

Personalized Medicine

Part I: Scientific & Commercial Aspects

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. He has also written "The Textbook of Gene Therapy", which was 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. His recent books include "Handbook of Nanomedicine" (Humana/Springer 2008; Chinese edition, Peking University Press 2011, 2nd ed Springer 2012, 3rd ed 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 edition 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 "Drug Delivery Systems", 2nd ed (Springer 2014, 3rd edn 2019 is in preparation) and "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.

**November 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 disease	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
Role of epigenetics in personalized medicine	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	54
Translational science and personalized medicine.....	54
Personalization of multimodal therapies.....	55
2. Molecular Diagnostics in Personalized Medicine	56
Introduction	56
Molecular diagnostic technologies	56
PCR-based methods	57
<i>DirectLinear™ Analysis</i>	57
<i>Denaturing high-performance liquid chromatography</i>	58
<i>Multiplex Allele-Specific Diagnostic Assay</i>	58
<i>Representational oligonucleotide microarray analysis</i>	58
<i>Restriction fragment length polymorphism (RFLP)</i>	58
<i>Real-time PCR for detection of CNVs</i>	59
Non-PCR methods.....	59
<i>Arrayed primer extension (APEX)</i>	59

<i>Enzymatic Mutation Detection (EMD)</i>	59
DNA sequencing	59
<i>Sanger-sequencing technology</i>	60
<i>ABI PRISM® 310 Genetic Analyzer</i>	61
<i>High-throughput paired end transcriptome sequencing</i>	61
Emerging sequencing technologies.....	61
<i>4300 DNA analyzer</i>	62
<i>Apollo 100</i>	62
<i>Cyclic array sequencing</i>	63
<i>CEQ™ 8000</i>	63
<i>DeepCAGE sequencing</i>	63
<i>Electron microscope-based DNA sequencing</i>	63
<i>Genometrica™ sequencer</i>	64
<i>GS-FLEX system (Roche/454)</i>	64
<i>IBS sequencing technology</i>	65
<i>Illumina's sequencing technology</i>	65
<i>MegaBACE 500</i>	66
<i>Microdroplet-based PCR for large-scale targeted sequencing</i>	67
<i>Multiplex amplification of human DNA sequences</i>	67
<i>Nanoscale sequencing</i>	67
<i>Next generation sequencing based on Lightning Terminators</i>	68
<i>Polonator sequencer</i>	68
<i>RainStorm™ microdroplet technology</i>	69
<i>Sequential DEXAS</i>	69
<i>SOLiD technology</i>	70
<i>Sequencing by hybridization</i>	71
<i>Whole genome sequencing</i>	71
<i>Bioinformatic tools for analysis of genomic sequencing data</i>	71
<i>Clinical Genomicist Workspace for managing NGS-based clinical tests</i>	72
<i>Detection of single molecules in real time</i>	72
<i>Direct observation of nucleotide incorporation</i>	72
<i>Molecular Combing</i>	72
<i>Nanopore sequencing</i>	73
<i>DNA sequence by use of nanoparticles</i>	73
<i>Zero-mode waveguide nanostructure arrays</i>	73
<i>Future prospects of sequencing</i>	73
<i>Role of DNA sequencing in development of personalized medicine</i>	74
<i>Role of RNA sequencing in development of personalized medicine</i>	76
Biochips and microarrays	76
Role of biochip/microarray technology in personalized medicine.....	76
Applications of biochip/microarray technology in personalized medicine	77
Standardizing the microarrays	78
Biochip technologies.....	78
<i>GeneChip</i>	78
<i>AmpliChip CYP450</i>	79
Microfluidics	80
<i>Lab-on-a-chip</i>	81
<i>Micronics' microfluidic technology</i>	81
<i>LabCD</i>	81
<i>Microfluidic automated DNA analysis using PCR</i>	81
<i>Integrated microfluidic bioassay chip</i>	82
Electronic detection of nucleic acids on microarrays.....	82
Strand displacement amplification on a biochip	83
Rolling circle amplification on DNA microarrays.....	83
Universal DNA microarray combining PCR and ligase detection reaction	83
Protein biochips	83
<i>ProteinChip</i>	84
<i>LabChip for protein analysis</i>	85
<i>TRINECTIN proteome chip</i>	85
<i>Protein expression microarrays</i>	85
<i>Microfluidic devices for proteomics-based diagnostics</i>	86
<i>New developments in protein biochips/microarrays</i>	86
<i>Protein biochips/microarrays for personalized medicine</i>	87
SNP genotyping	87
Genotyping and haplotyping.....	88
<i>Haplotype Specific Extraction</i>	89
<i>Computation of haplotypes</i>	89
<i>HapMap project</i>	89
<i>Haplotyping for whole genome sequencing</i>	90
<i>Predicting drug response with HapMap</i>	92
<i>Companies developing haplotyping technology</i>	92

Technologies for SNP analysis.....	92
Biochip and microarray-based detection of SNPs	93
<i>SNP genotyping by MassARRAY.....</i>	93
<i>BeadArray technology.....</i>	93
<i>SNP-IT primer-extension technology</i>	94
<i>Use of NanoChip for detection of SNPs.....</i>	94
Electrochemical DNA probes.....	94
Laboratory Multiple Analyte Profile	94
PCR-CTPP (confronting two-pair primers).....	95
TaqMan real-time PCR	95
Locked nucleic acid	95
Molecular inversion probe based assays.....	96
Pyrosequencing	96
Smart amplification process version 2	96
Zinc finger proteins	97
Mitochondrial SNPs.....	97
Limitations of SNP in genetic testing.....	97
Concluding remarks on SNP genotyping.....	98
Companies involved in developing technologies/products for SNP analysis	98
Impact of SNPs on personalized medicine	100
Detection of copy number variations	100
CNV algorithm for CNV detection.....	100
CNVnator for discovery of CNVs and genotyping	101
Study of rare variants in pinpointing disease-causing genes	101
Optical Mapping.....	102
Proteomics in molecular diagnosis.....	102
Proteomic strategies for biomarker identification.....	102
<i>Proteomic technologies for detection of biomarkers in body fluids</i>	<i>103</i>
Protein patterns.....	103
Layered Gene Scanning	103
Comparison of proteomic and genomic approaches in personalized medicine.....	104
Role of nanobiotechnology in molecular diagnostics.....	104
Cantilevers for personalized medical diagnostics	105
Role of biomarkers in personalized medicine.....	106
Role of biosensors in personalized medicine.....	108
Biomarkers for diagnostics	108
Biomarkers for drug development	109
Gene expression profiling	109
DNA microarrays.....	110
Analysis of single-cell gene expression.....	110
Gene expression profiling based on alternative RNA splicing	111
Whole genome expression array	111
Tangerine™ expression profiling	112
Gene expression analysis on biopsy samples	112
Profiling gene expression patterns of white blood cells.....	113
Serial analysis of gene expression (SAGE).....	113
Multiplexed Molecular Profiling	114
Gene expression analysis using competitive PCR and MALDI TOF MS.....	114
Companies involved in gene expression analysis	115
Monitoring in vivo gene expression by molecular imaging	115
Molecular imaging and personalized medicine.....	116
Combination of diagnostics and therapeutics	116
Use of molecular diagnostics for stratification in clinical trials	116
Companion diagnostics	117
Companies involved in companion diagnostics	118
Point-of-care diagnosis.....	120
Companies developing point-of-care diagnostic technologies	121
Point-of-care diagnosis of infections	123
Advantages versus disadvantages of point-of-care diagnosis	123
Future prospects of point-of-care diagnosis	124
Genetic testing for disease predisposition	124
Preventive genetics by early diagnosis of mitochondrial diseases	124
Direct-to-consumer genetic services.....	125
Role of diagnostics in integrated healthcare	126
Concept of integrated healthcare	126
Components of integrated healthcare	127
<i>Screening</i>	<i>127</i>
<i>Disease prediction.....</i>	<i>127</i>
<i>Early diagnosis</i>	<i>127</i>
<i>Prevention</i>	<i>127</i>
<i>Therapy based on molecular diagnosis.....</i>	<i>127</i>

