</i>	<i>417</i>
<i>Induced neural stem cells for personalized therapy of GBM</i>	<i>417</i>
<i>Molecular diagnostics for personalized management of GBM.....</i>	<i>418</i>
<i>Personalized vaccine for GBM</i>	<i>420</i>
<i>Personalized chemotherapy of GBM.....</i>	<i>420</i>
<i>Personalized therapy of oligodendroglial tumors.....</i>	<i>421</i>
<i>Personalized therapy of neuroblastomas</i>	<i>422</i>
<i>Personalized therapy of medulloblastomas</i>	<i>423</i>
<i>Personalized management of germ cell brain tumors.....</i>	<i>423</i>
<i>Personalized management of meningiomas</i>	<i>423</i>
<i>Supratentorial hemispheric diffuse low-grade gliomas.....</i>	<i>424</i>
<i>Targeted therapy of BRAF V600E mutant papillary craniopharyngioma.....</i>	<i>424</i>
<i>Future prospects of personalized therapy of malignant brain tumors.....</i>	<i>425</i>
Personalized management of breast cancer	425
<i>Biomarker-guided decisions for breast cancer therapy</i>	<i>425</i>
<i>Developing personalized drugs for breast cancer.....</i>	<i>426</i>
<i>Gene expression plus conventional predictors of breast cancer</i>	<i>426</i>
<i>Her2 testing in breast cancer as a guide to treatment.....</i>	<i>427</i>
<i>HER2/neu-derived peptide vaccine for breast cancer</i>	<i>429</i>
<i>Prediction of cell signaling pathways from gene expression patterns.....</i>	<i>429</i>
<i>Trends in treatment patterns and outcomes for DCIS</i>	<i>430</i>

<i>Molecular diagnostics in breast cancer</i>	430
<i>Molecular classification of infiltrating breast cancer</i>	433
<i>Monitoring of circulating tumor cells in breast cancer</i>	433
<i>Pharmacogenetics of breast cancer</i>	434
<i>Proteomics-based personalized management of breast cancer</i>	434
<i>Predicting response to chemotherapy in breast cancer</i>	434
<i>Prediction of resistance to chemotherapy in breast cancer</i>	438
<i>Prediction of adverse reaction to radiotherapy in breast cancer</i>	438
<i>Prediction of recurrence in breast cancer for personalizing therapy</i>	439
<i>Prognostic tests for breast cancer</i>	440
<i>Racial factors in the management of breast cancer</i>	443
<i>RATHER consortium to study personalized approach to breast cancer</i>	443
<i>Ribociclib as first-line therapy for HR-positive breast cancer</i>	444
<i>TAILORx (Trial Assigning Individualized Options for Treatment)</i>	444
<i>Tamoxin therapy for ER-positive breast cancer</i>	444
<i>Triple negative breast cancer</i>	444
<i>Current trends and future of breast cancer research</i>	445
<i>Understanding tumor diversity in mouse mammary cancer model</i>	447
Personalized management of ovarian cancer	447
<i>Early diagnosis of ovarian cancer</i>	447
<i>Determining response to chemotherapy in ovarian cancer</i>	448
<i>Prognosis of ovarian cancer based on CLOVAR</i>	448
<i>Recurrent and drug-resistant ovarian cancer</i>	449
<i>Pathway targeted therapies for ovarian cancer</i>	450
<i>Repurposing auranofin for treatment of ovarian cancer</i>	451
<i>Subtype-specific therapies for epithelial ovarian cancer</i>	452
<i>Targeting hematogenous metastasis of ovarian cancer</i>	452
<i>Vynfinit ® for platinum-resistant ovarian cancer</i>	452
Personalized management of head and neck cancer	453
<i>Molecular characterization of head and neck cancer using omics</i>	453
<i>Relevance of biomarkers of HPV-related head and neck cancer</i>	453
<i>Molecular targeted therapies for HNSCC</i>	454
Personalized management of hematological malignancies	454
<i>B cell malignancies</i>	455
<i>Personalized management of acute lymphoblastic leukemia</i>	455
<i>Personalized management of chronic lymphocytic leukemia</i>	456
<i>Personalized management of acute myeloid leukemia</i>	458
<i>Personalized management of chronic myeloid leukemia</i>	460
<i>Personalized management of multiple myeloma</i>	460
