Chapter 18
Future of Personalized Medicine

Introduction

Based on the current progress in biotechnology and molecular medicine, considerable advances and breakthroughs are expected in the second decade of the twenty-first century. These will involve progress towards finding a cure for cancer and making it a chronic manageable disease. Many of the advances will be through application of new technologies such as nanobiotechnology and refinements of cell therapy, particularly the use of stem cells. Automation, robotics and informatics will be partially integrated into clinical medicine. Advances in regenerative medicine and tissue engineering will enable repair and regeneration of damage in CNS and cardiac disorders. The emphasis in treatment of neurological disorders will be on neuroprotection rather than control of symptoms. Management of infectious diseases will improve although unpredictable challenges may arise from emerging viral infections.

In the setting of this progress, personalized medicine will be an important part of managing patients. Advances in molecular diagnostics and discovery of biomarkers will facilitate this development. Important advances relevant to personalized medicine will be:

- Pathomechanism of most of the currently known major diseases will be understood at the molecular level.
- Genomic, proteomics, metabolic data from various research and commercial sources will be integrated in clinical medicine.
- Most of the ethical and policy issues about genetic testing will be resolved and it will be a routine for some population groups.
- Pharmacogenetics will be applied to identify those at risk of adverse drug events from certain drugs.
- Improvements in targeted drug discovery and increase in pharmacogenomics-based clinical trials.
- Preventive medicine will be well recognized with acceptance of presymptomatic diagnosis and pre-emptive treatments.

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Ongoing Genomic Projects

Several studies of the human genome are still going on and some are planned. A selection is described briefly in the following pages.

Understanding the Genetic Basis of Diseases

Although molecular diagnostics has already made considerable advances, the technologies have not been applied to understanding the genetic basis of disease, which is important for developing personalized medicine. To some extent, it is due to lack of funding for research projects investigating the genetic basis of diseases. Some of the ethical and social issues of genetic screening also need to be resolved. One example of a project to investigate genetic basis of breast cancer is a pioneer step in this direction.

Since 2005, the University of Cambridge (UK), Cancer Research Technology, Cancer Research UK and Perlegen Sciences Inc are conducting a collaborative high-resolution, whole genome association study on breast cancer. Scientists will determine over 200 million individual genotypes in DNA samples collected from patients to further elucidate the genetic basis of the disease. As the most comprehensive search ever conducted into the genetic basis of breast cancer, this project may help to identify, more precisely, women at high risk of the disease, and may ultimately lead to improvements in the prevention, earlier detection and treatment of breast cancer. The study will be a genome-wide scan for common predisposing genetic variants that are associated with susceptibility to breast cancer. Genetic variants in genes such as BRCA1 and BRCA2, which predispose strongly to breast cancer, have been identified previously, but these are quite rare and account for less than 5% of breast cancer cases. This new study hopes to provide a more comprehensive understanding of the genetic basis of breast cancer.

Personal Genome Project

Low cost personal genome data is important for the implementation of personalized medicine on a large scale. A Personal Genome Project (PGP) has been launched as a sequel of the Human Genome project and volunteers are being recruited to make their own genomic and phenomic data available (Church 2006). These resources will include full (46-chromosome) genome sequences, digital medical records and other medical information that would become a part of personal health profile. It will include comprehensive data about RNA and protein, body and facial measurements and imaging such as MRI. Human cell lines representing each subject will be deposited in a repository at the National Institute of Genome Medical Sciences. The subjects will sign an informed consent and although the subjects will be fully identified, the privacy of the individual will be respected and the data

will be protected from hackers. Details of PGP can be found at the following web site: http://arep.med.harvard.edu/PGP/. According to this web site, the project is intended to stimulate a "critical mass of interested users, tools for obtaining and interpreting genome information, and supportive policy, research, and service communities." So far ten individuals, including Dr. Church, have enrolled. In time, organizers hope to enroll 100,000 participants. Personal Genomes Organization is committed to making research data from the PGP freely available to the public.

Genome-Wide Association Studies

The NIH is seeking public input on a proposed new policy designed to facilitate the research community's access to data resulting from NIH-funded, genome-wide association studies (GWAS), which would lead to the development of a centralized NIH data repository. GWAS rely on the newly available research tools and technologies to rapidly and cost-effectively analyze genetic differences between people with specific illnesses, such as diabetes or heart disease, compared to healthy individuals. The differences may point to genetic risk factors for the development or progression of disease. Several NIH institutes recently launched, or are planning, GWAS initiatives with the expectation that the results will accelerate the development of better diagnostic tools and the design of new, safe and highly effective treatments. This will be an important contribution to genomics-based health care and personalized medicine.

