Chapter 9
Development of Personalized Medicine

Introduction

In conventional medical practice, physicians rely on their personal experience in treating patients. In spite of advances in basic medical sciences and the introduction of new technologies, physicians continue to rely on their judgment and sometimes intuition because the practice of medicine is an art as well as a science.

Physicians of the last generation had limited access to information. With advances in molecular biology and its impact on medicine, a tremendous amount of new basic information has been generated, particularly in genomics and gene expression. Digitalization of information has made it accessible. The problem now is a flood of information, which requires strategies to sort out the relevant from the irrelevant. Information on a large number of studies with stratification of a large number of patients will have to be analyzed to make decisions about treatment for an individual. The massive amount of publications needs to be sorted out and analyzed for its relevance to individualized treatment.

The development of personalized therapy requires the integration of various segments of clinical medicine, pharmacology and biotechnology. Genotyping is an important part of such a system. Various technologies for genotyping have been described in the following chapter and their advantages as well as limitations have been pointed out. The vast majority of relevant gene variants are rare, making it difficult to demonstrate utility – in particular for the much more frequent heterozygous carriers who have only one affected allele. Moreover, multiple factors play a role such that genetic data represent only a portion of the information needed for effective therapeutic decisions. Therapeutic areas in which personalized medicine is expected to play an important role are listed in Table 9.1.

K.K. Jain, *Textbook of Personalized Medicine*,
DOI 10.1007/978-1-4419-0769-1_9, © Springer Science+Business Media, LLC 2009

Table 9.1 Important therapeutic areas for personalized medicine

Cancer
Cardiovascular disorders
Congestive heart failure
Hyperlipidemia
Hypertension
Inflammatory disorders
Asthma
Inflammatory bowel disease
Rheumatoid arthritis
Neurological disorders
Alzheimer's disease
Epilepsy
Parkinson's disease
Pain management
Psychiatric disorders
Schizophrenia
Depression
Viral infections
Hepatitis C virus
HIV
Miscellaneous Disorders
Hormone replacement therapy
Organ transplants
Renal disorders
Smoking cessation
Trauma and burns

Non-genomic Factors in the Development of Personalized Medicine

Although personalized medicine is supposed to be based mostly on pharmacogenomics, a number of other factors that vary among individuals are taken into consideration. Metabolomics was described in Chapter 7. Other factors are discussed briefly in this chapter.

Personalized Medicine Based on Circadian Rhythms

Diverse physiological and metabolic processes exhibit circadian rhythms, which are endogenous self-sustained oscillations within a period of ~24 h. They are coordinated by a biological clock situated in the suprachiasmatic nuclei of the hypothalamus. These rhythms persist under constant environmental conditions,

demonstrating their endogenous nature. Some rhythms can be altered by disease. Several clock genes and clock-controlled transcription factors regulate, at least in part, gene expression in central and/or peripheral clocks.

The rhythms of disease and pharmacology can be taken into account to modulate treatment over the 24 h period, and is known as chronotherapy. The term "chronopharmacology" is applied to variations in the effect of drugs according to the time of their administration during the day. "Chronopharmacokinetics" is defined as the predictable changes observed in the plasma levels of drugs and in the parameters used to characterize the pharmacokinetics of a drug. The half-life of a drug can vary as a function of the hour of administration.

The efficacy and toxicity of drugs depend on an individual's body time (BT). Drug administration at the appropriate BT can improve the outcome of pharmacotherapy by maximizing potency and minimizing the toxicity of the drug, whereas drug administration at an inappropriate BT can induce severe side effects. Information obtained by detection of individual BT via a single-time-point assay can be exploited to maximize potency and minimize toxicity during drug administration and thus will enable highly optimized medication. Genome-wide gene expression analyses using high-density DNA microarrays have identified clock-controlled genes. BT based on expression profiles of time-indicating genes reflects the endogenous state of the circadian clock. In clinical situations, methods for BT detection should be applicable for populations with heterogeneous genetic backgrounds.