<i>Personalized management of myelodysplastic syndrome</i>	462
<i>Personalized management B cell lymphomas</i>	463
<i>Personalized vaccine for follicular lymphoma</i>	464
<i>Pharmacoproteomics approach to diffuse large B cell lymphoma</i>	464
<i>Companion diagnostic for treatment of lymphoma with Adcentris™</i>	464
Personalized management of gastrointestinal tumors	465
<i>Personalized management of esophageal cancer</i>	465
<i>Personalized management of gastric cancer</i>	465
<i>Personalized management of gastrointestinal stromal tumors</i>	466
Personalized management of colorectal cancer	467
<i>Developing personalized therapies for CRC</i>	467
<i>Molecular diagnosis for guiding personalized management of CRC</i>	468
<i>Role of staging of CRC in prognosis and management decisions</i>	469
<i>Role of biomarkers in personalized management of CRC</i>	470
<i>Role of miRNA modeling in personalized management of CRC</i>	471
<i>Resistance to targeted EGFR blockade in CRC</i>	471
<i>Sequencing for personalized management of colorectal cancer</i>	472
<i>Systems biology approach to drug resistance in colorectal cancer</i>	473
Personalized management of liver cancer	474
<i>Prognosis of HCC in relation to management</i>	474
<i>Prediction of recurrence of hepatocellular carcinoma</i>	475
<i>Prediction of survival of patients with fibrolamellar HCC</i>	475
Personalized management of lung cancer	475
<i>ALK inhibitors for personalized management of NSCLC</i>	475
<i>Bronchial genomic classifier for diagnostic of lung cancer</i>	476
<i>Companion diagnosis for NSCLC therapeutics</i>	476
<i>Copy number variations as a diagnostic tool for lung cancer</i>	477
<i>EGFR tyrosine kinase inhibitor treatment</i>	477
<i>Development of resistance to EGFR inhibitors</i>	479
<i>Molecular subtyping of lung cancer</i>	479
<i>miRNA classifiers as diagnostic/prognostic tools in lung cancer</i>	480
<i>Personalized therapy of NSCLC based on KIF5B/RET fusion oncogene</i>	480

<i>Predicting response of NSCLC to platinum-based therapy</i>	480
<i>Proteomics for discovery of metabolic biomarkers of lung cancer</i>	481
<i>Role of a new classification system in the management of lung cancer</i>	481
<i>Selecting therapy of cancer arising from respiratory papillomatosis</i>	481
<i>Sequencing the genomes of SCLC</i>	481
<i>Testing for response to chemotherapy in lung cancer</i>	482
<i>Testing for prognosis of lung cancer</i>	482
<i>Testing for recurrence of lung cancer</i>	483
Personalized management of malignant melanoma	483
<i>Inhibitors of BRAF mutation for metastatic melanoma</i>	484
<i>Management of drug-resistant metastatic melanoma</i>	485
<i>Vaccine for malignant melanoma based on heat shock protein</i>	485
Personalized management of endocrine tumors	485
<i>Adosterone producing tumors</i>	485
<i>Neuroendocrine tumors</i>	486
<i>Parathyroid tumors</i>	486
<i>Personalized management of pheochromocytoma and paraganglioma</i>	487
Personalized management of osteosarcoma	487
Personalized management of pancreatic cancer	488
<i>Biomarkers of pancreatic cancer</i>	489
<i>Histone modifications predict treatment response in pancreatic cancer</i>	489
<i>Transport properties of pancreatic cancer and gemcitabine delivery</i>	490
Personalized management of prostate cancer	490
<i>Assessing susceptibility to prostate cancer by genotyping</i>	490
<i>Diagnostics for guiding therapy of prostate cancer</i>	491
<i>Detection of prostate cancer metastases</i>	491
<i>Early detection of cancer recurrence and guiding treatment</i>	492
<i>Effects of lifestyle changes shown by gene expression studies</i>	492
<i>Epigenetics-based assays for guiding decision to biopsy prostate</i>	493
<i>Genomic patterns of aggressiveness of prostate cancer</i>	493
