# Chapter 15
# Organization of Personalized Medicine

## Players in the Development of Personalized Medicine

Development of personalized medicine is a multidisciplinary undertaking and will need teamwork by many players. Pharmaceutical and biotechnology companies have taken a leading role in this venture in keeping with their future as healthcare enterprises rather than mere developers of technologies and manufacturers of medicines. The practicing physicians will play a vital role in implementing personalized medicine. Various players in the development of personalized medicine are listed in Table 15.1. The Personalized Medicine Coalition (PMC) contains many of these players.

### *Personalized Medicine Coalition*

PMC (http://www.personalizedmedicinecoalition.org/), located in Washington DC, is an independent, non-profit organization of leading pharmaceutical, diagnostic, biotechnology and information technology companies, as well as major academic institutions and governmental agencies. Members of the coalition are shown in Table 15.2.

The PMC was formed to fulfill a need for a nationwide, multi-industry policy consensus for personalized medicine. It provides a structure for achieving consensus positions on crucial public policy issues and serves as a forum for debate and education. The strength of the PMC is its multi-disciplinary approach to regulatory, scientific, legal and public policy issues. Its functions are:

- To provide forums for public policy discussions on
  - Personalized medicine: science, policy, and economics
  - Public attitudes toward genetics
  - Personalized medicine and cancer
  - Personalized medicine and psychiatry
  - Public attitudes and trends toward genomics
  - Personalized medicine and reimbursement
  - 'Race' and medicine in the genomics era

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**Table 15.1** Players in the development of personalized medicine

| Major pharmaceutical companies |
|---|
| Biotechnology companies |
| Clinical laboratories |
| Academic sector |
| Governments |
| Health insurance carriers |
| Physicians in practice |
| Patients |

**Table 15.2** Members of the PMC

| Industry | Procognia |
|---|---|
| Abbott Laboratories | Qiagen |
| Affymetrix | Siemens |
| Amgen | Theranos |
| AstraZeneca | Industry & Consumer Policy |
| Cogenics/Clinical Data | American Clinical Labs Association |
| DNA PrintGenomics | Biotechnology Industry Organization |
| Exagen Diagnostics | Genetic Alliance |
| Feinstein Kean Healthcare | PEW Genetics & Public Policy Center |
| Gene Logic | Pharmaceutical Research & Manufacturers of America |
| Genentech | Agency Partners |
| Genomas | Centers for Disease Control and Prevention |
| Genomic Health | Center for Medicare and Medicaid Services |
| Genzyme Inc | NCI |
| IBM Life Sciences Inc | National Human Genome Research Institute |
| Millennium Pharmaceuticals | FDA |
| Monogram Biosciences | Academia |
| Pathway Diagnostics | Duke Univeristy (Durham, NC) |
| Perlegen Sciences | George Washington University (Washington, DC) |
| Pfizer | Harvard Medical School-Partners (Boston, MA) |
| Princeton Group | Healthcare Center for Genetics and Genomics |

- To develop and conduct educational programs for stakeholder audiences
  - Serve as clearing house for information
  - Inform and educate the public and the media
- To facilitate dialogue between industry, government, patients, physicians and other stakeholders leading to consensus solutions

## *Role of Pharmaceutical Industry*

The pharmaceutical industry has taken a major initiative in the development of personalized medicine. Ten of these companies are profiled in the next chapter. This interest parallels the applications of knowledge gained from sequencing the genome

in drug development and molecular diagnostics. Use of pharmacogenetics and pharmacogenomics in clinical trials sponsored by the pharmaceutical industry is increasing as described in earlier chapters of this report.

In recent history, the pharmaceutical industry has played a major role in developing most of the innovations in therapy. Major pharmaceutical companies have the resources to do so. Eventually for clinical applications, the collaborations involve academic healthcare centers that have the patients. The major incentive for the pharmaceutical industry to participate in the development of personalized medicine is the increasing interest and technologies available for developing such medicines. In future, we will see more competition among the companies in this area, as those who do not remain on the forefront will be at a considerable disadvantage in the future healthcare market. Companies such as Hoffmann-La Roche are in a good position to develop such innovative healthcare systems as they have the largest molecular diagnostic facility and already have products in which diagnostics and therapeutics are packaged together. The integrated healthcare concept of the company fits in with personalized care. Technologies and data for the development of personalized medicine stem mostly from biotechnology companies. Principles of personalized medicine play an important role at all stages of the drug development process. Challenges of drug discovery for personalized medicine are discussed in detail elsewhere (Jain 2006b).