Monitoring of therapy	128
Advantages and limitations of integrated healthcare.....	128
Commercially available systems for integrated healthcare.....	128
Future of molecular diagnostics in personalized medicine	129

3. Pharmacogenetics	131
Basics of pharmacogenetics.....	131
Role of molecular diagnostics in pharmacogenetics.....	132
Role of pharmacogenetics in pharmaceutical industry.....	133
Study of the drug metabolism and pharmacological effects	133
Causes of variations in drug metabolism	133
Enzymes relevant to drug metabolism	134
Pharmacogenetics of phase I metabolism.....	134
CYP450.....	134
P450 CYP 2D6 inhibition by selective serotonin reuptake inhibitors.....	136
Cytochrome P450 polymorphisms and response to clopidogrel.....	137
Lansoprazole and cytochrome P450.....	137
Glucose-6-phosphate dehydrogenase	137
Pharmacogenetics of phase II metabolism.....	138
N-Acetyltransferase.....	138
Uridine diphosphate-glucuronosyltransferase.....	139
Measurement of CYP isoforms	139
Polymorphism of drug transporters	140
Genetic variation in drug targets.....	140
Polymorphisms of kinase genes	141
Effect of genetic polymorphisms on disease response to drugs	141
Ethnic differences in drug metabolism	142
Gender differences in pharmacogenetics	142
Role of pharmacogenetics in drug safety	143
Adverse drug reactions	143
Adverse drug reactions in children	144
Adverse drug reactions related to toxicity of chemotherapy.....	144
Genetically determined adverse drug reactions.....	144
Malignant hyperthermia	146
Pharmacogenetics of clozapine-induced agranulocytosis.....	146
Role of pharmacogenetics in warfarin therapy.....	147
Role of pharmacogenetics in antiplatelet therapy	148
Role of pharmacogenetics in carbamazepine therapy	149
Role of pharmacogenetics in statin therapy	149
FDA consortium linking genetic biomarkers to serious adverse events	150
Therapeutic drug monitoring, phenotyping, and genotyping	151
Therapeutic drug monitoring	151
Phenotyping	152
Genotyping	153
Genotyping vs phenotyping.....	153
Phenomics	154
Limitations of genotype-phenotype association studies	154
Molecular toxicology in relation to personalized medicines.....	154
Toxicogenomics	155
Biomarkers of drug toxicity	155
Drug-induced mitochondrial toxicity	155
Companies involved in molecular toxicology	156
Gene expression studies	156
Pharmacogenetics in clinical trials	157
Postmarketing pharmacogenetics.....	157
Clinical implications of pharmacogenetics	158
Application of CYP450 genotyping in clinical practice	158
Genotype-based drug dose adjustment.....	158
Pharmacogenomic biomarker information in drug labels.....	158
Standardized terminology for clinical pharmacogenetic test results.....	162
Use of pharmacogenetics in clinical pharmacology.....	162
Application of CYP2C19 pharmacogenetics for personalized medicine.....	162
Genotyping for identifying responders to sulfasalazine.....	162
HLA alleles associated with lumiracoxib-related liver injury	163
Pharmacogenetic basis of thiopurine toxicity	163
Tranilast-induced hyperbilirubinemia due to gene polymorphism.....	163
Linking pharmacogenetics with pharmacovigilance	164
Genetic susceptibility to ADRs.....	164
Linking genetic testing to postmarketing ADR surveillance	164
Recommendations for the clinical use of pharmacogenetics	164
Limitations of pharmacogenetics	165

Pharmacoepiggenomics vs pharmacogenetics in drug safety	166
Future role of pharmacogenetics in personalized medicine	166
4. Pharmacogenomics.....	167
Introduction	167
Basics of pharmacogenomics	168
Pharmacogenomics and drug discovery	168
<i>Preclinical prediction of drug efficacy</i>	<i>170</i>
Pharmacogenomics and clinical trials	170
Impact of genetic profiling on clinical studies.....	171
Limitations of the pharmacogenomic-based clinical trials.....	172
Pharmacogenomic aspects of major therapeutic areas.....	173
Oncogenomics	173
<i>Oncogenes</i>	<i>173</i>
<i>Tumor suppressor genes.....</i>	<i>174</i>
Cardiogenomics	175
Neuropharmacogenomics.....	177
<i>Pharmacogenomics of Alzheimer's disease</i>	<i>177</i>
<i>Pharmacogenomics of depression.....</i>	<i>178</i>
<i>Pharmacogenomics of bipolar disorder.....</i>	<i>178</i>
<i>Pharmacogenomics of schizophrenia.....</i>	<i>179</i>
<i>Companies involved in neurogenomics-based drug discovery.....</i>	<i>180</i>
Current status and future prospects of pharmacogenomics	180
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	186
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
Pharmacometabonomics.....	192
Metabonomic technologies for toxicology studies.....	193
Metabonomics/metabolomics and personalized nutrition.....	193
Metabolomics for personalized medicine	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.....	202
Introduction	202
Acupuncture	202
Personalized acupuncture therapy.....	202
Personalized hyperbaric oxygen therapy	203
Personalized nutrition.....	203
Nutrigenomics	204
<i>Evolutionary basis of nutrigenomics</i>	<i>205</i>
<i>Genomics of vitamin D and calcium supplementation.....</i>	<i>205</i>
<i>Nutrigenomics and functional foods</i>	<i>206</i>
<i>Nutrigenomics and personalized medicine</i>	<i>206</i>
<i>Nutriproteomics</i>	<i>206</i>
Nutrigenetics and personalized medicine.....	207
Personalized diet prescription	207
<i>Personalized nutrition and aging</i>	<i>208</i>
<i>Personalized diet for diabetics.....</i>	<i>209</i>
Role of systems medicine in personalized nutrition.....	209
Companies involved in personalized nutrition	209
Personalized physical exercise	209
Variations in response to aerobic exercise	210
Variations in exercise-induced muscle hypertrophy and strength.....	210
Personalized surgery	210
9. Personalized Medicine in Major Therapeutic Areas	212
Introduction	212
Personalized management of infections	213
Genetic susceptibility to infections.....	213
Management of HIV	213
<i>CD4 counts as a guide to drug therapy for AIDS</i>	<i>213</i>
<i>Drug-resistance in HIV</i>	<i>213</i>
<i>Genetics of human susceptibility to HIV infection</i>	<i>215</i>
<i>Measurement of Replication Capacity.....</i>	<i>215</i>
<i>Personalized vaccine for HIV.....</i>	<i>216</i>
<i>Prevention of adverse reactions to antiviral drugs</i>	<i>216</i>
<i>Pharmacogenetics and HIV drug safety.....</i>	<i>217</i>
<i>Pharmacogenomics of antiretroviral agents</i>	<i>217</i>
<i>Role of diagnostic testing in management of HIV</i>	<i>217</i>
<i>Role of genetic variations in susceptibility to HIV-1</i>	<i>218</i>
<i>Role of personalized HIV therapy in controlling drug resistance.....</i>	<i>218</i>
<i>PhenoSense® to test HIV drug resistance.....</i>	<i>219</i>
<i>Sequencing for detecting mutations to personalize HIV therapy</i>	<i>219</i>
Personalized treatment of hepatitis B	220
Personalized treatment of hepatitis C	220
<i>Responders vs non-responders to treatment for hepatitis C.....</i>	<i>221</i>
<i>Drug resistance in hepatitis C.....</i>	<i>222</i>
<i>Challenges for personalized management of hepatitis C.....</i>	<i>222</i>
Personalized management of tuberculosis	222
Personalized management of fungal infections.....	223
Psychiatric disorders	223
Psychopharmacogenetics/psychopharmacodynamics	224
<i>Serotonin genes.....</i>	<i>224</i>
<i>Calcium channel gene.....</i>	<i>224</i>
<i>Dopamine receptor genes</i>	<i>225</i>
<i>COMT genotype and response to amphetamine.....</i>	<i>225</i>
<i>Methylenetetrahydrofolate reductase</i>	<i>225</i>
<i>Genetic loci associated with risk of major depressive disorder.....</i>	<i>225</i>
<i>Role of gene mutations in ADHD</i>	<i>226</i>
<i>Genotype and response to methylphenidate in children with ADHD</i>	<i>226</i>
<i>GeneSight tests for individualized therapy of psychiatric disorders</i>	<i>226</i>
Personalized antipsychotic therapy.....	226
Personalized antidepressant therapy	229
<i>Biomarkers of response to antidepressant treatment</i>	<i>229</i>
<i>EEG to predict adverse effects and evaluate antidepressant efficacy.....</i>	<i>230</i>
<i>GeneSight pharmacogenomic test</i>	<i>231</i>
<i>Individualization of SSRI treatment</i>	<i>231</i>
<i>Role of protein sFRP3 in predicting response to antidepressants.....</i>	<i>232</i>
<i>Treatment resistant depression.....</i>	<i>233</i>
<i>Vilazodone with a test for personalized treatment of depression.....</i>	<i>233</i>