<i>Personalized peptide vaccine for prostate cancer</i>	493
<i>Selection of prostate cancer patients responsive to rucaparib therapy</i>	494
Personalized management of thyroid cancer.....	494
Future of cancer therapy	494
Challenges for developing personalized cancer therapies.....	495
Cancer Genome Atlas	495
Cancer Moonshot	496
<i>Blood Profiling Atlas</i>	496
<i>NCI collaborations</i>	496
COLTHERES consortium	497
Computer and imaging technologies for personalizing cancer treatment.....	498
Genomic Cancer Care Alliance	498
Integrated genome-wide analysis of cancer for personalized therapy	498
International Cancer Genome Consortium	499
National Cancer Institute of US.....	500
<i>Catalog of cancer genes for personalized therapy</i>	500
<i>NCI-designated Comprehensive Cancer Centers</i>	501
<i>Role of NCI Genomic Data Commons in personalized cancer therapy</i>	501
Precision Oncology Decision Support at MD Anderson Cancer Center	503
PREDICT Consortium	504
Quebec Clinical Research Organization in Cancer	504
The San Antonio 1000 Cancer Genomes Project.....	504
Companies involved in developing personalized oncology	504

11. Development of Personalized Medicine	509
Introduction	509
Non-genomic factors in the development of personalized medicine	509
Personalized medicine based on circadian rhythms.....	509
Cytomics as a basis for personalized medicine	511
Intestinal microflora	511
<i>Gut microbiome compared to human genome</i>	511
<i>Metabolic interactions of the host and the intestinal microflora</i>	512
Role of drug delivery in personalized medicine.....	512
Personalized approach to clinical trials	512
<i>Adaptive clinical trials</i>	513
<i>Bayesian approach in biomarker-based clinical trials</i>	514
<i>Clinical trials of therapeutics and companion diagnostics</i>	515
<i>Clinical trials on selected subpopulations of patients</i>	515
<i>Clinical trials networks</i>	515
<i>Creative clinical trial design</i>	516
<i>Individualizing risks and benefits in clinical trials</i>	516

Players in the development of personalized medicine.....	517
Personalized Medicine Coalition.....	517
Role of pharmaceutical industry.....	518
<i>Repositioning of drugs for personalized medicine</i>	519
<i>Discovery of personalized medicines</i>	519
<i>Personalized drug delivery</i>	519
<i>Production and distribution of personalized medicines</i>	520
Role of biotechnology companies	520
Role of life sciences industries	521
Role of biomedical engineering in wearable devices for personalized healthcare	521
Role of molecular imaging in personalized medicine	522
<i>Molecular imaging for personalized drug development in oncology</i>	522
<i>Molecular imaging and CNS drug development</i>	524
<i>Companies involved in molecular imaging</i>	524
Role of the clinical laboratories	525
Role of the US government in personalized medicine	525
<i>Precision Medicine Initiative</i>	526
<i>Department of Health and Human Services and personalized medicine</i>	529
<i>Agency for Healthcare Research and Quality</i>	530
<i>Comparative effectiveness research</i>	530
Role of the US Government agencies in personalized medicine	532
<i>NIH's Roadmap Initiative for Medical Research</i>	532
<i>NIH and personalized medicine</i>	532
<i>NIH collaboration with the FDA</i>	533
<i>NIH and Genetic Testing Registry</i>	533
<i>National Human Genome Research Institute</i>	533
<i>National Institute of General Medical Sciences</i>	533
<i>National Institute of Standards and Technology</i>	536
<i>Role of the Centers for Disease Control</i>	536
Role of academic institutions and health centers in the US	536
<i>Baylor College of Medicine</i>	536
<i>California Initiative to Advance Precision Medicine</i>	537
<i>Children's Hospital of Los Angeles</i>	537
<i>Clinical Proteomics Program of NCI & FDA</i>	537