Companies involved in developing personalized medicine belong to several categories: large pharmaceutical companies, molecular diagnostic companies, pharmacogenomic companies, etc. Some are dedicated to developing personalized medicine whereas others have technologies and products that fit in with this system of medicine. Top five companies involved in personalized medicine are shown in Table 15.3.

**Table 15.3** Top five companies involved in personalized medicine

| Company | Remarks |
|---|---|
| Hoffmann-La Roche | Largest company in molecular diagnostics as well as a major pharmaceutical company. Pioneer in integrating diagnostics and therapeutics. With acquisition of Ventana, it is the largest personalized medicine company. |
| GlaxoSmithKline | One of the largest pharmaceutical companies with drug development and clinical trials based on pharmacogenomics and pharmacogenetics. |
| AstraZeneca | AstraZeneca, a major pharmaceutical company, uses pharmacogenomics and pharmacoproteomics at all stages of drug development. |
| Perlegen Sciences Inc. | Uses high-density DNA chip sets that make it economically practical for the company's scientists to analyze over 1.7 million SNPs in thousands of individuals to find genetic regions that cause disease or affect drug response. Building its own version of a haplotype map to rapidly compare and analyze whole genomes. |
| Clinical Data Inc. (CDI) | With acquisition of Genaissance and Icoria, CDI became the premium provider of pharmacogenomic services/biomarker discovery relevant to personalized medicine. |

**Production and Distribution of Personalized Medicines**

With adoption of personalized approaches, there will be changes in production and distribution of pharmaceutical products. Possible scenarios are:

- The drug may be manufactured as previously but the amount manufactured may be less due to restricted use to a certain genotype.
- The drug may be split into batches with slight variations of the basic structure in each. This may require modifications of the manufacturing process.
- If a drug is linked to a diagnostic, both may be packed together but it will not affect the basic manufacturing process.
- In case of biologicals that may be customized according to the group or even an individual, the procedures have to be flexible based on the input from clinical use.

It is beyond the scope of this book to go into the manufacturing methods, which will obviously need to be modified for personalized medicines. Scientists involved in this area will have to become familiar with personalized medicine. Automated systems may be developed in future that may translate biological factors into manufacturing modifications required for individuals. An extreme scenario is filling of a prescription for a personalized drug finalized by a pharmacist at the pharmacy terminal based on a manufacturing process starting at the pharmaceutical company.

The economic aspects of such a modification will need to be worked out in detail for each product. According to the general statements made about the commercial aspects in Chapter 9, manufacturing personalized medicine may become more costly but can be priced higher than conventional medicines. Currently, it appears unlikely that a major biopharmaceutical company will provide a biological therapy that is custom made from a patient's tissues, e.g., a tumor vaccine based on the patient's cancer. Such a service is currently provided by small biotechnology companies.

The FDA is beginning to address these issues with a new initiative using a "risk-based approach" that employs the principles of Process Analytical Technology (PAT). PAT involves the design of in-line, on-line or at-line sensors that operate at critical points in a pharmaceutical manufacturing operation. These sensors will markedly reduce the cost of producing pharmaceutical products by allowing manufacturing activities to become decentralized. This will, in turn, allow for the manufacture of "personalized medicines" and broaden the number of therapeutic agents and drug delivery systems available for treating human disease by reducing stability and scale-up concerns that might ordinarily prevent life-saving therapies from becoming products. The University of Kentucky proposes to develop a center that would contribute to sensor research as well as address critical unmet needs of the FDA initiative: tested facilities for integrating sensor technology with lean manufacturing and visualization/virtual environments. The Center will be designed to complement existing research centers, federal funding agencies, and industrial initiatives focused on modern manufacturing processes for the pharmaceutical industry.

## *Role of Biotechnology Companies*

Most of the biotechnology companies profiled in part II of this report are involved in pharmacogenomics, pharmacogenetics, pharmacoproteomics and molecular diagnostics. Smaller biotechnology companies that may invent or develop technologies for advancing personalized medicine depend on collaborations with major pharmaceutical companies. Some of these companies are already on the way to become pharmaceutical companies. Apart from academic collaborations, many of these companies have alliances with other biotechnology companies as well as with pharmaceutical companies. Some of the companies are now designated as personalized medicine companies whereas others continue to categorize themselves on the basis of the basic technologies for personalized medicine. All of them play a role in the development of personalized medicine, which is not the exclusive domain of any one company.