A "molecular timetable" has been composed consisting of >100 "time-indicating genes," whose gene expression levels can represent internal BT (Ueda et al. 2004). The power of this method was demonstrated by the sensitive and accurate detection of BT and the sensitive diagnosis of rhythm disorders. These results demonstrate the feasibility of BT detection based on single-time-point sampling, suggest the potential for expression-based diagnosis of rhythm disorders, and may translate functional genomics into chronotherapy and personalized medicine.

Intestinal Microflora

Gut Microbiome Compared to Human Genome

The human intestinal microflora is composed of 10^{13} to 10^{14} microorganisms whose collective genome (microbiome) contains at least 100 times as many genes as the human genome. A study has analyzed approximately 78 million base pairs of unique DNA sequence and 2,062 PCR-amplified 16 S ribosomal DNA sequences obtained from the fecal DNAs of two healthy adults, one male and one female, who had not received any antibiotic in the past (Gill et al. 2006). Using metabolic function analyses of identified genes, the human genome was compared with the average content of previously sequenced microbial genomes. The gut microbiome has significantly enriched metabolism of glycans, amino acids, and xenobiotics; methanogenesis; and 2-methyl-d-erythritol 4-phosphate pathway-mediated biosynthesis

of vitamins and isoprenoids. This study concludes that humans are superorganisms whose metabolism represents an amalgamation of microbial and human attributes. Without understanding the interactions between human and microbial genomes, it is impossible to obtain a complete picture of human biology. The next frontier in the field of genetic research is called metagenomics. This has implications for clinical diagnosis and the treatment of many human diseases. With the knowledge gained in this area, one can use biomarkers to identify the bacterial population of the individual. Physicians can then manipulate the population of bacteria to be consistent with the optimal health of an individual. Such an analysis would also identify bacteria that are resistant to certain antibiotics, and enable the selection of the appropriate antibiotic for a patient. In the future, healthy individuals could undergo a metagenomic analysis of their gut to determine their immune status and susceptibility to certain diseases. Such an analysis may enable the assessment of the effects of age, diet and diseases such as inflammatory bowel disease, cancer and obesity on the microbial flora of the distal gut in persons living in different environments with different dietary habits.

Metabolic Interactions of the Host and the Intestinal Microflora

The mammalian gut microbes interact extensively with the host through metabolic exchange and co-metabolism of substrates. They influence both the biochemistry and immune system of the host. Their interactions with the host are poorly understood, but might be implicated in the etiology of many human diseases. The gut microflora may have effects that cannot be predicted from the patient's genome alone. Currently, when developing a new drug, factors such as the microflora are not taken into consideration but this may need to change. Many species produce compounds that switch on detoxification enzymes in the liver and certain microbial metabolites are necessary players in human metabolic pathways. Because the gut microbes influence the disposition, fate and toxicity of drugs in the host, an appropriate consideration of individual human gut microbial activities will be a necessary part of future personalized health-care paradigms. Several pharmaceutical companies are developing a metabonomic technology that will identify metabolomic patterns that predict both a drug's toxicity and the biochemical pathway involved. Such data need to be integrated statistically with information from other "omics" such as proteomics and transcriptomics for a complete picture of the drug action.

Role of Drug Delivery in Personalized Medicine

Along with other technologies, refinements in drug delivery will play an important role in the development of personalized medicine. One well known example is glucose sensors regulating the release of insulin in diabetic patients. Gene therapy, as a sophisticated drug delivery method, can be regulated according to the needs of

individual patients. ChipRx Inc is developing a true "responsive therapeutic device" in which biosensors, electronic feedback and drug/countermeasure release are fully integrated.