<i>Coriell Personalized Medicine Collaborative™</i>	538
<i>Delaware Valley Personalized Medicine Project</i>	538
<i>Duke University Medical Center and genomic medicine</i>	539
<i>Evaluation of genetic tests and genomic applications</i>	539
<i>Indiana University Institute for Personalized Medicine</i>	540
<i>Inova Center for Personalized Health</i>	540
<i>Institute of Medicine's role in personalized medicine</i>	541
<i>Jackson Laboratory for Genomic Medicine</i>	541
<i>Johns Hopkins Center for Personalized Cancer Medicine Research</i>	542
<i>Mayo Clinic's Centers for Individualized Medicine</i>	542
<i>Mt. Sinai Medical Center's Personalized Medicine Research Program</i>	543
<i>North Shore University's Center for Personalized Medicine</i>	543
<i>P4 Medicine Institute</i>	543
<i>Personalized Medicine Partnership of Florida</i>	544
<i>Personalized oncology at Massachusetts General Hospital</i>	544
<i>Personalized oncology at Oregon Health & Science University</i>	544
<i>Pharmacogenetics Research Network and Knowledge Base</i>	545
<i>Southeast Nebraska Cancer Center's Personalized Medicine Network</i>	545
<i>Spectrum Health Center for personalized cancer care</i>	545
<i>Stanford Center for Genomics and Personalized Medicine</i>	546
<i>UAB-HudsonAlpha Center for Genomic Medicine</i>	546
<i>University of Colorado's Center for Personalized Medicine</i>	546
<i>UNC Institute for Pharmacogenomics and Individualized Therapy</i>	547
<i>Weill Cornell's Englander Institute for Precision Medicine</i>	547
<i>Wisconsin Genomics Initiative</i>	548
Role of academic collaborations with companies	548
<i>New York Genome Center</i>	548
Role of healthcare organizations	548
Role of the medical profession	549
<i>The American Medical Association and personalized medicine</i>	549
<i>Education of the physicians</i>	549
<i>Off-label prescribing and personalized medicine</i>	550
<i>Medical education</i>	550
Role of patients	550
<i>Monitoring of patient compliance with therapy</i>	551
<i>Public attitude towards personalized medicine</i>	551
<i>Patient participation in disease management decisions</i>	552

<i>Patient engagement in clinical trials of personalized medicine</i>	553
Role of genetic banking systems and databases	553
Role of biobanks in development of personalized medicine	553
UK Biobank	554
Biobanking and development of personalized medicine in EU	554
<i>BBMRI-ERIC</i>	554
CARTaGENE for biobanks in Canada	555
Personalized medicine based on PhysioGenomics™ technology	555
Role of bioinformatics in development of personalized medicine	556
Biosensing and wearable devices for monitoring of health	557
Biosimulation techniques for developing personalized medicine	557
Digitalized medicine	558
Genomic data analysis	558
Exploration of disease-gene relationship	559
Health information management	559
Electronic health records	559
<i>Analysis of -omic and EHR data of the patient</i>	560
<i>Cost of EHR and savings on healthcare expenses in the US</i>	560
<i>EHRs and genome-wide studies</i>	560
<i>Linking patient medical records and genetic information</i>	560
<i>Management of personal genomic data</i>	561
<i>Use of EHRs for improving safety of new medicines</i>	561
<i>Use of EHRs for genetic research</i>	562
<i>Use of EHRs for personalized drug discovery and development</i>	563
Personalized prognosis of disease	563
Integration of technologies for personalized medicine	563
Global scope of personalized medicine	564
<i>Global Alliance for Genomics and Health</i>	564
Personalized medicine in Canada	564
<i>Personalized medicine at Ontario Institute for Cancer Research</i>	564
<i>Personalized Medicine Partnership for Cancer in Quebec</i>	566
<i>Quebec Center of Excellence in Personalized Medicine</i>	566
Personalized medicine in the EU	567