## *Role of life Sciences Industries*

BioIT Alliance (http://bioitalliance.org/) unites the pharmaceutical, biotechnology, hardware and software industries to explore new ways to share complex biomedical data and collaborate among multidisciplinary teams to ultimately speed the pace of drug discovery and development. By bringing together people from innovative life sciences organizations that span the biomedical industry, the BioIT Alliance plays an important role in the development of solutions that transform today's data into knowledge and improve the quality of millions of lives. Life science companies have unique technical challenges such as the need for more comprehensive data integration solutions, better technical collaboration and stronger knowledge management capabilities. The BioIT Alliance brings together science and technology leaders to consider innovative ways to address these challenges and use technology to reduce costs, streamline research and market their products more effectively. Founding members of the alliance have already begun to collaborate on solutions that target common technology problems faced by life science companies.

The first of these solutions is the Collaborative Molecular Environment, which will provide a means for data capture, visualization, annotation and archiving using Microsoft® Office, Windows® Presentation Foundation and SharePoint® Technologies. Microsoft is partnering with alliance member company InterKnowlogy LLC on the project, which is being tested by several other alliance members. In addition to making data easier to manage, early efforts of the alliance are focused on making data easier to share. Two member companies working on this are Affymetrix and Life Technologies. The BioIT Alliance will also provide independent software vendors with industry knowledge that will help them to commercialize informatics solutions more quickly with less risk. Most efforts to unite the life science and information technology industries are focused on developing technology to

enable the early-stage drug discovery process. By addressing the technology issues that companies face throughout the development cycle and by working with some of world's top technology providers, the alliance will help the industry move closer to making personalized medicine a reality.

## *Collaboration Between the Industry and the Academia*

The industry has taken an initiative in developing personalized medicine but collaboration with the academic basic scientists and healthcare professionals will facilitate its application. Pharmacogenetics is increasingly driven by industrial researchers, partly because of their ready access to clinical trial data on which pharmacogenetic research can be carried out. Few academic groups can afford to do so. Teaching institutions can play an important role in collecting patient data and DNA samples in clinical trials and organizing the results of their findings in databases with the help of the commercial bioinformatic tools developed by the companies. The future generation of physicians in training should be learning about personalized medicine at their formative stage and the current restrictions about the participation of the commercial sector in this effort needs to be relaxed.

The industry can maintain its lead in the use of modern communication tools, such as the Internet, to allow patients to provide samples for future research yet retain control of them in the light of future developments. An example of success of such collaboration is the SNP Consortium (http://snp.cshl.org/), which included 13 companies and five leading academic centers. Both industry and academic researchers have a common goal in that both want to bring innovative solutions into clinical practice to improve health care. There is no reason why the collaboration should not be a success.

## *Role of the Clinical Laboratories*

The role of the clinical laboratories in pharmacogenomics is established now, as there are several such facilities that provide technologies to improve the efficacy and safety of drugs by using genetic testing to determine patient therapy. Currently, clinical laboratories assist pharmaceutical sponsors in preclinical pharmacogenetic testing. In the future, clinical laboratories will participate in genetic test development and validation, high-throughput genotyping of patients in clinical trials, and personalized medicine.

However, when molecular diagnostic technology advances to the point-of-care stage, a patient's genotype may be determined on the spot and not sent to a laboratory. Similarly, with merging of diagnostics and therapeutics in integrated healthcare, diagnostic kits may be sold along with the therapeutics and laboratory procedures would be done at the comprehensive healthcare clinics. Clinical laboratories, however, will

continue to serve the pharmaceutical industry during the drug development stage. The volume of SNP genotyping required for clinical trials would be beyond the capacity of any on-site point of care (POC) testing system and would be better delegated to a clinical laboratory. Moreover, the quality control of such testing or regulatory oversight may not be possible unless an approved laboratory conducts these tests. To keep up with the challenges of the future, clinical laboratories will have to get involved in research in pharmacogenomic technologies and participate in the development of POC tests.

## *Role of the US Government*

US healthcare system is facing a crisis because of high cost and lack of health insurance for a significant percentage of population. Improvement of healthcare is a priority for the US government. Implementation of personalized healthcare will depend on the final plan that will be implemented. Meanwhile, research and development relevant to personalized medicine continues in the USA.