As numerous GWAS programs get underway, NIH seeks to harmonize the policies by which the results will be made available to researchers. The proposed GWAS Policy calls-on NIH-funded GWAS investigators to quickly submit genetic data (genotypes) along with relevant health information (phenotypes) about individuals to a centralized NIH data repository. Data will be submitted in a form that protects the privacy and confidentiality of research participants. The data will be made freely available to all approved researchers to accelerate their studies. The draft policy also proposes terms and conditions for investigators to access GWAS data for research purposes. Data will be released in a manner that preserves the privacy and confidentiality of research participants.

NIH encourages patenting of intellectual property that addresses public need, such as creating new treatments that can be brought to the clinic, but seeks to prevent premature or inappropriate patents that impede future research. Because publication credit is critical to academic promotion, the proposed NIH policy also defines a grace period during which GWAS data will be available for access, but principal investigators submitting the data would be the only ones allowed to publish analyses in scientific journals. The policy also asks that recipients of GWAS data acknowledge the submitting investigator in any published works.

The NIH set aside $6 million in funding from 2007 to 2009 to support the development of methods for identifying gene-environment interactions in GWASs. NIH is seeking applicants who will "develop and test innovative, informative, and cost-effective methods and analytical strategies for identifying gene-environment interactions in

GWASs, sequencing studies, linkage analyses, or candidate gene approaches with broad applicability in complex diseases." Examples of approaches are:

- Analytical methods that model combinations of SNPs and environmental exposures to detect nonlinear interactions.
- Analytical methods that incorporate environmental covariates in genotype-to-phenotype mapping relationships.
- Algorithms and strategies to evaluate non-genetic factors on phenotypes of complex diseases and test associations between SNPs or haplotypes and phenotypes.
- Novel approaches to analyze findings from pharmacogenomic studies.

The 1000 Genomes Project

It was announced in 2008 that the 1000 Genomes Project will be carried out by an international consortium including the Wellcome Trust's Sanger Institute in the UK, the US National Human Genome Research Institute, and the Beijing Genomics Institute in China. The estimated cost is $30–$50 million. A thousand persons will have their genomes sequenced in an ambitious 3-year project that will create the most comprehensive catalogue so far of human genetic variation. These volunteers have already been recruited from Africa, Asia, America, and Europe. They have given informed consent for their DNA to be analyzed and placed in public databases. The donors are anonymous and will not have any of their medical information collected because the project is developing a basic resource to provide information on genetic variation.

The goal of the 1000 Genomes Project is to uncover the genetic variants that are present at a frequency of 1% or more in the human genome. The collaborators expect to finish sequencing 1,200 human genomes by the end of 2009. Meanwhile, the three 1000 Genomes pilot projects, which began in 2008 and are aimed at achieving low coverage of 180 individuals, high coverage of two parent-offspring trios, and targeted sequencing of 1,000 genes in approximately 1,000 individuals, are nearing completion. Those efforts seem to be generating high–quality data and have already uncovered new genetic variants. So far, the 1000 Genomes Project has generated 3.8 terabases of data and is expected to increase that dramatically, producing a petabyte of data.

Beyond the direct implications of the 1000 Genomes Project, the effort has spurred researchers to pioneer and evaluate methods that benefit other research efforts as well. For example, researchers have been working with high-throughput sequencing, developed new approaches for exchanging and analyzing data, discovering SNPs and CNVs, and making imputations based on next-generation sequence data. There is a need, however, for developing shared data formats for different stages of the analysis. In the absence of standard formats or a clear framework for such analysis, efforts to decipher the genetic information would be delayed. Consequently, team members are working to develop draft formats to aid this analysis.