Neurological disorders	234
Introduction to personalized neurology	234
Personalized management of Alzheimer's disease	234
Personalized management of Parkinson's disease.....	236
<i>Brain imaging for diagnosis of neurodegenerative parkinsonism</i>	236
<i>Direct-to-consumer genetic testing in PD</i>	236
<i>Discovery of subgroup-selective drug targets in PD</i>	237
<i>Personalized cell therapy for PD</i>	237
<i>Pharmacogenetics of PD</i>	238
<i>Use of wearable sensors to monitor PD response to levodopa therapy</i>	238
Personalized management of amyotrophic lateral sclerosis	238
Personalized management of epilepsy	239
<i>Adverse effects of AEDs</i>	239
<i>An algorithm for personalized management of epilepsy</i>	239
<i>Biomarkers of epilepsy</i>	240
<i>Drug resistance in epilepsy</i>	242
<i>Genetics/genomics of epilepsy</i>	243
<i>Pharmacogenomics of epilepsy</i>	244
<i>Rasmussen's encephalitis</i>	245
<i>Selection of the right AED</i>	246
<i>Future of management of epilepsy</i>	246
Personalized management of migraine.....	247
<i>Individualization of use of triptans for migraine</i>	247
<i>Multitarget therapeutics for personalized treatment of headache</i>	247
<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>	249
Personalized management of stroke	249
<i>Anticoagulation for stroke prevention</i>	251
<i>Application of proteomics for personalizing stroke management</i>	252
<i>Brain imaging for personalized management of stroke</i>	252
<i>Personalized management of intracerebral hemorrhage</i>	253
<i>Revascularization procedures in chronic post-stroke stage</i>	254
<i>Personalized cell therapy for management of stroke</i>	254
<i>Management of stroke according to stage</i>	254
Personalized treatment of multiple sclerosis	255
<i>Autologous bone marrow stem cell therapy for multiple sclerosis</i>	256
<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>	257
<i>Pharmacogenomics of IFN-β therapy in multiple sclerosis</i>	257
<i>Preclinical detection of multiple sclerosis in children</i>	259
<i>Predictive models of individual treatment response in MS</i>	259
<i>T cell-based personalized vaccine for MS</i>	259
<i>Targeting MS therapy to cell type of lesion</i>	260
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>	266
<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	268
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	276
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>	279
<i>BiDil</i>	280
Management of atrial fibrillation	280
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 diabetes</i>	287
<i>Personalized management of hypertensive patients with albuminuria</i>	288
<i>Personalized management of hypertension in the elderly</i>	288
<i>Personalized management of hypertension in women</i>	289
<i>Pharmacogenomics of diuretic drugs</i>	289
<i>Pharmacogenomics of ACE inhibitors</i>	290
<i>Prediction of antihypertensive activity of rosfuroxin</i>	290
<i>Role of pharmacogenetics in management of hypertension</i>	291
<i>Scheme for management of hypertension by personalized approach</i>	291
Personalized lipid-lowering therapies	292
<i>NIR spectroscopy of plaques to guide cholesterol-lowering therapy</i>	292
<i>Polymorphisms in genes involved in cholesterol metabolism</i>	292
<i>Role of eNOS gene polymorphisms</i>	293
<i>Prediction of response to statins</i>	293
<i>Personalized management of women with hyperlipidemia</i>	294
<i>Therapeutic alternatives in patients with statin intolerance</i>	294
<i>Treatment of familial hypercholesterolemia</i>	295
<i>PCSK9 inhibitors</i>	295
Thrombotic disorders	296
<i>Factor V Leiden mutation</i>	296
<i>Anticoagulant therapy</i>	297
<i>Antiplatelet therapy</i>	298
Personalized management of aortic aneurysms	298
Clinical trials of personalized therapy of cardiovascular diseases	299
Project euHeart for personalized management of heart disease	300
Modification of life style factors in management of cardiovascular disorders	300
Multimorbidity in patients with cardiovascular disease	301
Systems biology approach to personalized cardiology	301
Concluding remarks on personalized management of cardiovascular diseases	301
Personalized management of pulmonary disorders	302
Role of genetic ancestry in lung function	302
Targeted drug delivery for personalized management of pulmonary disorders	302
Personalized therapy of asthma	302
<i>Asthma phenotyping for improving therapeutic precision</i>	303
<i>Biomarkers for predicting response to corticosteroid therapy</i>	303
<i>Genetic polymorphism and response to β_2-adrenergic agonists</i>	304
<i>Genotyping in asthma</i>	304
<i>IgE as guide to dosing of omalizumab for asthma</i>	305
<i>Lebrikizumab for personalised treatment of asthma</i>	305
Personalized management of chronic obstructive pulmonary disease	305
Personalized management of idiopathic pulmonary fibrosis	306
Personalized management of skin disorders	307
Genetic testing for personalized skin care	307