Role of Molecular Imaging in Personalized Medicine

Technologies encompassed within molecular imaging include optical, magnetic resonance imaging (MRI) and nuclear medicine techniques. Positron emission tomography (PET) is the most sensitive and specific technique for imaging molecular pathways in vivo in humans. PET uses positron emitting radionuclides to label molecules, which can then be imaged in vivo. The inherent sensitivity and specificity of PET is the major strength of this technique. Indeed, PET can image molecular interactions and pathways, providing quantitative kinetic information down to subpicomolar levels. Generally, the isotopes used are short-lived. Once the molecule is labeled, it is injected into the patient. The positrons that are emitted from the isotopes then interact locally with negatively charged electrons and emit what is called annihilating radiation. This radiation is detected by an external ring of detectors. It is the timing and position of the detection that indicates the position of the molecule in time and space. Images can then be constructed by tomography, and regional time activities can be derived. The kinetic data produced provide information about the biological activity of the molecule. Molecular imaging provides in vivo information in contrast to the in vitro diagnostics. Moreover, it provides a direct method for the study of the effect of a drug in the human body. Personalized medicine will involve the integration of in vitro genotyping and in vivo phenotyping techniques.

Personalized Approach to Clinical Trials

Use of Bayesian Approach in Clinical Trials

The statistical method used nearly exclusively to design and monitor clinical trials today, a method called frequentist or Neyman-Pearson (for the statisticians who advocated its use), is so narrowly focused and rigorous in its requirements that it limits innovation and learning. A solution is to adopt a system called the Bayesian method, a statistical approach more in line with how science works (Berry 2006). The main difference between the Bayesian approach and the frequentist approach to clinical trials has to do with how each method deals with uncertainty, an inescapable component of any clinical trial. Unlike frequentist methods, Bayesian methods assign anything unknown a probability using information from previous experiments. In other words, Bayesian methods make use of the results of previous experiments, whereas frequentist approaches assume we have no prior results. This approach is being put to the test at M. D. Anderson Cancer Center (Houston, TX),

where more than 100 cancer-related phase I and II clinical trials are being planned or carried out using the Bayesian approach. The Bayesian approach is better for doctors, patients who participate in clinical trials and for patients who are waiting for new treatments to become available. Physicians want to be able to design trials to look at multiple potential treatment combinations and use biomarkers to determine who is responding to what medication. They would like to treat that patient optimally depending on the patient's disease characteristics. If interim results indicate that patients with a certain genetic makeup respond better to a specific treatment, it is possible to recruit more of those patients to that arm of the study without compromising the overall conclusions. The use of the Bayesian approach may make it possible to reduce the number of patients required for a trial by as much as 30%, thereby reducing the risk to patients and the cost and time required to develop therapeutic strategies.

Using the Bayesian approach, in contrast to the standard approach, the trial design exploits the results as the trial is ongoing and is adapted based on these interim results. In order to have personalized medicine, it will be necessary to be more flexible in how we evaluate potential new treatments. Moreover, it is possible to reduce the exposure of patients in trials to ineffective therapy using the Bayesian approach. Whether the Bayesian approach will gain acceptance in clinical trials depends greatly on its acceptance by the FDA in determining the safety and efficacy of new treatments. The Food and Drug Administration of USA (FDA) has already approved the drug Pravigard Pac (Bristol-Myers Squibb) for the prevention of secondary cardiac events based on data evaluated using the Bayesian approach.

Individualizing Risks and Benefits in Clinical Trials

One study has comprehensively reviewed the basic and clinical evidence that explains how drugs like rofecoxib, celecoxib, and valdecoxib confer a small, but absolute, risk of heart attack and stroke (Grosser et al. 2006). The size of this risk is likely to be conditioned by the underlying risk in a given patient of thrombosis and heart disease; the dose and duration of action of a drug; and the duration of dosing and concurrent therapies, such as low-dose aspirin. Among the questions that remain to be addressed are the following: (a) whether this hazard extends to all or some of the traditional non-steroidal antiinflammatory drugs (NSAIDs); (b) whether adjuvant therapies, such as low-dose aspirin, will mitigate the hazard and if so, at what cost; (c) whether cyclooxygenase-2 (COX-2) inhibitors result in cardiovascular risk transformation during chronic dosing; and (d) how we might identify individuals most likely to benefit or suffer from such drugs in the future. Lessons are drawn from the experience of the COX-2 inhibitors, particularly the need to develop a more interdisciplinary approach to drug development and monitoring of drug safety and how an emphasis on individualizing benefit and risk can be used to refine the design of clinical trials.