A bill was introduced in the US Congress in 2006 by Senator Barack Obama (now- President of the United States) titled "Genomics and Personalized Medicine Act of 2006" that aimed to advance personalized medicine and pharmacogenomics. It will be replaced in the upcoming Congress by another bill that includes a new tax incentive for personalized medicine research. The Genomics and Personalized Medicine Act of 2008 (H.R.6498) adds tax and test credit incentives to lure researchers into the field. The bill was introduced and referred to the House Ways and Means Committee and to the House Energy and Commerce Committee. The core focus of the act is on the following points:

- It would create a Genomics and Personalized Medicine Interagency Working Group that would include the NIH, the FDA, the Centers for Disease Control and Prevention, and other groups outside of the Department of Health and Human Services (HHS).
- It also would start a National Biobanking Initiative that would create a database for collecting and integrating genomics data with environmental and clinical health information. It also would use funding to improve training for diagnosis of genetic diseases and disorders, and for treatment and counseling.
- The final part of the bill would implement an oversight matrix for regulating genetic tests and pharmacogenomic tests, and would encourage the development of companion diagnostics by drug sponsors and by device companies.
- An amendment will include tax credit for research expenses incurred in the development of a companion diagnostic test.

The description of the act focuses on genomics and genetic testing and misses the broad contest of personalized medicine as discussed in this report. Although it is an encouraging step, it remains to be seen if it will facilitate the introduction of personalized medicine and add to the advances already made by the industrial sector in this domain.

In November 2008, the Department of HHSs released an update of its ongoing efforts in the personalized healthcare arena and the vision that the outgoing US government had for this new medical area in diagnostics, treatment, and research. The full 300-page report, Personalized Health Care: Pioneers, Partnerships, Progress is available on line at: http://www.hhs.gov/myhealthcare/. In a prologue to the report, meant as a note for the next government, it is explained that personalizing healthcare "is not a niche concern. Its promise is central to the future of healthcare." However, a warning put the effective personalized healthcare system in place as "the work of a generation." According to the report, within 10 years "it will be the norm for consumers and practitioners to anticipate that treatments should be individually targeted, with diagnostics and therapies commonly associated as a paired unit" and "within 15 years major clinical data sources can be securely linked in a manner that gives most Americans the option of allowing their own de-identified health information to be employed in the quest for ever-more individualized understanding of health and disease." It is further stated that "within 20 years data and informatics will have advanced to the point of supporting meaningful individual prediction regarding an individual's life-long health prospects, including specific, proven steps that he or she can take to protect and enhance health."

Although this report is encouraging, the timeline seems to be close to that of the Royal Society of UK, a critical review of which will be presented later in this Chapter. Personalized medicine has made the most advances currently in the USA. It is expected that the current US government, which has shown interest in implementing personalized medicine, will move faster.

## *Role of US Government Institutions in Development of Personalized Medicine*

### NIH's Roadmap Initiative for Medical Research

The NIH supports many programs that facilitate the development of personalized medicine although they are not labeled as such. The NIH infused $30 million into its Roadmap initiative in 2008 as part of an effort to advance and assess several new 'omics areas. Themes of the NIH's "Roadmap Initiative for Medical Research" are:

- New pathways to discovery
- Research teams of the future
- Re-engineering the clinical research enterprise

New Pathways to Discovery focus on areas that range from molecular imaging and the study of personalized profiles of cell and tissue function at an individual level (leading to better diagnosis and treatment) to studies of biological pathways and networks. This work will help accelerate the achievement of the 2010 predictions of routine genetic testing, personalized medicine and improved quality of patient care.

New initiatives covered under the updated Roadmap involve metagenomics, epigenetics, protein capture, proteome tools, and phenotypic tools. Coordination groups

will consider drafting new efforts in pharmacogenomics and bioinformatics. Major new roadmap initiatives that have been approved for funding include a Human Microbiome Project to characterize microbial content in the human body; an epigenetics and epigenomics study that measures changes in gene expression and gene function; and a pilot study for a genetic connectivity map that could help demonstrate linkages between diseases, drug candidates, and genetic manipulation.

## NIH and Personalized Medicine

One US project relevant to personalized healthcare and information-based medicine was initiated in 2003. The NCI created Cancer Biomedical Informatics Grid (caBIG) to connect cancer research-related elements of data, tools, individuals and organizations and leverage their strengths and expertise globally. caBIG will help redefine how research is conducted, care is provided and patients and participants interact with the biomedical research enterprise. Participation in this network – based on universal standards for information security and ethical use – means that all stakeholders must adhere to strict security measures for accessing, utilizing and transmitting patient data.

In its funding agreements and its own internal research programs, the NIH is implementing policies to facilitate the exchanges of these research tools and related resources for personalized medicine. NIH's Research Tools Policy defines research tools very broadly, recognizing that the tools may serve as a product in addition to being a research tool. These tools may include cell lines, model organisms, monoclonal antibodies, reagents, growth factors, databases and computer software. All of these have important uses in the development of personalized medicine. Future genomic advances would require a greater collaboration between the NIH, the universities and the industry. This is a new paradigm in the pharmaceutical industry with relation to intellectual property (IP) similar to the situation in case of SNP Consortium. If pharmacogenomic-based tests and associated therapeutics are sold as a package, there may be an opportunity for IP sharing between the upstream and downstream partners in drug discovery and development.