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

Personalized care of trauma patients	335
Personalized medical care of astronauts during space flights	335
Personalized management of motion sickness.....	336
Personalized treatment of rare diseases.....	336
Personalized management of DNA repair disorders	337
Personalized preventive medicine	337
10. Personalized Therapy of Cancer	338
Introduction	338
Challenges of cancer classification.....	338
Molecular biology of cancer as basis for personalized management	339
<i>Cancer epigenetics/epigenomics and personalized therapy</i>	<i>340</i>
<i>Cell division and mitotic spindles.....</i>	<i>340</i>
<i>Chromosomes and cancer</i>	<i>340</i>
<i>Chromosomal instability.....</i>	<i>341</i>
<i>DNA damage, repair and cancer.....</i>	<i>341</i>
<i>Gene mutations and cancer.....</i>	<i>342</i>
<i>Telomeres and cancer.....</i>	<i>343</i>
Systems biology of cancer.....	343
Relationships of technologies for personalized management of cancer	343
Impact of molecular diagnostics on the management of cancer	344
A universal NGS-based oncology test system	345
Analysis of RNA splicing events in cancer	345
Analysis of chromosomal alterations in cancer cells	346
Cancer classification using microarrays	346
Cancer gene panel for detection of genetic alterations	347
Companion diagnostics for cancer	347
Circulating tumor cells isolation and characterization	347
Circulating cell-free DNA for monitoring personalized cancer therapy.....	348
Detection of loss of heterozygosity	348
Diagnostics for detection of minimal residual disease.....	349
DNA repair biomarkers	349
DNA sequencing for prognosis of cutaneous T cell lymphoma	349
Fluorescent in situ hybridization.....	350
Gene expression profiling.....	350
<i>Gene expression profiling in hematological cancers</i>	<i>350</i>
<i>Gene expression profiling in prostate cancer.....</i>	<i>351</i>
<i>Gene expression profiles predict chromosomal instability in tumors.....</i>	<i>351</i>
<i>OncoMatch tumor genotyping.....</i>	<i>352</i>
<i>Synthetic dosage lethality predicts tumor growth and patient survival</i>	<i>352</i>
GPS Cancer test.....	352
Modulation of CYP450 activity for cancer therapy	352
NanoFlares for detection of CTCs	353
Pathway-based analysis of cancer	353
<i>Conversion of gene-level information into pathway-level information.....</i>	<i>353</i>
<i>Personalized therapies based on oncogenic pathways signatures.....</i>	<i>353</i>
Quantum dot-based test for DNA methylation.....	354
Role of molecular imaging in personalized therapy of cancer	354
<i>Functional diffusion MRI.....</i>	<i>355</i>
<i>FDG-PET/CT for personalizing cancer treatment.....</i>	<i>355</i>
<i>Image-guided personalized drug delivery in cancer</i>	<i>356</i>
<i>Optoacoustic imaging and nanoparticles in cancer management</i>	<i>356</i>
<i>Tumor imaging and elimination by targeted gallium corrole.....</i>	<i>356</i>
<i>Future prospects of molecular imaging in management of cancer.....</i>	<i>357</i>
Unraveling the genetic code of cancer	357
Cancer prognosis	357
Personalized cancer prevention	358
Detection of mutations for cancer risk assessment and prevention	358
Impact of biomarkers on management of cancer.....	359
HER-2/neu oncogene as a biomarker for cancer.....	359
L-asparaginase treatment of cancer guided by a biomarker.....	360
miRNA biomarkers for personalized management of cancer.....	360
Oncogene GOLPH3 as a cancer biomarker	360
Predictive biomarkers for efficacy of anticancer therapy	360
Sequencing to discover biomarkers to personalize cancer treatment.....	361
VeraTag™ assay system for cancer biomarkers.....	361
Determination of response to therapy	362
Biomarker-based assays for predicting response to anticancer therapeutics	362
Ex vivo testing of tumor biopsy for chemotherapy sensitivity	362
Genomic approaches to predict response to anticancer agents.....	363
<i>Gene expression patterns to predict response of cancer to therapy</i>	<i>363</i>

<i>Genomic analysis of tumor biopsies</i>	363
<i>Genotype-dependent efficacy of pathway inhibition in cancer</i>	364
<i>Mutation detection at molecular level</i>	364
<i>Predicting response to checkpoint inhibitors</i>	364
<i>RNA Disruption Assay™</i>	365
<i>Role of genetic variations in susceptibility to anticancer drugs</i>	365
Non-genetic factors for variations in response of cancer cells to drugs	365
Profiling of cancer therapy in zebrafish xenografts to predict response	365
Proteomic analysis of tumor biopsies to predict response to treatment	366
Real-time apoptosis monitoring	366
Serum nucleosomes as indicators of sensitivity to chemotherapy	366
Targeted microbubbles to tumors for monitoring anticancer therapy	367
PET imaging for determining response to chemotherapy	367
<i>PET imaging with tyrosine kinase inhibitors</i>	368
Concluding remarks about predicting response to anticancer therapy	368
Molecular diagnostics combined with cancer therapeutics	368
Aptamers for combined diagnosis and therapeutics of cancer	368
Combining diagnosis and therapy of metastatic cancer	369
Detection and destruction of CTCs with nanoparticles and X-rays	370
Molecular profiling of cancer	370
Targeted cancer therapies	370
Targeting glycoproteins on cell surface	370
Targeting pathways in cancer	371
Targeted personalized anticancer medicines in clinical use	371
Immunotherapy of cancer	371
Monoclonal antibodies for personalized management of cancer	372
Targeted MAb-based immune therapy of cancer	373
<i>MAbs targeted to alpha fetoprotein receptor</i>	373
<i>MAbs targeted to tumor blood vessels</i>	373
<i>MAbs that selectively target cancer</i>	374
<i>Velociximab</i>	374
MAbs for immune activation	374
Functional MAb-based therapies	375
Immunotherapy of dormant cancer	375
Combined use of MAbs and cytokines	376
Antibody-drug conjugates for personalized therapy of cancer	376
Combining diagnostics with therapeutics based on MAbs	377
<i>Radiolabeled antibodies for detection and targeted therapy of cancer</i>	377
Cancer immunotherapy based on suppression of enzymes	378
Personalized cancer vaccines	378
Antigen-specific vaccines	379
<i>Active immunotherapy based on antigen specific to the tumor</i>	379
Tumor-derived vaccines	379
<i>FANG vaccine</i>	380
<i>MyVax</i>	381
<i>OncoVAX</i>	381
<i>Tumor cells treated with dinitrophenyl</i>	381
<i>Prophage</i>	382
<i>Melacine</i>	382
Patient-specific cell-based vaccines	382
<i>Dendritic cell-based vaccines</i>	382
Adoptive cell therapy	384
<i>Combination of antiangiogenic agents with ACT</i>	385
<i>Genetically targeted T cells for treating B cell malignancies</i>	386
<i>Genetic engineering of tumor cells</i>	386
<i>Hybrid cell vaccination</i>	386
Personalized peptide cancer vaccines	387
Targeting core mutations in cancer	387
Current status and future prospects of personalized cancer vaccines	388
Personalized radiation therapy	389
Peptide receptor radionuclide therapy	390
Use of radiation sensitivity biomarkers to personalized radiotherapy	390
Use of imaging to monitor radioimmunotherapy of non-Hodgkin lymphoma	391
Role of nanobiotechnology in personalized management of cancer	391
Design of future personalized cancer therapies	391
Personalized therapy of cancer based on cancer stem cells	392
Role of CRISPR-Cas9 in personalized cancer gene therapy	392
Role of epigenetics in development of personalized cancer therapies	393
<i>Cancer epigenetics and immunotherapy</i>	394
Selective destruction of cancer cells while sparing normal cells	394
<i>Sphingolipids</i>	394