Genomics of Aging in a Genetically Homogeneous Population

According to UNESCO's Preservation of Parsi Zoroastrian Project, 31% of the Parsis in India lives beyond the age of 60, compared to the national average of 7% of survival beyond 60 in the whole population of India (http://www.unescoparzor.com/). A better understanding of the genetic causes of longevity could have a major impact on the Indian Government's healthcare budget and drug companies' marketing efforts. Affymetrix signed an agreement with Avesthagen Ltd. (Bangalore, India), whereby Affymetrix' microarray technology will be used for the AVESTAGENOME Project™, which will explore the genetic basis of longevity and create a genetic, genealogic and medical database of the Parsi-Zoroastrian population. The use of Affymetrix technology will enable researchers to correlate genes with longevity, as well as neurodegenerative conditions, breast cancer, diabetes and other complex diseases that affect the Parsi community. The Parsi community was selected because of its longevity and its relatively genetically homogeneous population. This project takes a systems biology approach that encompasses not only genotyping but also expression profiling and transcriptomics. The genotyping phase of the project, which began in 2007, consisted of 10,000 samples in the first year. By 2008, the team had performed expression profiling and transcript mapping experiments across a subset of the samples. The project is expected to be completed before 2013. All of the genetic information for The AVESTAGENOME Project™ is being collected following informed consent. Data confidentiality is being maintained as in accordance with the Indian Council of Medical Research guidelines.

Translational Science and Personalized Medicine

Translational medicine deals with transfer of technologies from preclinical research into clinical application. Methods of translational medicine that are relevant to personalized medicine are shown in Table 18.1. Biomarkers play an important role and this has been discussed earlier in the report.

Translation of Genomic Research into Genetic Testing for Healthcare

Advances in genomics have led to mounting expectations with regard to their impact on health care and disease prevention. There is a need for a comprehensive research agenda to move human genome discoveries into health practice in a way that maximizes health benefits and minimizes harm to individuals and populations. A framework was presented for the continuum of multidisciplinary translation research that builds on previous characterization efforts in genomics and other areas in health care and prevention (Khoury et al. 2007). The continuum includes four phases of translation research that revolve around the development of evidence-based guidelines:

Table 18.1 Methods of translational science that are relevant to personalized medicine

Biomarkers
Biomarker discovery and development, e.g., imaging or serum
Biomarker scoring systems to grade their predictive potency
Translational toxicology using biomarkers
Preclinical to clinical studies
Animal models that are representative of human disease
Cautious transfer of results of preclinical studies to predict clinical effects
Careful early human exploratory clinical trial design prior to phase I/II trials
Following a consistent set of biomarkers from preclinical studies to phase III trials
Image analysis software should be the same for preclinical and clinical studies
Bioinformatics
Human genetics
Systems biology approaches

- Phase 1 translation (T1) research seeks to move a basic genome-based discovery into a candidate health application (e.g., genetic test/intervention).
- Phase 2 translation (T2) research assesses the value of a genomic application for health practice leading to the development of evidence-based guidelines.
- Phase 3 translation (T3) research attempts to move evidence-based guidelines into health practice, through delivery, dissemination, and diffusion research.
- Phase 4 translation (T4) research seeks to evaluate the "real world" health outcomes of a genomic application in practice.

Because the development of evidence-based guidelines is a moving target, the types of translation research can overlap and provide feedback loops to allow integration of new knowledge. Although it is difficult to quantify genomics research is T1, no more than 3% of published research focuses on T2 and beyond. Evidence-based guidelines and T3 and T4 research are scarce. With continued advances in genomic applications, however, the full continuum of translation research needs adequate support to realize the promise of genomics for human health.

Long-Term Behavioral Effects of Personal Genetic Testing

In 2008, Scripps Translational Science Institute (STSI), Navigenics, Affymetrix, and Microsoft embarked on a decade-long study to determine the long-term behavioral effects of personal genetic testing. Genetic scans will be offered to up to 10,000 Scripps Health system employees, family members, and friends in the study, the first of its kind, said STSI. Eventually, researchers hope to determine whether participating in personal genomic testing spurs individuals to make beneficial lifestyle changes such as improving their diet and exercise regimes. The team plans to track participants' lifestyle changes using self-reported health questionnaires. Participants will complete

the questionnaires at baseline and again 3 and 6 months after receiving the personal genetic test, which is designed to assess each individuals' genetic propensity for more than 20 health conditions, including diabetes, hearts disease, and some cancers. Those enrolled will also be asked to participate in surveys periodically over the next 20 years. The results will be compiled in a database hosted by the Scripps Genomic Medicine program. To maintain participants' genetic privacy, researchers will de-identify both saliva samples and health assessment questionnaires, encrypt the data, and store it in a secure database. In addition, researchers plan to use genetic variations identified in the study to improve their understanding of the genetics underlying the diseases and the application of this genetic information for preventing, diagnosing, and treating diseases. Affymetrix will perform the genome scans, while Navigenics will interpret the results and offer guidance on steps individuals can take to try to decrease health risks based on their personal genetic information.