Another study builds on the theme of individualized therapy, demonstrating a marked variation in individual response to COX-2 inhibitors, as measured by plasma

drug levels and the degree of COX-2 inhibition within an individual (Fries et al. 2006). The researchers found a marked degree of variability in individuals dosed with either rofecoxib or celecoxib, even when they studied apparently healthy, relatively young individuals in a carefully controlled environment. This rigorous study suggests that approximately 30% of the variability found in patients is attributable to differences between individuals, suggesting the contribution of genetics to a variety of biomarkers of drug response. Exploitation of variability in response can lead to tests which identify patients most likely to benefit or suffer from drugs. This study provides a starting point for the development of diagnostics that will enable the conservation of benefit while managing the risk of COX-2 inhibitors.

Clinical Trials of Therapeutics and Companion Diagnostics

Clinical trial designs and adaptive analysis plans for the prospective design of pivotal trials of new therapeutics and companion diagnostics require a careful analysis strategy (Simon 2008). The target populations for analysis should be prospectively specified based on the companion diagnostic. Clear separation is generally required of the data used for developing the diagnostic test, including the threshold of positivity, from the data used for evaluating treatment effectiveness in subsets determined by the test. Adaptive analysis can be used to provide flexibility to the analysis but the use of such methods requires careful planning and prospective definition in order to assure that the pivotal trial adequately limits the chance of erroneous conclusions.

Role of Genetic Banking Systems and Databases

Genetic databases will be an important source of information for the development of personalized medicine. Most of these are covered under the term “biobanks”.

Role of Biobanks in the Development of Personalized Medicine

A biobank is a collection of biological samples and associated clinical data. There are biobanks for diagnostics as well as therapeutics. With the advent of the genomic era, the traditional purpose of biobanks, such as blood banks, for the storage and distribution of blood, has not been expanded to include research into specific populations or specific diseases. These facilities are important for the development of personalized medicine. However, serious ethical issues have been raised about biobanks and considerable work will be required to resolve the concerns about privacy and consent. Some of the proposed or operational biobanks in the public, private and academic sectors are shown in Table 9.2.

Table 9.2 Biobanks relevant to personalized medicine

Name of biobank	Web site	Function
CARTaGENE (Quebec, Canada)	www.cartagene.qc.ca/	See text for details
deCODE Genetics	www.decode.com	Secure Robotized Sample Vault: for banking genetic samples of 100,000 Icelanders linked to Icelandic Health Database and genealogical records
Estonian Genome Project	www.geenivaramu.ee	Government effort to establish a national genetic/medical database of one million volunteers
Genomic Research in the African Diaspora	www.genomecenter.howard.edu	Howard University project to collect DNA and health information from 25,000 Americans of African descent
Karolinska Institute (Stockholm, Sweden)	http://ki.se/kiBiobank	Swedish academic bank collecting human biological material for molecular and genetic research
UK Biobank	www.ukbiobank.ac.uk	Government plan to collect genetic samples from 500,000 volunteers between the ages of 45 and 69
EU Biobanking	www.biobanks.eu	See text for details

UK Biobank

The UK Biobank project will be the world's biggest resource for the study of the role of nature and nurture in health and disease. The project is funded by the Medical Research Council of UK, the Wellcome Trust biomedical research charity, the Department of Health and the Scottish Executive. Up to 500,000 participants aged between 45 and 69 years will be involved in the project. They will be asked to contribute a blood sample, lifestyle details and their medical histories to create a national database of unprecedented size.

This information will create a powerful resource for biomedical researchers. It will enable them to improve their understanding of the biology of disease and develop improved diagnostic tools, prevention strategies and personalized treatments for disorders that appear in later life. UK Biobank will seek active engagement with participants, research users and society in general throughout the lifetime of the resource. Data and samples will only be used for ethically and scientifically approved research. Strong safeguards will be maintained to ensure the confidentiality of the participants' data. UK Biobank published a Science Protocol for public comment in 2005. Following ethical approval, pilot studies commenced in 2006.