<i>European Personalized Medicine Diagnostics Association</i>	567
<i>UK National Health Service and medical genetics</i>	567
<i>UK's Precision Medicine Catapult</i>	568
<i>Personalized medicine in Germany</i>	568
<i>Ubiquitous Pharmacogenomics project</i>	569
Personalized medicine in Israel	569
Personalized medicine in Japan	570
Personalized medicine in the developing countries	571
<i>Personalized medicine in the Middle East</i>	571
<i>Personalized medicine in China</i>	571
Advantages of personalized medicine	572
Limitations of personalized medicine	573
Non-genomic factors in response to drugs	573
Incidental findings in genetic screening and clinical sequencing	573
Future of personalized medicine	575
Ongoing genomic projects	575
<i>Understanding the genetic basis of diseases</i>	575
<i>Personal Genome Project</i>	575
<i>Genome-wide association studies</i>	576
<i>The 1000 Genomes Project</i>	577
<i>Genomics of aging in a genetically homogeneous population</i>	577
Translational science and personalized medicine	578
<i>Translation of genomic research into genetic testing for healthcare</i>	578
<i>Long-term behavioral effects of personal genetic testing</i>	579
Personalized predictive medicine	579
Connected health and personalized medicine	580
Opportunities and challenges	580
<i>Comparative-effectiveness research and personalized medicine</i>	580
<i>Genetic testing and concerns about equality of healthcare</i>	580
<i>Initiative for delivery for precision medicine</i>	581
<i>IGNITE network – implementing personalized medicine in clinical care</i>	581
<i>Prospects and limitations of genetic testing</i>	582
<i>Personalized medicine and public health</i>	583
<i>Pharmacotyping</i>	583
<i>Medicine in the year 2023</i>	584
Concluding remarks about the future of personalized medicine	584

12. Ethical, Legal and Regulatory Aspects of Personalized Medicine. 587

Introduction to ethical issues	587
Ethical issues of pharmacogenetics	587
Ethical aspects of genetic information	587
<i>Ethical issues of whole genome analysis</i>	<i>587</i>
<i>Ethical aspects of direct-to-consumer genetic services</i>	<i>588</i>
<i>Privacy issues in personalized medicine</i>	<i>589</i>
<i>Genetic Information Nondiscrimination Act in the US</i>	<i>590</i>
<i>UNESCO and ethical aspects of personalized medicine</i>	<i>590</i>
Genotype-specific clinical trials	590
Social issues in personalized medicine	591
<i>Race and personalized medicine</i>	<i>591</i>
Legal issues of personalized medicine	593
Gene patents and personalized medicine	594
Regulatory aspects	594
FDA and personalized medicine	595
<i>FDA oversight of NGS for personalized medicine</i>	<i>595</i>
FDA and molecular diagnostics in relation to personalized medicine	596
<i>CLSI guideline for the use of RNA controls in gene expression assays</i>	<i>596</i>
<i>Evaluation of companion diagnostics/therapeutic</i>	<i>597</i>
<i>FDA oversight of laboratory developed tests</i>	<i>598</i>
<i>FDA regulation of multivariate index assays</i>	<i>599</i>
<i>FDA guidelines for the role of IVD in personalized medicine</i>	<i>600</i>
<i>IVD device and drug co-development</i>	<i>601</i>
Regulatory aspects of pharmacogenetics	602
Regulation of direct-to-consumer genetic testing	602
<i>Need for regulatory oversight of DTC</i>	<i>602</i>
FDA and pharmacogenomics	605
<i>FDA guidance for pharmacogenomic data submissions</i>	<i>606</i>
<i>Joint guidelines of the FDA and EU regulators for pharmacogenomics</i>	<i>606</i>
<i>Pharmacogenomic/pharmacogenetic information in drug labels</i>	<i>607</i>
<i>FDA guidelines for pharmacogenomics-based dosing</i>	<i>607</i>
<i>FDA and validation of biomarkers</i>	<i>608</i>
FDA and predictive medicine	609
13. Commercial Aspects of Personalized Medicine	611
Introduction	611
Perceived financial concerns	611