<i>Hyperbaric oxygen as adjunct to radiotherapy</i>	395
<i>Targeting response to transformation-induced oxidative stress</i>	395
<i>Targeting enzymes to prevent proliferation of cancer cells</i>	395
Tissue systems biology approach to personalized management of cancer.....	396
Role of oncoproteomics in personalized therapy of cancer	396
Cancer tissue proteomics	396
Proteomics technologies to guide targeted drug selection for cancer	396
<i>LC-MS/MS proteomics as a companion diagnostic</i>	397
<i>Personalized cancer therapy based on targeted proteomics</i>	398
Role of metabolomics in personalized therapy of cancer	399
Role of sequencing in personalized therapy of cancer	400
Pharmacogenomic-based chemotherapy	401
Whole genome technology to predict drug resistance	401
Anticancer drug selection based on molecular characteristics of tumor.....	401
Testing microsatellite-instability for response to chemotherapy.....	401
Pharmacogenetics of cancer chemotherapy	402
CYP 1A2	403
Thiopurine methyltransferase	403
Dihydropyrimidine dehydrogenase	403
UGT1A1 test as guide to irinotecan therapy.....	404
Role of computational models in personalized anticancer therapy	404
A computational model of kinetically tailored treatment	404
Mathematical modeling of tumor microenvironments.....	405
Modeling signaling pathways to reposition anticancer drugs	405
Therapy resistance in cancer	406
Mechanism of therapy resistance in cancer.....	406
<i>Cancer stem cells and radioresistance</i>	406
<i>Expression of P-glycoprotein gene by tumor</i>	407
<i>Overexpression of multidrug resistance gene</i>	407
<i>P53 mutations</i>	407
<i>Role of splice variants in resistance to cancer therapy</i>	407
Detection of drug resistance.....	408
<i>Anaplastic lymphoma kinase</i>	408
<i>CRISPR for studying mechanism of drug-resistance in cancer</i>	408
<i>Metabolic profiling of cancer</i>	408
Management of drug resistance in cancer	409
<i>Chemogenomic approach to drug resistance</i>	409
<i>Determination of chemotherapy response by topoisomerase levels</i>	409
<i>Management of drug resistance in leukemia</i>	409
<i>Patient-derived xenograft mouse models in drug resistant cancer</i>	410
<i>Resistance to vaccines in cancer recurrence after surgery</i>	411
<i>Systems biology approach to drug-resistant cancer</i>	411
Personalized therapy of cancer metastases	411
Technologies for analysis of CTCs.....	411
<i>Microfluidic technologies</i>	412
<i>BEAMing technology for analysis of circulating tumor DNA</i>	412
<i>Technologies for detection of interplay of environments and CTCs</i>	413
Systemic antitumor effect of localized radiotherapy for cancer metastases	413
Diagnosis of cancer of an unknown primary.....	414
Personalized management of cancers of various organs/systems	414
Personalized management of bladder tumors	414
Personalized management of brain tumors	415
<i>Aptamers for selective targeting of tumor initiating cells in GBM</i>	415
<i>Bioinformatic approach to personalizing treatment of GBM</i>	415
<i>Biosimulation approach to personalizing treatment of brain cancer</i>	416
<i>Brain cancer chip for personalized drug screening</i>	416
<i>Combination of gene therapy and CAR-T cell therapy for GBM</i>	416
<i>Drug resistance in GBM</i>	417
<i>Genetics and genomics of GBM</i>	417
<i>Genomic analysis as a guide to personalized therapy of GBM</i>	419
<i>Induced neural stem cells for personalized therapy of GBM</i>	419
<i>Molecular diagnostics for personalized management of GBM</i>	419
<i>Personalized vaccine for GBM</i>	422
<i>Personalized chemotherapy of GBM</i>	422
<i>Personalized therapy of oligodendroglial tumors</i>	423
<i>Personalized therapy of neuroblastomas</i>	424
<i>Personalized therapy of medulloblastomas</i>	425
<i>Personalized management of germ cell brain tumors</i>	425
<i>Personalized management of meningiomas</i>	425
<i>Supratentorial hemispheric diffuse low-grade gliomas</i>	426
<i>Targeted therapy of BRAF V600E mutant papillary craniopharyngioma</i>	426

<i>Future prospects of personalized therapy of malignant brain tumors</i>	426
Personalized management of breast cancer	427
<i>Biomarker-guided decisions for breast cancer therapy</i>	427
<i>Developing personalized drugs for breast cancer</i>	427
<i>Gene expression plus conventional predictors of breast cancer</i>	428
<i>Her2 testing in breast cancer as a guide to treatment</i>	429
<i>HER2/neu-derived peptide vaccine for breast cancer</i>	431
<i>Prediction of cell signaling pathways from gene expression patterns</i>	431
<i>Trends in treatment patterns and outcomes for DCIS</i>	431
<i>Molecular diagnostics in breast cancer</i>	432
<i>Molecular classification of infiltrating breast cancer</i>	434
<i>Monitoring of circulating tumor cells in breast cancer</i>	435
<i>Pharmacogenetics of breast cancer</i>	436
<i>Proteomics-based personalized management of breast cancer</i>	436
<i>Predicting response to chemotherapy in breast cancer</i>	436
<i>Adjuvant endocrine therapy in premenopausal breast cancer</i>	440
<i>Prediction of resistance to chemotherapy in breast cancer</i>	440
<i>Prediction of adverse reaction to radiotherapy in breast cancer</i>	441
<i>Prediction of recurrence in breast cancer for personalizing therapy</i>	441
<i>Prognostic tests for breast cancer</i>	442
<i>Racial factors in the management of breast cancer</i>	445
<i>RATHER consortium to study personalized approach to breast cancer</i>	445
<i>Ribociclib as first-line therapy for HR-positive breast cancer</i>	446
<i>TAILORx (Trial Assigning Individualized Options for Treatment)</i>	446
<i>Tamoxin therapy for ER-positive breast cancer</i>	446
<i>Triple negative breast cancer</i>	447
<i>Treatment resistance in hormone receptor-positive breast cancer</i>	448
<i>Current trends and future of breast cancer research</i>	448
<i>Understanding tumor diversity in mouse mammary cancer model</i>	449
Personalized management of ovarian cancer	450
<i>Early diagnosis of ovarian cancer</i>	450
<i>Determining response to chemotherapy in ovarian cancer</i>	450
<i>Prognosis of ovarian cancer based on CLOVAR</i>	451
<i>Recurrent and drug-resistant ovarian cancer</i>	452
<i>Pathway targeted therapies for ovarian cancer</i>	453
<i>Repurposing auranofin for treatment of ovarian cancer</i>	454
<i>Subtype-specific therapies for epithelial ovarian cancer</i>	454
<i>Targeting hematogenous metastasis of ovarian cancer</i>	455
<i>Vynfinit® for platinum-resistant ovarian cancer</i>	455
Personalized management of head and neck cancer	455
<i>Molecular characterization of head and neck cancer using omics</i>	455
<i>Relevance of biomarkers of HPV-related head and neck cancer</i>	456
<i>Molecular targeted therapies for HNSCC</i>	456
Personalized management of hematological malignancies	457
<i>B cell malignancies</i>	457
<i>Personalized management of acute lymphoblastic leukemia</i>	458
<i>Personalized management of chronic lymphocytic leukemia</i>	459
<i>Personalized management of acute myeloid leukemia</i>	461
<i>Personalized management of chronic myeloid leukemia</i>	463
<i>Personalized management of multiple myeloma</i>	463
<i>Personalized management of myelodysplastic syndrome</i>	465
<i>Personalized management B cell lymphomas</i>	466
<i>Personalized vaccine for follicular lymphoma</i>	466
<i>Pharmacoproteomics approach to diffuse large B cell lymphoma</i>	467
<i>Companion diagnostic for treatment of lymphoma with Adcentris™</i>	467
Personalized management of gastrointestinal tumors	467
<i>Personalized management of esophageal cancer</i>	467
<i>Personalized management of gastric cancer</i>	468
<i>Personalized management of gastrointestinal stromal tumors</i>	469
Personalized management of colorectal cancer	469
<i>Developing personalized therapies for CRC</i>	470
<i>Molecular diagnosis for guiding personalized management of CRC</i>	470
<i>Role of staging of CRC in prognosis and management decisions</i>	471
<i>Role of biomarkers in personalized management of CRC</i>	472
<i>Role of miRNA modeling in personalized management of CRC</i>	474
<i>Resistance to targeted EGFR blockade in CRC</i>	474
<i>Sequencing for personalized management of colorectal cancer</i>	475
<i>Systems biology approach to drug resistance in colorectal cancer</i>	476
Personalized management of liver cancer.....	476
<i>Prognosis of HCC in relation to management</i>	476
<i>Prediction of recurrence of hepatocellular carcinoma</i>	477