## National Institute of General Medical Sciences

In January 2008, the US National Institute of General Medical Sciences of USA (NIGMS) released a strategic plan that outlines its goals over the next 5 years, including the emphasis on continued support for its large-scale research programs such as the Pharmacogenetics Research Network, the National Centers for Systems Biology, the Protein Structure Initiative, and the Models of Infectious Disease Agents Study. NIGMS' "Investing in Discovery" plan is aimed at guiding the initiatives over the next 5 years, and how it will make strategic investments to maximize the benefits of the public funds entrusted to it. NIGMS has three central goals it will focus on through the plan, including maintaining a balanced research portfo-

lio, fostering a robust, stable and diverse scientific workforce, and promoting an open dialogue with the scientific community and helping them communicate with the public. NIGMS has allocated up to $10 million per year for as many as three grants to fund the creation of the Systems Biology centers, including a 5-year grant of a total of $14.5 million to Duke University.

Other points of emphasis over the following 5 years will include encouraging development of databases designed to handle genomics and other biomedical research information. NIGMS also plans to continue to support the creation of resources such as sample repositories, databases, interoperable software, and equipment used in exchanging data between various types of researchers. The plan also calls for more inter-institute collaborations and programmatic linkages, including the corollary programs or links to NIH Roadmap initiatives such as the Clinical and Translational Sciences Award through programs like the Medical Scientists Training Program.

In March 2009, NIGMS announced that it will grant up to $3 million in the current year to fund one pharmacogenomics knowledge resource that will serve the needs of the entire research community through a NIH funding opportunity. Direct costs for the program are limited to $2 million per year for the Pharmacogenomics Knowledge Base (PharmGKB) over a period of up to 5 years. This program will enable new and renewal applications for an earlier program called the Pharmacogenetics and Pharmacogenomics Knowledge Base. The goal is to support a program that will present complete, comprehensive, and current knowledge in pharmacogenomics, backed by critical datasets, and the most compelling literature. It should support and extend modern research approaches that could help to achieve the goal of using pharmacogenomics to help guide physicians' treatment and therapy decisions. Research topics could include a variety of efforts including comprehensive listings of known genes and gene variants that predict drug responses; definitions of drug responses; current knowledge of genotype-phenotype relationships; accessible views of drug pathways of metabolism, disposition, and sites of action; drug structures, structure–function relationships, and alterations in variants; data-sharing capabilities for addressing questions that can be solved through harmonizing new and existing data sets; possible sources for reagents and models; and other efforts.

### National Institute of Standards and Technology

According to a listing in the Federal Register in December 2008, the National Institute of Standards and Technology (NIST) would like genomics, proteomics, and other biomedical researchers to submit ideas about needed advances in personalized medicine, and has asked for white papers detailing the same. The NIST call is part of a new program asking for input on a number of subjects it has deemed as areas of critical national need, including personalized medicine, and the advice will be used to develop new competitions for funding under its Technology Innovation Program. Researchers could describe needs for advances in genomics and proteomics that could be used to help doctors develop personalized drug treatments and dosages. NIST is not seeking proposals; it is asking for descriptions of the need and associated

societal challenge, why government support is needed, the consequences of inaction, and potential technical solutions. According to NIST, personalized medicine, based on genetic, environmental, and metabolic influences on disease, could be a key to addressing the trial and error nature of treatment in the current health care system.

White papers covering personalized medicine could include descriptions of the challenges of cost-effective tools and techniques for genomics and proteomics research, technologies used in identifying biomarkers, drug and vaccine delivery systems, and better methods of integrating and analyzing biological data when it is combined with environmental and patient history information.

## *Role of Academic Institutions in the USA*

Universities are not directly involved in the development of personalized medicine but research in pharmacogenomics and pharmacogenetics is in progress at several academic centers and non-profit institutes, which has potential applications for personalized care of patients. Many of these programs are supported by the US government through NIH. There are some collaborative programs between the academia and the industry that are relevant to personalized medicine. A few of these programs will be described here briefly.

### Clinical Proteomics Program

An example of application of proteomics to the development of personalized medicine is the collaboration between the FDA and the National Cancer Institute (NCI). The new program, called Clinical Proteomics Program, starts with laboratory analyses of cells from tissue samples taken from cancer patients. Normal cells, pre-cancerous cells and tumor cells from a single patient are then isolated using tools that maintain the original protein pattern of the cells. The protein patterns of tumor cells taken from a patient after treatment is analyzed to determine how a particular therapy affects the protein pattern of a cell. Through the Clinical Proteomics Program, the NCI and FDA hope to develop individualized therapies, which are optimal for a particular patient rather than to a population and to determine the effects, both toxic and beneficial, of a therapy before using it in patients. Additionally, the partners hope the program will allow for earlier diagnosis and improved understanding of tumors at the protein level.