Biobanking and Development of Personalized Medicine in the EU

The Biobanking and Biomolecular Research Infrastructure (BBMRI, www.biobanks.eu), which started the preparatory phase in February 2008, will pool all

the information of the major biobanks in Europe. Together these represent approximately 12 million blood, body fluid, and tissue samples. In the following 2 years, BBMRI will try to create the preconditions to make the biological materials and data available, and standardize the analyses platforms and sample preparation. The project not only includes the organization and funding of the EU biobank, but also aims to establish a complete resource for EU life scientists, including a variety of affinity binders and molecular tools, as well as a biocomputing infrastructure that will work with standardized protocols, making data generated from those materials more comparable. The BBMRI was selected for FP7 funding as one of the six EU infrastructure projects that are supposed to benefit all EU researchers. It is still awaiting the grant agreement from the European Commission.

No single biobank can be large enough to generate statistically significant data of specific disease subtypes and it takes more than a few dozen or even hundreds of cases in well-defined diseases to correlate disease history or patient response to a certain therapy and biomarkers. The 134 associated partners of the BBMRI could together provide about 2.4 million samples from population-based biobanks, and a further 10 million from disease-orientated biobanks. The project will seek to overcome the current fragmentation in biobanking, and could also become an interesting tool for the biopharmaceutical industry when validating biomarkers. The information generated from BBMRI will be useful for the development of personalized medicine.

The joint initiative, which will tie together Europe's top research groups across almost every area of molecular and cell biology, also has a political dimension. Because the protection of the data obtained from biological samples continues to be a sensitive subject, the initiative will need to conform to all the national legislations involved. For that purpose, the partners plan to establish a widely accepted and harmonized set of practices in line with the heterogeneous landscape of European and national regulations. For instance, the protocol to be added to the Convention of Human Rights, which was approved by the EU Council in 2007 and has now been sent out to member nations for ratification, states that the confidentiality of the information obtained through diagnostic, predictive and pharmacogenetic tests of the samples must be assured. The researchers will have to find procedures that assure a high degree of data protection while simultaneously allowing the use of the patient data to acquire deeper insights into the causes of disease.

CARTaGENE for Biobanks in Canada

In 2007, the Canadian government and the government of Québec announced a grant of CA$34.5 million (US $31.9 million) for a human genomics consortium. The Public Population Project in Genomics, or P3G, could receive as much as CA$64.5 million when funds from other partners are counted. The primary aim of the Montreal-based P3G consortium is to foster "collaboration

between researchers and projects in the field of population genomics." The group also includes the ongoing CARTaGENE project. One of the major projects will be the creation of a large bio-bank, which will comprise data from 20,000 residents of Québec between the ages of 40 and 69. The infrastructure will function as a precursor for the development and testing of standards for large biobanks in Canada.

Personalized Medicine Based on PhysioGenomics™ Technology

PhysioGenomics™ (Genomas Inc.) is a proprietary technology based on systems biology, which rapidly analyzes multiple genes and baseline determinants of environmental responses for an individual. This technology unravels preexisting genetic (inherited DNA variability) and physiological determinants of response to each intervention, be it exercise, diet or drug (Ruano et al. 2006).

PhysioGenomics integrates genotypic and phenotypic measures to analyze variability among individuals within a population. Genotypes and physiological or clinical phenotypes are analyzed to discover statistical associations to environmental responses in individuals similarly exposed or challenged, to exercise, diet or drugs. Variability in a genomic marker among individuals that tracks with the variability in the quantitative response establishes associations and possible mechanistic links with specific genes. PhysioGenomics integrates the engineering systems approach with molecular probes stemming from genomic markers available from industrial technologies and the Human Genome Project. The strategy of "predict response and intervene" is quite distinctive from pure gene discovery for disease diagnosis. PhysioGenomics marks the entry of genomics into systems biology. The unintended and largely poorly understood effects of exercise, diet, and drugs are multicomponent interventions suitable for PhysioGenomics and systems biology.