<i>Prediction of survival of patients with fibrolamellar HCC</i>	477
Personalized management of lung cancer.....	478
<i>ALK inhibitors for personalized management of NSCLC</i>	478
<i>Bronchial genomic classifier for diagnostic of lung cancer</i>	479
<i>Companion diagnosis for NSCLC therapeutics</i>	479
<i>Copy number variations as a diagnostic tool for lung cancer</i>	479
<i>EGFR tyrosine kinase inhibitor treatment</i>	480
<i>Development of resistance to EGFR inhibitors</i>	481
<i>Molecular subtyping of lung cancer</i>	482
<i>miRNA classifiers as diagnostic/prognostic tools in lung cancer</i>	482
<i>Personalized therapy of NSCLC based on KIF5B/RET fusion oncogene</i>	483
<i>Predicting response of NSCLC to platinum-based therapy</i>	483
<i>Predicting recurrence of lung cancer for prevention</i>	483
<i>Proteomics for discovery of metabolic biomarkers of lung cancer</i>	483
<i>Role of a new classification system in the management of lung cancer</i>	484
<i>Selecting therapy of cancer arising from respiratory papillomatosis</i>	484
<i>Sequencing the genomes of SCLC</i>	484
<i>Testing for response to chemotherapy in lung cancer</i>	485
<i>Testing for prognosis of lung cancer</i>	485
<i>Testing for recurrence of lung cancer</i>	486
Personalized management of malignant melanoma	486
<i>Inhibitors of BRAF mutation for metastatic melanoma</i>	487
<i>Management of drug-resistant metastatic melanoma</i>	488
<i>Vaccine for malignant melanoma based on heat shock protein</i>	488
Personalized management of endocrine tumors	488
<i>Adosterone producing tumors</i>	488
<i>Neuroendocrine tumors</i>	488
<i>Parathyroid tumors</i>	489
<i>Personalized management of pheochromocytoma and paraganglioma</i>	490
Personalized management of osteosarcoma	490
Personalized management of pancreatic cancer	491
<i>Biomarkers of pancreatic cancer</i>	492
<i>Histone modifications predict treatment response in pancreatic cancer</i>	492
<i>Transport properties of pancreatic cancer and gemcitabine delivery</i>	492
Personalized management of prostate cancer.....	493
<i>Assessing susceptibility to prostate cancer by genotyping</i>	493
<i>Diagnostics for guiding therapy of prostate cancer</i>	494
<i>Detection of prostate cancer metastases</i>	494
<i>Early detection of cancer recurrence and guiding treatment</i>	495
<i>Effects of of lifestyle changes shown by gene expression studies</i>	495
<i>Epigenetics-based assays for guiding decision to biopsy prostate</i>	496
<i>Genomic patterns of aggressiveness of prostate cancer</i>	496
<i>Personalized peptide vaccine for prostate cancer</i>	496
<i>Selection of prostate cancer patients responsive to rucaparib therapy</i>	497
Personalized management of thyroid cancer.....	497
Future of cancer therapy	497
Challenges for developing personalized cancer therapies.....	498
Personalizing anticancer drug combinations.....	498
Cancer Genome Atlas	499
Cancer Moonshot	499
<i>Blood Profiling Atlas</i>	499
<i>NCI collaborations</i>	500
COLTHERES consortium.....	500
Computer and imaging technologies for personalizing cancer treatment.....	501
Genomic Cancer Care Alliance	501
Integrated genome-wide analysis of cancer for personalized therapy	501
International Cancer Genome Consortium	502
National Cancer Institute of US.....	503
<i>Catalog of cancer genes for personalized therapy</i>	503
<i>NCI-designated Comprehensive Cancer Centers</i>	504
<i>Role of NCI Genomic Data Commons in personalized cancer therapy</i>	504
Precision Oncology Decision Support at MD Anderson Cancer Center	506
PREDICT Consortium	507
Quebec Clinical Research Organization in Cancer	507
The San Antonio 1000 Cancer Genomes Project.....	507
Companies involved in developing personalized oncology	507
11. Development of Personalized Medicine	511
Introduction	511
Non-genomic factors in the development of personalized medicine	511
Personalized medicine based on circadian rhythms.....	511

Cytomics as a basis for personalized medicine	513
Intestinal microflora	513
<i>Gut microbiome compared to human genome</i>	513
<i>Metabolic interactions of the host and the intestinal microflora</i>	514
Role of drug delivery in personalized medicine.....	514
Personalized approach to clinical trials	514
<i>Adaptive clinical trials</i>	515
<i>Bayesian approach in biomarker-based clinical trials</i>	516
<i>Clinical trials of therapeutics and companion diagnostics</i>	517
<i>Clinical trials on selected subpopulations of patients</i>	517
<i>Clinical trials networks</i>	517
<i>Creative clinical trial design</i>	518
<i>Individualizing risks and benefits in clinical trials</i>	518
Players in the development of personalized medicine.....	519
Personalized Medicine Coalition.....	519
Role of pharmaceutical industry	520
<i>Repositioning of drugs for personalized medicine</i>	521
<i>Discovery of personalized medicines</i>	521
<i>Personalized drug delivery</i>	522
<i>Production and distribution of personalized medicines</i>	522
Role of biotechnology companies	523
Role of life sciences industries	523
Role of biomedical engineering in wearable devices for personalized healthcare	523
Role of molecular imaging in personalized medicine	524
<i>Molecular imaging for personalized drug development in oncology</i>	524
<i>Molecular imaging and CNS drug development</i>	526
<i>Companies involved in molecular imaging</i>	527
Role of the clinical laboratories	527
Role of the US government in personalized medicine.....	528
<i>Precision Medicine Initiative</i>	529
<i>Department of Health and Human Services and personalized medicine</i>	531
<i>Agency for Healthcare Research and Quality</i>	532
<i>Comparative effectiveness research</i>	532
Role of the US Government agencies in personalized medicine	534
<i>NIH's Roadmap Initiative for Medical Research</i>	534
<i>NIH and personalized medicine</i>	534
<i>NIH collaboration with the FDA</i>	535
<i>NIH and Genetic Testing Registry</i>	535
<i>National Human Genome Research Institute</i>	535
<i>National Institute of General Medical Sciences</i>	536
<i>National Institute of Standards and Technology</i>	538
<i>Role of the Centers for Disease Control</i>	538
Role of academic institutions and health centers in the US	538
<i>Baylor College of Medicine</i>	539
<i>California Initiative to Advance Precision Medicine</i>	539
<i>Children's Hospital of Los Angeles</i>	539
<i>Clinical Proteomics Program of NCI & FDA</i>	540
<i>Coriell Personalized Medicine Collaborative™</i>	540
<i>Delaware Valley Personalized Medicine Project</i>	540
<i>Duke University Medical Center and genomic medicine</i>	541
<i>Evaluation of genetic tests and genomic applications</i>	541
<i>Indiana University Institute for Personalized Medicine</i>	542
<i>Inova Center for Personalized Health</i>	543
<i>Institute of Medicine's role in personalized medicine</i>	543
<i>Jackson Laboratory for Genomic Medicine</i>	543
<i>Johns Hopkins Center for Personalized Cancer Medicine Research</i>	544
<i>Mayo Clinic's Centers for Individualized Medicine</i>	544
<i>Mt. Sinai Medical Center's Personalized Medicine Research Program</i>	545
<i>North Shore University's Center for Personalized Medicine</i>	545
<i>P4 Medicine Institute</i>	546
<i>Personalized Medicine Partnership of Florida</i>	546
<i>Personalized oncology at Massachusetts General Hospital</i>	546
<i>Personalized oncology at Oregon Health & Science University</i>	547
<i>Pharmacogenetics Research Network and Knowledge Base</i>	547
<i>Southeast Nebraska Cancer Center's Personalized Medicine Network</i>	547
<i>Spectrum Health Center for personalized cancer care</i>	548
<i>Stanford Center for Genomics and Personalized Medicine</i>	548
<i>UAB-HudsonAlpha Center for Genomic Medicine</i>	548
<i>University of Colorado's Center for Personalized Medicine</i>	549
<i>UNC Institute for Pharmacogenomics and Individualized Therapy</i>	549
<i>Weill Cornell's Englander Institute for Precision Medicine</i>	549