### Coriell Personalized Medicine Collaborative™

Coriell Personalized Medicine Collaborative™ (CPMC™) is a research study at Coriell Institute for Medical Research (http://www.coriell.org/), which is located on

the campus of the University of Medicine and Dentistry of New Jersey in Camden. CPMC™ puts the Institute at the forefront of personalized medicine. By combining a functioning biobank facility with modern microarray technology, Coriell has created the ideal environment for this innovative project. CPMC™ is a forward-thinking, collaborative effort involving volunteers, physicians, scientists, ethicists, genetic counselors and information technology experts whose goal is to better understand the impact of genome-informed medicine and to guide its ethical, legal and responsible implementation. CPMC™ seeks to explore the utility of using genome information in clinical decision-making. The project also aims to understand why people often respond differently to treatments and to discover presently unknown genes that elevate a person's risk of cancer and other complex diseases. All volunteers will control their genetic profile. Participants who wish to view it will be able to view potentially medically actionable information about their genomic profiles through a secure web-browser-based system. A variety of educational material on genomics and medicine will also be provided through streaming video and downloads. This initiative will take an evidence-based approach to determine which genome information is clinically useful while ensuring that patient privacy is vigorously protected. The study seeks to enroll 10,000 participants by the end of 2009, with an ultimate goal of 100,000 individuals. Coriell is committed to ensuring that the participant population of CPMC™ study resembles the demographics of the Delaware Valley (see following section) as historically, the presence of minority populations in genome-wide association studies has been minimal.

In 2007, Coriell established a multimillion-dollar Genotyping and Microarray Center – the facility that performs the genome analyses for the CPMC™. This high-capacity facility consists of state-of-the-art equipment and receives samples from laboratories around the world requesting genotyping, microarray and gene expression analysis. The facility also processes up to 2,000 DNA or RNA samples per month. Biobanking repositories provided support to the Human Genome Project, a world-wide program to map the entire human genome, and to the International HapMap Project, a project providing an efficient tool to identify disease causing genes. The Coriell Institute maintains contracts from the NIGMS and the National Institute of Aging (NIA) to establish and maintain what has become one of the largest cell repositories for the study of genetic and aging-related diseases.

### Delaware Valley Personalized Medicine Project

The Delaware Valley Personalized Medicine Project (DVPMP) was established in 2007 with a goal of genotyping up to 100,000 patient volunteers for studies of the use of genetic risk factors in patient care. At the time of its launch, DVPMP enrolled 10,000 participants for the project over the next 3 years and eventually plans to reach 100,000 participants. Partners in the DVPMP include the Fox Chase Cancer Center, Cooper University Hospital, and Virtua Health. In March 2008, Coriell Institute for Medical Research (see preceding section) started partnership with Cooper University Hospital, which is the core clinical campus for the Robert Wood

Johnson Medical School in Camden, as part of the DVPMP. The collaborators intend to enroll 2,000 Cooper employees and their families in the project.

## Evaluation of Genetic Tests and Genomic Applications

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) group's recommendations are part of a pilot project developed in 2004 by the National Office of Public Health Genomics at the US Centers for Disease Control and Prevention. The project aims to evaluate genetic tests and other genomic applications currently in transition from research to clinical use. In 2008, EGAPP released a draft of three new sets of recommendations about gene expression profiling in breast cancer, genetic testing for Lynch syndrome in colorectal cancer patients, and testing for UGT1A1 in colorectal cancer patients treated with irinotecan. Of the three recommendations, the one investigating gene expression profiling in breast cancer is the furthest along. There is limited evidence of analytic validity, limited evidence of clinical validity but no direct evidence, i.e., controlled trials testing clinical outcomes or clinical utility. There are mixed estimates of cost-effectiveness. In spite of these concerns, there is a positive balance with potential benefits versus potential harms.

Earlier EGAPP reports evaluated cytochrome P450 testing with AmpliChip (Roche) or other tests to guide physicians treating patients with depression who are taking selective serotonin reuptake inhibitors (SSRIs) (EGAPP Recommendation Statement 2007). There was insufficient evidence to support a recommendation for or against the use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression. In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed.