The gene variability, measured by single nucleotide polymorphism (SNPs), is correlated to the physiological responses of a population, or the output. PhysioGenomics technology determines how the SNP frequency varies among individuals similarly responding to the input over the entire range of the response distribution. The unintended and poorly understood mechanisms of adverse drug reaction (ADR's) involve multiple physiological pathways suitable for PhysioGenomics analysis. The medical management products derived from PhysioGenomics technology is termed "PhyzioType™ Systems" (Genomas Inc), which is PhyzioType™ is used to predict responses to diet, exercise and drug treatments, and to select the best treatment for the patient from these options. It is a novel product in healthcare for guiding treatment based on unique integration of existing modes of medical management with genetic information on treatment responses. In a fundamental way the PhyzioType™ seamlessly combines "nurture", how the patient presents in middle age with decades worth of environmental, cultural and life-style influences on his own health, with "nature", the patient's genetic constitution inherited at birth.

Role of Bioinformatics in Development of Personalized Medicine

Bioinformatics is the use of highly sophisticated computer databases to store, analyze and share biological information. This is a new discipline at the interface of computer sciences and biology. The massive amount of information generation by the Human Genome Project, the detection of SNPs, and proteomic data would require bioinformatic tools for cataloguing and analysing the information. Personalized medicine is often referred to as information-based medicine. Bioinformatics tools will integrate various technologies and sources of information to facilitate the development of personalized medicine and informed therapeutic decision-making by the physicians as shown in Table 9.3.

A large amount of information on the function and interaction of human genes has accumulated from functional genomic projects. This information is valuable with respect to molecular diagnostics. Advances in bioinformatics have helped in lowering the cost of individual genetic screening. The speed with which individuals can be screened for known genetic conditions and variations has increased. Bioinformatics has provided a large number of software tools for classifying expression profiles and reduction of dimensions of data followed by regularized

Table 9.3 Role of bioinformatics in the development of personalized medicine

Role of bioinformatics in molecular diagnostics as applied to personalized medicine
Analysis and classification of gene expression profiles
Analysis of single nucleotide polymorphisms
Computational diagnostics
Diagnosis of subtype of a disease to select the probability of success of optimal treatment
Genetic screening
Role of bioinformatics in pharmacogenomics
Genotyping for stratification of clinical trials
Selection of targets in pharmacogenomics-based drug discovery
Use of pharmacogenomic data to develop rational therapies
Role of bioinformatics in pharmacogenetics
Analyzing the role of polymorphisms in interindividual variations in drug response
Computational tools for predicting drug metabolism, toxicity and efficacy
Integration of pharmacogenetic data with clinical outcomes to facilitate diagnosis
Link pharmacogenetic data to literature on adverse reactions and drug-drug interactions
Role of bioinformatics in pharmacoproteomics
Analysis of data from protein microarrays
Measurement of protein expression
Search engines for proteomic databases
Applications in organization of personalized medicine
Personalized prognosis of disease
Linking patient-specific and knowledge-based information
Linking patient medical records and genetic information

classification. Classification can predict clinical outcome based on the chosen features. Computational diagnostics includes the identification of novel, molecularly defined entities of a disease. For many clinical decision problems where a large number of features are used to monitor a disease, neural networks and other machine-learning approaches can help to manage the situation.

The impact of having the human sequence and personalized digital images in hand has also created tremendous demands for developing powerful supercomputing, statistical learning and artificial intelligence approaches to handle the massive bioinformatics and personalized healthcare data, which will obviously have a profound effect on how biomedical research will be conducted toward the improvement of human health and prolonging of human life in the future. The International Society of Intelligent Biological Medicine (http://www.isibm.org) touches future bioinformatics and personalized medicine through current efforts in promoting the research, education and awareness of the upcoming integrated inter/multidisciplinary field (Yang et al. 2008).