<i>Wisconsin Genomics Initiative</i>	550
Role of academic collaborations with companies	550
<i>New York Genome Center</i>	550
Role of healthcare organizations	551
Role of the medical profession	551
<i>The American Medical Association and personalized medicine</i>	551
<i>Education of the physicians</i>	551
<i>Off-label prescribing and personalized medicine</i>	552
<i>Medical education</i>	552
Role of patients	553
<i>Monitoring of patient compliance with therapy</i>	553
<i>Public attitude towards personalized medicine</i>	553
<i>Patient participation in disease management decisions</i>	554
<i>Patient engagement in clinical trials of personalized medicine</i>	555
Role of genetic banking systems and databases	555
Role of biobanks in development of personalized medicine	555
UK Biobank	556
Biobanking and development of personalized medicine in EU	556
<i>BBMRI-ERIC</i>	556
CARTaGENE for biobanks in Canada	557
Personalized medicine based on PhysioGenomics™ technology	557
Role of bioinformatics in development of personalized medicine	558
Artificial intelligence in personalized medicine	559
Biosensing and wearable devices for monitoring of health	559
Biosimulation techniques for developing personalized medicine	559
Digitalized medicine	560
Genomic data analysis	560
Exploration of disease-gene relationship	561
Health information management	561
Electronic health records	561
<i>Analysis of -omic and EHR data of the patient</i>	562
<i>Cost of EHR and savings on healthcare expenses in the US</i>	562
<i>EHRs and genome-wide studies</i>	562
<i>Linking patient medical records and genetic information</i>	563
<i>Management of personal genomic data</i>	563
<i>Use of EHRs for improving safety of new medicines</i>	564
<i>Use of EHRs for genetic research</i>	564
<i>Use of EHRs for personalized drug discovery and development</i>	565
Personalized prognosis of disease	565
Integration of technologies for personalized medicine	565
Global scope of personalized medicine	566
<i>Global Alliance for Genomics and Health</i>	566
Personalized medicine in Canada	566
<i>Personalized medicine at Ontario Institute for Cancer Research</i>	566
<i>Personalized Medicine Partnership for Cancer in Quebec</i>	568
<i>Quebec Center of Excellence in Personalized Medicine</i>	568
Personalized medicine in the EU	569
<i>European Personalized Medicine Diagnostics Association</i>	569
<i>UK National Health Service and medical genetics</i>	569
<i>UK's Precision Medicine Catapult</i>	570
<i>Personalized medicine in Germany</i>	570
<i>Ubiquitous Pharmacogenomics project</i>	571
Personalized medicine in Israel	571
Personalized medicine in Japan	572
Personalized medicine in the developing countries	573
<i>Personalized medicine in the Middle East</i>	573
<i>Personalized medicine in China</i>	573
Advantages of personalized medicine	574
Limitations of personalized medicine	575
Non-genomic factors in response to drugs	575
Incidental findings in genetic screening and clinical sequencing	575
Future of personalized medicine	577
Ongoing genomic projects	577
<i>Understanding the genetic basis of diseases</i>	577
<i>Personal Genome Project</i>	577
<i>Genome-wide association studies</i>	578
<i>The 1000 Genomes Project</i>	579
<i>Genomics of aging in a genetically homogeneous population</i>	580
Translational science and personalized medicine	580
<i>Translation of genomic research into genetic testing for healthcare</i>	580
<i>Long-term behavioral effects of personal genetic testing</i>	581

Personalized predictive medicine.....	581
Connected health and personalized medicine.....	582
Opportunities and challenges.....	582
<i>Comparative-effectiveness research and personalized medicine</i>	582
<i>Genetic testing and concerns about equality of healthcare</i>	583
<i>Initiative for delivery for precision medicine</i>	583
<i>IGNITE network – implementing personalized medicine in clinical care</i>	584
<i>Prospects and limitations of genetic testing</i>	584
<i>Personalized medicine and public health</i>	585
<i>Pharmacotyping</i>	586
<i>Medicine in the year 2023</i>	586
Concluding remarks about the future of personalized medicine	587
12. Ethical, Legal and Regulatory Aspects of Personalized Medicine. 589	
Introduction to ethical issues	589
Ethical issues of pharmacogenetics	589
Ethical aspects of genetic information.....	589
<i>Ethical issues of whole genome analysis</i>	589
<i>Ethical aspects of direct-to-consumer genetic services</i>	590
<i>Privacy issues in personalized medicine</i>	591
<i>Genetic Information Nondiscrimination Act in the US</i>	592
<i>UNESCO and ethical aspects of personalized medicine</i>	592
Genotype-specific clinical trials	592
Social issues in personalized medicine	593
<i>Race and personalized medicine</i>	593
Legal issues of personalized medicine	595
Gene patents and personalized medicine.....	596
Regulatory aspects	596
FDA and personalized medicine.....	597
<i>FDA oversight of NGS for personalized medicine</i>	597
FDA and molecular diagnostics in relation to personalized medicine.....	598
<i>CLSI guideline for the use of RNA controls in gene expression assays</i>	598
<i>Evaluation of companion diagnostics/therapeutic</i>	599
<i>FDA oversight of laboratory developed tests</i>	600
<i>FDA regulation of multivariate index assays</i>	601
<i>FDA guidelines for the role of IVD in personalized medicine</i>	602
<i>IVD device and drug co-development</i>	603
Regulatory aspects of pharmacogenetics.....	603
Regulation of direct-to-consumer genetic testing	604
<i>Need for regulatory oversight of DTC</i>	604
FDA and pharmacogenomics	607
<i>FDA guidance for pharmacogenomic data submissions</i>	607
<i>Joint guidelines of the FDA and EU regulators for pharmacogenomics</i>	608
<i>Pharmacogenomic/pharmacogenetic information in drug labels</i>	608
<i>FDA guidelines for pharmacogenomics-based dosing</i>	609
<i>FDA and validation of biomarkers</i>	610
FDA and predictive medicine	611
13. Commercial Aspects of Personalized Medicine 613	
Introduction	613
Perceived financial concerns.....	613
Personalized medicine and orphan drug syndrome	613
Commercial aspects of pharmacogenomics	613
Cost of DNA testing	613
Cost of sequencing the human genome	614
Cost of genotyping	616
Cost of pharmacogenomics-based clinical trials.....	617
Business development of pharmacogenomic companies	617
Cost of personalized healthcare	617
The rising healthcare costs in the US.....	617
<i>Genetic testing and cost of healthcare</i>	618
Reducing healthcare costs by combining diagnostics with therapeutics	618
<i>Cost-effectiveness of pharmacogenetic testing</i>	619
<i>Cost-effectiveness of CYP genotyping-based pharmacotherapy</i>	620
<i>Cost effectiveness of HIV genotyping in treatment of AIDS</i>	620
<i>Cost-effectiveness of warfarin pharmacogenomics</i>	621
<i>Cost-benefit analysis of KRAS and BRAF screening in CRC</i>	621
<i>Lowering the high costs of cancer chemotherapy</i>	621
Overall impact of personalized medicine on healthcare	622
Drivers for the development of personalized medicine	622
Evolution of medicine as a driver for personalized therapy markets	622

Collaboration between the industry and the academia	623
Personalized medicine and drug markets	624
Segmentation of therapeutic drug markets.....	624
Reasons for increase of market values of personalized medicines.....	624
Growth of markets relevant to personalized medicine.....	625
<i>Biochips for diagnosis</i>	625
<i>Pharmacogenetics</i>	625
<i>Pharmacogenomics</i>	626
<i>Pharmacoproteomics</i>	626
<i>Point-of-Care</i>	626
<i>SNP market</i>	626
Markets for personalized medicines according to therapeutic areas	626
<i>Market for personalized cancer therapy</i>	627
Markets for personalized medicines according to geographical regions.....	627
Market opportunities for personalization of medicine	627
Impact of personalized medicine on other industries.....	628
Strategies for developing and marketing personalized medicine.....	629
<i>Education of the public</i>	629
<i>Role of the Internet in development of personalized medicine</i>	630
<i>Marketing companion diagnostics for personalized medicine</i>	630
14. References.....	633