A report on ovarian cancer detection and management, evaluated tests for single gene products, genetic variations affecting risk of ovarian cancer, gene expression, and proteomics for CA-125 and BRCA1/2. Although there was no evidence to suggest that genomic tests for ovarian cancer have adverse effects beyond those common to other ovarian cancer tests, i.e., the risks of false-positive results and delayed or inappropriate treatment because of false-negative results, model simulations suggest that annual screening with these tests will not reduce ovarian cancer mortality by more than 50%.

## Genomic-Based Prospective Medicine Project

In 2003, the Center for the Advancement of Genomics (TCAG) and Duke University Medical Center (DUMC) announced a formal collaboration to create the first fully-integrated, comprehensive practice of genomic-based prospective medicine. Through this new collaboration, Duke and TCAG are generating predictive and prognostic data on specific diseases that can aid both doctors and patients in the earlier detection and better treatment of these illnesses. The activities will include

focused research in genomic predictors of diseases; the design of future clinical practice models including personalized health planning and strategies to tackle ethical and legal issues that will arise as a result of advances in genomics. Initially funded internally by both organizations, TCAG and Duke will seek outside funding through government grants, foundations and philanthropic donations. The Duke/TCAG genomic-based medicine collaboration has several initial goals:

1. To integrate high-throughput DNA sequencing technologies and state-of-the-art analysis with distinctive medical expertise by re-sequencing and genotyping the relevant genetic material (genes and regulatory regions) of selected patients from Duke's clinical population. These are patients who have been well characterized through detailed retrospective medical records. By sequencing the DNA of this patient population and associating these profiles with phenotype and disease outcomes, researchers at TCAG and Duke plan to correlate genetic variations to disease states, to be able to initiate preventive steps or earlier treatment of disease.
2. To focus initially on major disease areas, including cardiovascular, hematologic and infectious diseases, as well as cancer. Physicians at Duke's medical center plan to draw up lists of human genes considered likely to play a role in diseases of interest, like the 100 or so genes that may, when mutated, play a role in coronary artery disease. TCAG would sequence the full DNA of these 100 genes from large numbers of patients, looking for the mutations that seemed to be linked to the disease. These mutations could then be used to assess the risk for coronary artery disease in the population at large.
3. To create a futuristic personalized health plan and medical record including genomic information to predict health risks and outcomes from therapy.
4. To leverage the unique high-end computing center that TCAG is currently building as part of its next generation, and the high-throughput DNA sequencing center (the JTC) that is equipped with 100 ABI 3730XL automated DNA sequencers. These will initially enable to sequence 45 billion base pairs of DNA per year. TCAG and Duke along with several technology partners will create unique computing, storage, database and software solutions to manage and mine the massive datasets that will be generated through the genomic medicine collaboration.
5. The collaboration will spur innovation and lower costs of DNA sequencing technologies and TCAG scientists will continue to work toward the goal of a $1,000 genome.

**Personalized oncology at Massachusetts General Hospital**

In March 2009, oncologists at the Massachusetts General Hospital (MGH), Boston, started to personalize cancer therapy. They plan to read the genetic fingerprints of nearly all the new patients' tumors within a year in a strategy designed to customize treatment. They will search for 110 abnormalities on 13 major cancer genes, that can predict whether drugs already available or in development might be effective against a patient's cancer. High throughput techniques will be used for sequencing 5,000 to 6,000 patients a year, replacing labor-intensive techniques that had been used only selectively for

a handful of cancers. Routine tumor screening has already started with lung cancer, but the focus is more on the genetic profile of a tumor and less on whether it is in the lung, breast, or prostate. The genes inside the malignancy are considered to be more important than the location of the cancer. The testing could be especially useful for patients with rare cancers, usually neglected by cancer researchers or pharmaceutical companies, as they may share genetic signatures with more common tumors already being successfully treated. One example of usefulness of this approach was a female non-smoker patient with lung cancer that had not responded to surgery and standard chemotherapy. Genetic screening revealed that the patient's cancer carried the mutation EML4-ALK, which is being targeted by a drug in development, and this patient responded to the drug. One limitation is the cost as the hospital charges $2,000 for the test and it may not be covered by the health insurance companies.