Drivers for the Development of Personalized Medicine

Various drivers for the development of personalized medicine in the next decade are listed in Table 18.2.

Table 18.2 Drivers for the development of personalized medicine

Political and socio-economic drivers
Public pressure on the government for safer and more effective treatments
Pressure from the regulatory agencies on the pharmaceutical industry to reduce adverse effects of drugs
Push from the insurance industry to make genetic screening more widespread
Threat of malpractice may pressure physicians to use genetic tests and personalized therapies
Political pressures to reduce cost of health care by reduction of wastage on ineffective drug therapy and care of patients with adverse reactions to drugs
Scientific drivers
Availability of genomic knowledge from sequencing of the human genome and developments of proteomics in the post-genomic era.
Availability of new technologies that enable development of personalized medicine: biochips, bioinformatics, and molecular diagnostics
Retirement of physicians educated in the pre-biotechnology era and increasing awareness of pharmacogenomics, pharmacogenetics and molecular medicine among the younger generation of physicians
Introduction of personalized medicine in the academic medical centers
Industrial drivers
Proliferation of biotechnology companies interested in personalized medicine
Advances in molecular diagnostic technologies that can be applied in personalized medicine
Increase in the number of companies combining diagnostics with therapeutics
Major pharmaceutical companies developing personalized medicine

Evolution of Medicine as a Driver for Personalized Therapy Markets

There are no revolutions in medicine but evolution. This process has already been set in motion by the advent of the genomic era and will continue. The developments as shown in Fig. 18.1 will act as drivers for the markets.

Personalized Predictive Medicine

There has been an increasing emphasis on preventive medicine during the past decade and now predictive medicine is gaining popularity as an approach to improve healthcare in the future. Predictive medicine involves prediction of risk of disease in an individual and its personalized management. It is sometimes referred to as

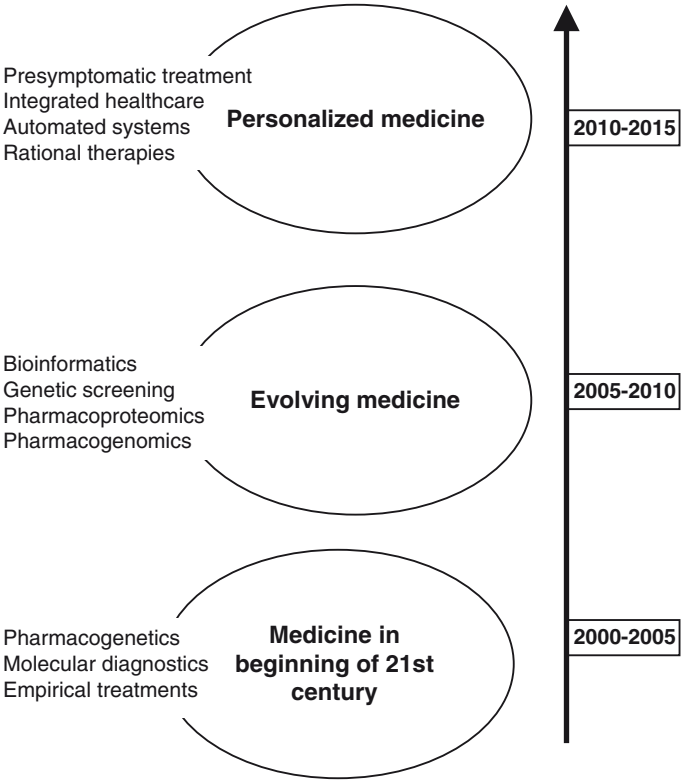

Fig. 18.1 Evolution of personalized medicine as a market driver. © Jain PharmaBiotech

preemptive approach as it involves treatment before the disease develops. By the time most diseases are diagnosed, some damage is already done and in some situations it is irreparable. Moreover, chances of cure of diseases such as cancer would be anticipated to improve with this approach. Advances in molecular diagnostics, proteomics, and metabolomics are facilitating the development of tests for predictive medicine. The concept of predictive medicine is extended further to predict response of the disease to a particular therapeutic care. A significant reduction in disease-related mortality as well as a reduction in costs can be expected if prevention and screening are focused on individuals at risk. In the pharmaceutical industry, predictive modeling of disease can be used to test efficacy of drugs before developing them.