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	52
Table 2-1: Molecular diagnostic technologies used for personalized medicine	56
Table 2-2: Applications of biochip technology relevant to personalized medicine.....	77
Table 2-3: Companies developing haplotyping technology	92
Table 2-4: Technologies for SNP analysis.....	92
Table 2-5: A sampling of companies involved in technologies for SNP genotyping	98
Table 2-6: Comparison of proteomic and genomic approaches in personalized medicine	104
Table 2-7: Selected methods for gene expression profiling.....	109
Table 2-8: A selection of companies with gene expression technologies	115
Table 2-9: Drugs requiring biomarker/companion diagnostic information in the label	117
Table 2-10: Companies involved in companion diagnostics.....	118
Table 2-11: Applications of point-of-care diagnosis	120
Table 2-12: Companies developing point-of-care diagnostic tests	121
Table 2-13: Companies offering genetic screening tests directly to consumers	125
Table 3-1: Pharmacogenetic vs. pharmacogenomic studies	132
Table 3-2: Enzymes relevant to drug metabolism	134
Table 3-3: Examples of mutation of the enzyme CYP450	135
Table 3-4: Frequency distribution of drugs metabolized by major isoforms of CYP450.	135
Table 3-5: Commonly prescribed medications, which are metabolized by CYP2D6.....	135
Table 3-6: Polymorphisms in drug target genes that can influence drug response.....	141
Table 3-7: Effect of genetic polymorphisms on disease response to drugs.....	142
Table 3-8: Examples of genetically determined adverse reactions to drugs	145
Table 3-9: Examples of genotyping and phenotyping in some diseases.....	153
Table 3-10: Companies with novel molecular toxicology technology.....	156
Table 3-11: Pharmacogenomic biomarkers in drug labeling	159
Table 4-1: Role of pharmacogenomics in variable therapy targets.....	167
Table 4-2: Role of pharmacogenomics in clinical trials	170
Table 4-3: Examples of pharmacogenomics-based clinical studies.....	171
Table 4-4: Tumor suppressor genes, their chromosomal location, function and associated tumors.	174
Table 4-5: Gene polymorphisms relevant to cardiovascular disease management	175
Table 4-6: Companies involved in cardiovascular genomics.....	177
Table 4-7: SNPs in genes implicated in response of bipolar disorder to lithium.....	179
Table 4-8: A sampling of companies involved in neuropharmacogenomics	180
Table 5-1: Applications of pharmacoproteomic biomarkers in personalized medicine	188
Table 8-1: Companies involved in personalized nutrition.....	209
Table 9-1: Important therapeutic areas for personalized medicine	212
Table 9-2: Enzymes that metabolize antipsychotics.....	228
Table 9-3: Enzymes that metabolize antidepressants	229
Table 9-4: Biomarkers of response to antidepressant treatment	230
Table 9-5: Brain imaging for diagnosis of neurodegenerative parkinsonism	236
Table 9-6: Biomarkers of epilepsy.....	240

Table 9-7: Influence of gene polymorphisms on efficacy of antiepileptic drugs.....	244
Table 9-8: Biomarkers of stroke	250
Table 9-9: Role of cell therapy in management of stroke according to stage.....	254
Table 9-10: Gene expression as biomarker of response to IFN- β in multiple sclerosis.....	258
Table 9-11: Biomarkers of traumatic brain injury	260
Table 9-12: P450 isoforms in the metabolism of drugs used in the management of pain.....	264
Table 9-13: Personalized management of neuropathic pain based on mechanism	268
Table 9-14: Genes that cause cardiovascular diseases.....	270
Table 9-15: Classification of diabetes into 5 clusters	317
Table 9-16: Genetic influences on pharmacotherapy of alcoholism	327
Table 10-1: Factors that drive the development of personalized therapy in cancer	338
Table 10-2: Impact of molecular diagnostics on the management of cancer	344
Table 10-3: FDA-approved companion diagnostics for cancer	347
Table 10-4: Marketed anticancer personalized medicines	371
Table 10-5: Monoclonal antibodies for cancer approved by the FDA	372
Table 10-6: Clinical trials of personalized cancer vaccines.....	388
Table 10-7: Future developments in oncology relevant to personalized management	497
Table 10-8: Selected companies involved in developing personalized oncology	507
Table 11-1: Bayesian versus frequentist approaches in clinical trials	516
Table 11-2: Players in the development of personalized medicine	519
Table 11-3: Members of the Personalized Medicine Coalition	519
Table 11-4: Biobanks relevant to personalized medicine	556
Table 11-5: Role of bioinformatics in the development of personalized medicine.....	558
Table 11-6: Advantages of personalized medicine for the biopharmaceutical industry.....	574
Table 11-7: Advantages of personalized medicine for the patients	574
Table 11-8: Advantage of personalized medicine for the physicians.....	574
Table 11-9: Advantage of personalized medicine for the healthcare providers	575
Table 11-10: Limitations of personalized medicine	575
Table 11-11: Recommendations of the Association for Molecular Pathology on incidental findings	576
Table 11-12: Methods of translational science that are relevant to personalized medicine.....	580
Table 11-13: Companies involved in predictive healthcare	582
Table 11-14: Delivery for precision medicine	583
Table 12-1: Drugs with genetic information in their labels.....	609
Table 13-1: Drivers for the development of personalized medicine	622
Table 13-2: Growth of markets relevant to personalized medicine 2017-2027	625
Table 13-3: Markets for personalized medicine according to therapeutic area 2017-2027.....	626
Table 13-4: Markets for personalized medicine in major regions 2017-2027.....	627
Table 13-5: Lack of efficacy in current therapy	628
Table 13-6: Impact of personalized medicine on other industries	628
Table 13-7: Strategies to develop personalized medicine	629
Table 13-8: Role of the Internet in development of personalized medicine	630

Figures

Figure 1-1: Relation of personalized medicine to other technologies.....	44
Figure 1-2: Relation of systems pharmacology to personalized medicine.....	51
Figure 2-1: Role of sequencing in personalized medicine.....	74
Figure 2-2: Role of biochip/microarray technology in personalized medicine	77
Figure 2-3: Application of biochips/microarrays in personalized therapy.....	78
Figure 2-4: Affymetrix GeneChip technology	79
Figure 2-5: Role of CYP450 genotyping in development of personalized medicine	80
Figure 2-6: Role of SNPs in personalized medicine	88
Figure 2-7: A scheme of integrated healthcare and personalized medicine	126
Figure 3-1: Pharmacogenetics as a link between genotype and phenotype.....	131
Figure 3-2: Role of pharmacogenetic technologies in personalized medicine	132
Figure 4-1: Impact of new technologies at various stages of the drug discovery process.....	169
Figure 4-2: Steps in the application of pharmacogenomics in clinical trials	171
Figure 7-1: Role RNAi in development of personalized medicine.....	201
Figure 8-1: A scheme of various factors in personalized nutrition.....	204
Figure 9-1: Workflow of genotypic resistance analysis for personalized HIV therapy	219
Figure 9-2: Components of multimodal therapy for neurological disorders.....	234
Figure 9-3: Scheme of iPSCs use for personalized cell therapy of Parkinson disease	237
Figure 9-4: An algorithm for personalized management of epilepsy	240
Figure 9-5: Algorithm for anticoagulant therapy to prevent stroke in atrial fibrillation.....	252
Figure 9-6: Spot sign of extravasation and expansion of intracerebral hematoma	253
Figure 9-7: A scheme of personalized therapy of multiple sclerosis	256
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	292
Figure 9-15: Basis of personalized approach to idiopathic pulmonary fibrosis (IPF)	307
Figure 9-16: Steps in growing a new heart in vitro for transplantation	323
Figure 10-1: Relationships of technologies for personalized management of cancer.....	344
Figure 10-2: Integration of technologies for personalized prevention of cancer	358
Figure 10-3: CRISPR-Cas9 in personalized cancer gene therapy	393
Figure 10-4: Use of LC-MS/MS to select appropriate targeted therapy for cancer	398
Figure 10-5: Personalized cancer therapy based on targeted proteomics.....	399
Figure 10-6: Applications of NCI Genomic Data Commons	505
Figure 10-7: Workflow for development of gene pages for personalized cancer therapy	506
Figure 11-1: Integration of technologies for the development of personalized medicine	565
Figure 12-1: Strategy for drug and test co-development.....	603
Figure 13-1: Cost of sequencing per genome	616
Figure 13-2: Evolution of personalized medicine as a market driver	623