Personalized medicine and orphan drug syndrome	611
Commercial aspects of pharmacogenomics	611
Cost of DNA testing	611
Cost of sequencing the human genome	612
Cost of genotyping	614
Cost of pharmacogenomics-based clinical trials	615
Business development of pharmacogenomic companies	615
Cost of personalized healthcare	615
The rising healthcare costs in the US	615
<i>Genetic testing and cost of healthcare</i>	<i>616</i>
Reducing healthcare costs by combining diagnostics with therapeutics	617
<i>Cost-effectiveness of pharmacogenetic testing</i>	<i>617</i>
<i>Cost-effectiveness of CYP genotyping-based pharmacotherapy</i>	<i>618</i>
<i>Cost effectiveness of HIV genotyping in treatment of AIDS</i>	<i>618</i>
<i>Cost-effectiveness of warfarin pharmacogenomics</i>	<i>619</i>
<i>Cost-benefit analysis of KRAS and BRAF screening in CRC</i>	<i>619</i>
<i>Lowering the high costs of cancer chemotherapy</i>	<i>619</i>
Overall impact of personalized medicine on healthcare	620
Drivers for the development of personalized medicine	620
Evolution of medicine as a driver for personalized therapy markets	621
Collaboration between the industry and the academia	621
Personalized medicine and drug markets	622
Segmentation of therapeutic drug markets	622
Reasons for increase of market values of personalized medicines	622
Growth of markets relevant to personalized medicine	623
<i>Biochips for diagnosis</i>	<i>623</i>
<i>Pharmacogenetics</i>	<i>624</i>
<i>Pharmacogenomics</i>	<i>624</i>
<i>Pharmacoproteomics</i>	<i>624</i>
<i>Point-of-Care</i>	<i>624</i>
<i>SNP market</i>	<i>624</i>
Markets for personalized medicines according to therapeutic areas	624
<i>Market for personalized cancer therapy</i>	<i>625</i>
Markets for personalized medicines according to geographical regions	625

Market opportunities for personalization of medicine	625
Impact of personalized medicine on other industries.....	626
Strategies for developing and marketing personalized medicine	627
<i>Education of the public</i>	627
<i>Role of the Internet in development of personalized medicine</i>	628
<i>Marketing companion diagnostics for personalized medicine</i>	628

14. References..... 631

Tables

Table 1-1: Selected terms relevant to the concept of personalized medicine.....	27
Table 1-2: Landmarks in the historical development of personalized medicine	28
Table 1-3: Genetic variations in the human genome.....	34
Table 1-4: Examples of systems medicine-based diagnostic/therapeutic approaches	51
Table 2-1: Molecular diagnostic technologies used for personalized medicine	57
Table 2-2: Applications of biochip technology relevant to personalized medicine	79
Table 2-3: Companies developing haplotyping technology	94
Table 2-4: Technologies for SNP analysis	94
Table 2-5: A sampling of companies involved in technologies for SNP genotyping	100
Table 2-6: Comparison of proteomic and genomic approaches in personalized medicine	106
Table 2-7: Selected methods for gene expression profiling.....	112
Table 2-8: A selection of companies with gene expression technologies	117
Table 2-9: Drugs requiring biomarker/companion diagnostic information in the label	119
Table 2-10: Companies involved in companion diagnostics.....	120
Table 2-11: Applications of point-of-care diagnosis	122
Table 2-12: Companies developing point-of-care diagnostic tests	123
Table 2-13: Companies offering genetic screening tests directly to consumers	127
Table 3-1: Pharmacogenetic vs. pharmacogenomic studies	134
Table 3-2: Enzymes relevant to drug metabolism	136
Table 3-3: Examples of mutation of the enzyme CYP450	137
Table 3-4: Frequency distribution of drugs metabolized by major isoforms of CYP450.	137
Table 3-5: Commonly prescribed medications, which are metabolized by CYP2D6.....	137