Health Information Management

Bioinformatics can also help in health care information management. Personalized medicine involves linking two types of information: patient-specific and knowledge-based (Fierz 2004). Personal information is documented in patient records. Some personal medical documents, which are already in use to various extents in different countries, include the personal emergency card, the mother–child record, and the vaccination certificate. A more valuable but under-used source of personal medical information is the data stored in the electronic medical record, which needs to be used universally for facilitating the development of personalized medicine.

Electronic Health Records

Electronic health records (EHRs) are important for improving healthcare and for widening the scope of personalized medicine as they can be shared online by different doctors and hospitals. They can improve the quality and safety of patient care by reducing errors in prescriptions. In the aftermath of Hurricane Katrina in New Orleans in 2005, government and private health care officials were rushing to build an electronic database of prescription drug records for hundreds of thousands of people who lost their records in the storm. This tragic happening powerfully demonstrated the need for EHRs. Major healthcare organizations like Kaiser Permanente Group, the Mayo Clinic and many medical centers across the US are spending billions of dollars to convert to EHRs. Medicare and some employers are paying incentives to medical providers that can achieve better efficiency and patient care through improved information management. Smaller medical practices, where the majority of US patients are treated, lagged behind in adopting EHRs because of the

high initial costs involved and the need for support and training. Only 13% of US physicians have a basic EHR system and 4% report having an extensive, fully functional EHR system (DesRoches et al. 2008). Financial barriers are viewed as having the greatest effect on decisions about the adoption of EHR.

To improve this situation, the Taconic Health Information Network in New York State is introducing an affordable and practical system for computerization of patient records in small medical practices. Although many technical problems need to be resolved EHRs are touted for their ability to reduce medication errors and redundant procedures while improving diagnostic accuracy and facilitating electronic prescribing. All these lead to the reduction of healthcare costs while improving patient care. EHRs can trim costs from the US national healthcare budget for those who suffer from one or more of four or five diseases that produce 75% of healthcare costs: diabetes mellitus, asthma, congestive heart failure and coronary artery disease.

In 2007, the National Human Genome Research Institute (NHGRI) announced plans to fund the development of methods and procedures for using EHRs in genome-wide studies that rely on biorepositories. NHGRI will issue a request for applications in 2007 that will fund groups affiliated with existing biorepositories to develop methods and procedures for genome-wide studies in participants with phenotypes and environmental exposures defined by electronic medical records, with the intent of widespread sharing of the resulting individual genotype-phenotype data. The program will consider and address issues of consent and consultation connected to biorepository-based research, genome-wide technologies, and data sharing. The institute will support studies such as harmonizing phenotypes, developing data-capture methods and analytic strategies, assessing data quality and potential biases, and evaluating or improving consent or data protection processes.

Linking Patient Medical Records and Genetic Information

IBM's Genomic Messaging System (GMS) provides a basic computer language that can be inserted into DNA sequences to bridge the gap between patient medical records and genetic information (Robson and Mushlin 2004). GMS was originally developed as a tool for assembling clinical genomic records of individual and collective patients, and was then generalized to become a flexible workflow component that will link clinical records to a variety of computational biology research tools, for research and ultimately for a more personalized, focused, and preventative healthcare system. GMS is being developed at IBM R&D Labs (Haifa, Israel). Prominent among the applications linked are protein science applications, including the rapid automated modeling of patient proteins with their individual structural polymorphisms. In an initial study, GMS formed the basis of a fully automated system for modeling patient proteins with structural polymorphisms as a basis for drug selection and ultimately design on an individual patient basis.

Genetic data obtained by the use of micro arrays need to be integrated with existing medical records and then be made readily accessible to the practicing physician in a standardized format that enables information from one patient to be

readily compared to another. Affymetrix is collaborating with IBM to facilitate the integration of genomic research and patient clinical data from several databases into a centrally organized format. The combination of standard medical information with micro array genetic data will then be cross-referenced against the databases enabling genetic clinical research to be translated into clinical application. A US Department of Health and Human Services team is focused on integrating genomic data with medical records to facilitate the development of personalized medicine.