Opportunities and Challenges

Prospects and Limitations of Genetic Testing

Genotyping will be for twenty-first century medicine what the x-rays were for twentieth century clinical practice. Currently, there are some reservations about the value of genetic testing in prediction of disease as there are multiple factors involved. It is currently being debated if it is worthwhile to continue with the multi-million dollar genomewide studies or to decode the entire genomes of individual patients. Although genomewide association studies have worked better and faster than expected, they have not explained as much of the genetic component of many diseases and conditions as was anticipated, and suggestion has been made to turn more sharply toward the study of rare variants (Goldstein 2009). Thus, schizophrenia would be caused by combinations of 1,000 rare genetic variants, not of 10 common genetic variants. However, deCODE Genetics, which also offers a personal genome testing service, alerts clients to pay attention to diseases for which testing shows their risk is three times as great as average, but not for trivial increases in risk. According to deCode scientists the undiscovered share of genetic risk for common diseases probably lies not with rare variants, but in unexpected biological mechanisms. DeCODE has found, e.g., that the same genetic variant carries risks that differ depending on whether it is inherited from the mother or the father.

According to another expert opinion, which disagrees with skeptics, genomewide association studies will have yielded important new biologic insights for at least four common diseases or polygenic traits by 2012 and that efforts to develop new and improved treatments and preventive measures on the basis of these insights will be well under way (Hirschhorn 2009). The rapid progress being made through meta-analyses suggests that many more common variants conferring a risk of disease will be identified in the next several years, leading to increasing stability of individual risk estimates. Once risk estimates are more stable, the usefulness of genetic screening will need to be considered for each disease, and recommendations

about potential interventions will need to be made for persons whose predicted risk exceeds some threshold. The situation may be very different by 2012. Appropriate guidelines are urgently needed to help physicians advise patients who are considering this form of genetic testing as to how to interpret, and when to act on, the results as they become more stable (Kraft and Hunter 2009).

Genetic testing will eventually improve predictions about what diseases we are predisposed to, the timing of their onset, their extent and eventual severity as well as which treatments or medications are likely to be efficacious or deadly. Genotyping, however, does not necessarily correlate with response to medications and other factors such as environmental have to be taken into consideration in personalizing treatment. Finally, all diseases do not require personalized treatment.

Challenges in Delivery of Personalized Medicine

Pharmacogenomics and pharmacogenetics are providing the basis for the development of molecular diagnostics to improve drug selection, identify optimal dosing, maximize drug efficacy or minimize the risk of toxicity. Rapid advances in basic research have identified many opportunities for the development of personalized treatments for individuals and/or subsets of patients defined by genetic and/or genomic tests. However, the integration of these tests into routine clinical practice remains a major multidisciplinary challenge. Although physicians and patients are optimistic about the health benefits that genetic testing might provide, neither group is well informed, and there are too few experts available to meet growing demands for genetic testing. Attempts to integrate genomic medicine into clinical practice are still in the early stages, and as a result, many questions surround the current state of this translation. Researchers from RAND Corporation (Santa Monica, CA), based on a review of published studies relevant to personalized medicine, concluded that many gaps in knowledge about organization, clinician, and patient needs must be filled to translate basic and clinical science advances in genomics of common chronic diseases into practice (Scheuner et al. 2008). There is a need for a large-scale effort to educate both health professionals and the public about genomic medicine, and to develop and evaluate new ways to deliver genetic services.

Genomics-based molecular profiling and related technologies may impact the delivery of healthcare even before genomics-based drugs hit the market. Identification of genetic factors affecting the prognosis of disease is likely to be of most clinical relevance. Relationships of known genes, such as BRCA1 and BRCA2, with risk factors will be clarified permitting evidence based preventive action in people at high genetic risk and better quantification of risk in family members. Greatest progress will be made in understanding the genetic contribution to the intermediate phenotypes linking genes and disease, and thus the biology of the disorder, as in atherosclerotic disease. The greatest impact of personalized medicine will be in the treatment of cancer, cardiovascular diseases, infections and neurological disorders.