Table 3-6: Polymorphisms in drug target genes that can influence drug response	143
Table 3-7: Effect of genetic polymorphisms on disease response to drugs.....	144
Table 3-8: Examples of genetically determined adverse reactions to drugs	147
Table 3-9: Examples of genotyping and phenotyping in some diseases.....	155
Table 3-10: Companies with novel molecular toxicology technology	158
Table 3-11: Pharmacogenomic biomarkers in drug labeling	161
Table 4-1: Role of pharmacogenomics in variable therapy targets.....	169
Table 4-2: Role of pharmacogenomics in clinical trials	172
Table 4-3: Examples of pharmacogenomics-based clinical studies.....	173
Table 4-4: Tumor suppressor genes, their chromosomal location, function and associated tumors.	176
Table 4-5: Gene polymorphisms relevant to cardiovascular disease management	177
Table 4-6: Companies involved in cardiovascular genomics.....	179
Table 4-7: SNPs in genes implicated in response of bipolar disorder to lithium.....	180
Table 4-8: A sampling of companies involved in neuropharmacogenomics	182
Table 5-1: Applications of pharmacoproteomic biomarkers in personalized medicine	188
Table 8-1: Companies involved in personalized nutrition.....	210
Table 9-1: Important therapeutic areas for personalized medicine	213
Table 9-2: Enzymes that metabolize antipsychotics.....	229
Table 9-3: Enzymes that metabolize antidepressants	230
Table 9-4: Biomarkers of response to antidepressant treatment	231
Table 9-5: Biomarkers of epilepsy.....	241
Table 9-6: Influence of gene polymorphisms on efficacy of antiepileptic drugs.....	245
Table 9-7: Role of cell therapy in management of stroke according to stage.....	254
Table 9-8: Gene expression as biomarker of response to IFN- β in multiple sclerosis.....	258
Table 9-9: Biomarkers of traumatic brain injury.....	260
Table 9-10: P450 isoforms in the metabolism of drugs used in the management of pain	264
Table 9-11: Personalized management of neuropathic pain based on mechanism	268
Table 9-12: Genes that cause cardiovascular diseases.....	270
Table 9-13: Classification of diabetes into 5 clusters	316
Table 9-14: Genetic influences on pharmacotherapy of alcoholism	327
Table 10-1: Factors that drive the development of personalized therapy in cancer	337
Table 10-2: Impact of molecular diagnostics on the management of cancer	343
Table 10-3: FDA-approved companion diagnostics for cancer	346
Table 10-4: Marketed anticancer personalized medicines	370
Table 10-5: Monoclonal antibodies for cancer approved by the FDA	371
Table 10-6: Clinical trials of personalized cancer vaccines	386

Table 10-7: Future developments in oncology relevant to personalized management	495
Table 10-8: Selected companies involved in developing personalized oncology	504
Table 11-1: Bayesian versus frequentist approaches in clinical trials	514
Table 11-2: Players in the development of personalized medicine	517
Table 11-3: Members of the Personalized Medicine Coalition	517
Table 11-4: Biobanks relevant to personalized medicine	553
Table 11-5: Role of bioinformatics in the development of personalized medicine	556
Table 11-6: Advantages of personalized medicine for the biopharmaceutical industry	572
Table 11-7: Advantages of personalized medicine for the patients	572
Table 11-8: Advantage of personalized medicine for the physicians	572
Table 11-9: Advantage of personalized medicine for the healthcare providers	572
Table 11-10: Limitations of personalized medicine	573
Table 11-11: Recommendations of the Association for Molecular Pathology on incidental findings	574
Table 11-12: Methods of translational science that are relevant to personalized medicine	578
Table 11-13: Companies involved in predictive healthcare	579
Table 11-14: Delivery for precision medicine	581