Management of Personal Genomic Data

Patient genomic data would be important for clinical decision making in a personalized medical system. The management of such sizeable, yet fine-grained, data in compliance with privacy laws and best practices presents significant security and scalability challenges. GenePING, an extension to the PING personal health record system, is the first personal health record management system to support the efficient and secure storage and sharing of large genomic datasets (Adida and Kohane 2006). The design and implementation of GenePING has been published. It supports secure storage of large, genome-sized datasets, as well as efficient sharing and retrieval of individual data points (e.g., SNPs, rare mutations, gene expression levels). Even with full access to the raw GenePING storage, it would be difficult for a hacker to access any stored genomic datapoint on any single patient. Given a large-enough number of patient records, an attacker cannot discover which data corresponds to which patient, or even the size of a given patient's record. The computational overhead of GenePING's security features is a small constant, making the system usable, even in emergency care, on today's hardware.

Personalized Prognosis of Disease

Genomic and clinical data have been combined for personalized prediction in disease outcome studies. A typical integrated clinicogenomic modeling framework is based on statistical classification tree models that evaluate the contributions of multiple forms of data, both clinical and genomic, to define interactions of multiple risk factors that associate with the clinical outcome and derive predictions customized to the individual patient level. Gene expression data from DNA microarrays is represented by multiple, summary measures termed metagenes; each metagene characterizes the dominant common expression pattern within a cluster of genes. A case study of primary breast cancer recurrence demonstrates that models using multiple metagenes, combined with traditional clinical risk factors, improve prediction accuracy at the individual patient level, delivering predictions more accurate than those made by using a single genomic predictor or clinical data alone. The analysis also highlights issues of communicating uncertainty in prediction and identifies combinations of clinical and genomic risk factors playing predictive roles. Implicated metagenes

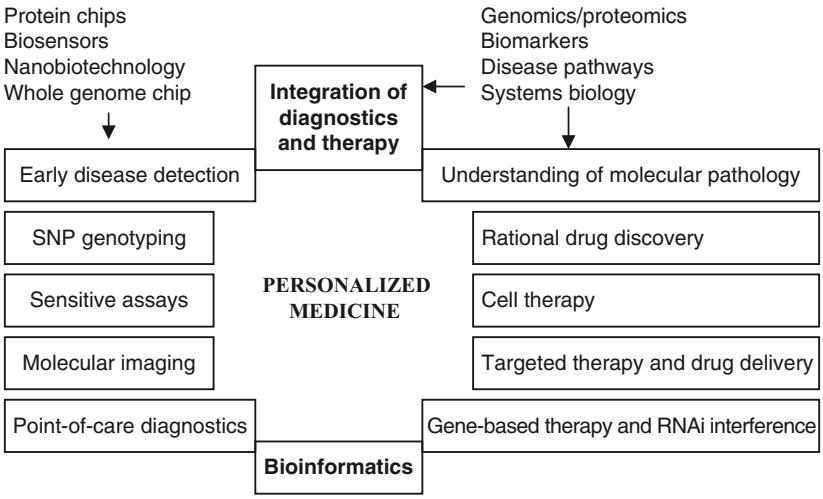

Fig. 9.1 Integration of technologies for the development of personalized medicine. © Jain Pharma-Biotech

identify gene subsets with the potential to aid biological interpretation. This framework will extend to incorporate any form of data, including emerging forms of genomic data, and facilitate development of personalized prognosis.

Integration of Technologies for Development of Personalized Medicine

The concept of personalized medicine is the best way to integrate all the cutting edge technologies for optimal application in healthcare as shown in the Fig. 9.1.

Summary

This chapter deals with various factors that influence the effect of drugs and should be taken into consideration for the development of personalized medicine. These include chronobiology and metabolic interactions of the host and the intestinal microflora. Drug delivery and molecular imaging are also important considerations. Clinical trials involving personalized therapies require special methods and statistical approaches. Other important issues concern biobanking, bioinformatics and electronic records for implementation of a personalized healthcare system. Finally integration of several technologies is an important feature for developing personalized medicine.