The emerging fields of metabonomics (metabolite profiling to identify genotype-phenotype associations) and phenomics might offer solutions to anticipating and decreasing risk for adverse drug reactions in each individual patient but tests based on these approaches are not expected to become generally available to the practicing clinician for at least the next 5 years.

Pharmacotyping

Pharmacotyping is individualized drug selection and dosage profiling by the physician based on clinical evaluation of the patient's genotyping and haplotyping data for genes involved in the pharmacokinetics and pharmacodynamics of drugs in the body (Vizirianakis 2007). Pharmacotyping could be a new dimension of pharmacogenetics/pharmacogenomics and its application in routine clinical practice in the post-genomic era could better depict drug selection and dosage. This means a transition from a drug-selection process mainly based on the physician's own experience, into a more, highly integrated, information-based and computer-aided pharmacotherapy-based decision, thus making drug delivery digitized, more efficient and safer. The recent advances in silico modeling for predicting the absorption, distribution, metabolism, and excretion (ADME) could be incorporated into this system.

Pharmacogenomics is already used in clinical trials and will become the standard. Companies that do not use pharmacogenomic testing in drug development will lose out to the ones that do so. Personalized medicine should be widely available by the year 2010. Although some of the pharmacogenomics-new drugs being discovered now may not have completed the development by this time, use of some of the older drugs is being individualized and several components of personalized medicine are being put into place now. Molecular and diagnostic tests have a shorter time to approval than drugs and some are already in the market. Low throughput genotyping for some disease markers is already in use. Integration of diagnostics and therapeutics is also taking place and it is anticipated that personalized medicine will develop parallelly with the introduction of pharmacogenomic-based medicines.

Concluding Remarks about the Future of Personalized Medicine

Going back to the year 1998, when the first edition of this report was published, there was little interest in personalized medicine. Currently, there is a tremendous interest in this topic, but there are still many misconceptions about the scope of personalized medicine. Some accept that personalized medicine will come but try to put the date off into the distant future.

A report published by the Royal Society of the UK in 2005 identified important areas of application and the problems facing development of personalized medicine,

and concluded "its true potential may not become apparent for 15–20 years, during which time a great deal more information may become available about the practicalities of applying information derived from complex multifactorial systems in the clinic" (Anonymous 2005). This conclusion has been disputed (Jain 2006a). Even though the Royal Society claims to have consulted a broad spectrum of persons and organizations involved in personalized medicine, they took scant evidence from the most important players – the biopharmaceutical industry. The Royal Society's view of personalized medicine seems to be restricted to pharmacogenetics/pharmacogenomics and ignores several other technologies such as pharmacoproteomics and metabolomics. If one reviews the progress in molecular diagnostics during the past decade, current developments have surpassed the forecasts. Molecular diagnostics that are already in the market, or would become available in the next 5 years, will fulfill many of the needs of personalized medicine. The concept of personalized medicine is being accepted by the medical profession, regulatory authorities, health insurance organizations, and the biopharmaceutical industry.

We do not have to wait for 15–20 years to realize the potential of personalized medicine. Also, to state that it will take that long for personalized medicine to become mainstream raises the question as to what is required to justify the use of the term "mainstream" in medicine. There are no definite criteria by which this term can be applied to personalized medicine. Not all the diseases will need personalized medicines or combination of diagnostics with therapeutics. Application of new technologies and medicines depends on the personal judgment and decision of the treating physician in each case. Personalized approaches will be available and are expected to be used where they are deemed appropriate.

In conclusion, the progress in personalized medicine and related technologies justifies a more optimistic view. There will be significant activity relevant to personalized medicine in the clinical as well as biopharmaceutical sectors in the USA by the year 2013 and in the UK by the year 2015. The interest in personalized medicine is worldwide although the implementation may be delayed due to socio-economic factors in some developing Asian countries. Japan, with an advanced healthcare system and a preeminent position of research activity in genomic medicine, has good prospects for introduction of personalized medicine.

Summary

In the setting of anticipated progress in healthcare in the second decade of the twenty-first century, personalized medicine will be an important part of managing patients. The ongoing projects will improve our understanding of the disease as a basis for personalized medicine. Various drivers for the development of personalized medicine, both scientific and socioeconomic, have been identified. Controversies about the value of genetic information in predicting disease are being resolved. Overall there are good prospects for wider acceptance of personalized medicine by the year 2013 in the USA.