Table 12-1: Drugs with genetic information in their labels	607
Table 13-1: Drivers for the development of personalized medicine	620
Table 13-2: Growth of markets relevant to personalized medicine 2017-2027	623
Table 13-3: Markets for personalized medicine according to therapeutic area 2017-2027	625
Table 13-4: Markets for personalized medicine in major regions 2017-2027	625
Table 13-5: Lack of efficacy in current therapy	626
Table 13-6: Impact of personalized medicine on other industries	626
Table 13-7: Strategies to develop personalized medicine	627
Table 13-8: Role of the Internet in development of personalized medicine	628

Figures

Figure 1-1: Relation of personalized medicine to other technologies	44
Figure 1-2: Relation of systems pharmacology to personalized medicine	50
Figure 2-1: Role of sequencing in personalized medicine	75
Figure 2-2: Role of biochip/microarray technology in personalized medicine	79
Figure 2-3: Application of biochips/microarrays in personalized therapy	80
Figure 2-4: Affymetrix GeneChip technology	81
Figure 2-5: Role of CYP450 genotyping in development of personalized medicine	82
Figure 2-6: Role of SNPs in personalized medicine	90
Figure 2-7: A scheme of integrated healthcare and personalized medicine	129
Figure 3-1: Pharmacogenetics as a link between genotype and phenotype	133
Figure 3-2: Role of pharmacogenetic technologies in personalized medicine	134
Figure 4-1: Impact of new technologies at various stages of the drug discovery process	171
Figure 4-2: Steps in the application of pharmacogenomics in clinical trials	173
Figure 7-1: Role RNAi in development of personalized medicine	201
Figure 8-1: A scheme of various factors in personalized nutrition	205
Figure 9-1: Workflow of genotypic resistance analysis for personalized HIV therapy	220
Figure 9-2: Components of multimodal therapy for neurological disorders	235
Figure 9-3: Scheme of iPSCs use for personalized cell therapy of Parkinson disease	238
Figure 9-4: An algorithm for personalized management of epilepsy	241
Figure 9-5: Algorithm for anticoagulant therapy to prevent stroke in atrial fibrillation	251
Figure 9-6: Spot sign of extravasation and expansion of intracerebral hematoma	253
Figure 9-7: A scheme of personalized therapy of multiple sclerosis	255
Figure 9-8: Personalized targeting of therapeutic agents to lesions of multiple sclerosis	260
Figure 9-9: Essential components of personalized management of pain	262
Figure 9-10: Genetic and non-genetic factors affecting efficacy and side effects of opioids	265
Figure 9-11: An algorithm for personalized management of pain	267
Figure 9-12: Assessment of stable coronary artery disease	276
Figure 9-13: Flow chart of personalized approach to management of atrial fibrillation	282
Figure 9-14: A scheme of personalized approach to management of hypertension	291
Figure 9-15: Basis of personalized approach to idiopathic pulmonary fibrosis (IPF)	306
Figure 9-16: Steps in growing a new heart in vitro for transplantation	322
Figure 10-1: Relationships of technologies for personalized management of cancer	343
Figure 10-2: Integration of technologies for personalized prevention of cancer	357
Figure 10-3: CRISPR-Cas9 in personalized cancer gene therapy	391
Figure 10-4: Use of LC-MS/MS to select appropriate targeted therapy for cancer	396
Figure 10-5: Personalized cancer therapy based on targeted proteomics	397
Figure 10-6: Applications of NCI Genomic Data Commons	502
Figure 10-7: Workflow for development of gene pages for personalized cancer therapy	503
Figure 11-1: Integration of technologies for the development of personalized medicine	563
Figure 12-1: Strategy for drug and test co-development	601
Figure 13-1: Cost of sequencing per genome	614
Figure 13-2: Evolution of personalized medicine as a market driver	621