### Pharmacogenetics Research Network and Knowledge Base

Pharmacogenetics Research Network and Knowledge Base maintain PharmGKB (http://pharmgkb.org/) at Stanford University (Palo Alto, California). This program is funded by $12 million grant from the NIH and has the support of the academia, the regulated industry and regulatory agencies such as the FDA. This is an integrated resource about how variation in human genes leads to variation in our response to drugs. Current studies include the gene–drug effects associated with asthma, cardiac problems, and cancer; the roles of genetic variability in drug response in ethnic populations; genetic differences and estrogen receptors and the effects of gene variability on membrane transporters, which interact with one-third of all prescription drugs. Consumers of the new information will include pharmacogeneticists interested in the interaction of particular drugs with phenotype and statisticians who are more broadly tackling the phenotype–genotype problem. Genomic data, molecular and cellular phenotype data, and clinical phenotype data are accepted from the scientific community at large. These data are then organized and the relationships between genes and drugs are then categorized into the following categories:

- Clinical outcome
- Pharmacodynamics and drug responses
- Pharmacokinetics
- Molecular and cellular functional assays
- Genotype

### Quebec Center of Excellence in Personalized Medicine

In February 2008, Montreal Heart Institute and Génome Québec have formed the Center of Excellence in Personalized Medicine, which will be funded with more than $22 million in investments from government and commercial entities over 5 years. Canada's Centers of Excellence for Commercialization and Research program will provide $13.8 million of the total funding, with the remainder coming from

private and public partners including the ministère du Développement économique, de l'Innovation et de l'Exportation of Québec. The goal of the new center is to develop approaches and methods that will optimize treatment and ensure their rapid and productive transition from the research stage to use in clinical practice. The Montreal Heart Institute will house the new center, which was developed in collaboration with pharmaceutical and biotech companies.

#### Southeast Nebraska Cancer Center's Personalized Medicine Network

In 2005, the Southeast Nebraska Cancer Center (http://www.sncc-of-lincoln.com/) was awarded $1.5 million in US Department of Defense (DoD) appropriations for the current fiscal year to support a network and database of cancer patients' tissue samples. The center is a part of the DoD's National Functional Genomics Center, and will use the funding to create a network to collect cancer tissue samples and to follow the patients' progress through therapy, which would be merged into a national database. This large-scale effort combines government, academic and private-sector resources. The program also uses a "systems biology" approach that brings together advanced science in pharmaceuticals, molecular biology, genetic screening, bioinformatics and other technologies. The system will allow personalized cancer treatment decisions based on patients' molecular profiles. This research will help us identify genomic sequence changes associated with cancer in individual patients. The center's aim for the future is that a physician can run a simple test on a small tumor sample and use a quick genetic analysis to tailor the best therapy for the patient as an individual.

#### Wisconsin Genomics Initiative

In October 2008, four Wisconsin-based research institutions started collaboration to form the Wisconsin Genomics Initiative with a focus on personalized healthcare research. The collaborators include the Marshfield Clinic, the Medical College of Wisconsin, the University Of Wisconsin School Of Medicine and Public Health, and the University of Wisconsin-Milwaukee. The institutions will combine resources to conduct research on predicting individual susceptibility to disease, targeting personalized treatments, determining how patients respond to specific treatments, and disease prevention. One of the participants, Marshfield Clinic, is home to the Personalized Medicine Research Project, a population-based genetic research project that has so far collected DNA and medical records from around 20,000 persons.

## *Role of Healthcare Organizations and Hospitals*

Initially, Healthcare organizations did not show much interest in the implementation of personalized medicine. The first example in the USA is the Signature

Genetics program in Texas. Among the hospitals, the Mayo Clinic is developing a system for personalized medicine and DUMC (Durham, NC) is also involved in personalized medicine. Major health insurance companies such as Blue Cross and Blue Shield are now interested in this topic.

### Signature Genetics

Signature Genetics™ (Seryx LLC) is a new tool of personalized medicine introduced at the HealthTexas Provider Network (Baylor College of Medicine), which is designed to assist physicians in customizing drug prescriptions based on an individual patient's unique genetic makeup, as well as identify potential drug interactions. This technology combines the results of genetic testing for a specific patient with scientific knowledge on how genetic variations impact drug metabolism. This is an ongoing service that can be used throughout the patient's lifetime as medications are prescribed.

First, the patient visits the physician's office and has his or her blood drawn and a cheek swab analysis. These samples are sent to a laboratory. Four to six weeks later, the report, which covers more than 150 of the most commonly prescribed medications, over the counter drugs and herbal remedies metabolized by CY P450 enzymes, is sent to the physician's office. This report also provides information on drug interactions with these enzymes. Once a patient has been tested and an initial report issued, the physician can easily query Signature Genetics regarding any additional drugs under consideration for that patient. Through this process, the physician receives information specific to both the drug and the patient before actually prescribing the new drug.

### The Mayo Clinic Genetic Database

The Mayo Clinic (Rochester, MN), in collaboration with the International Business Machines Corporation (IBM), has set up Mayo Clinic Life Sciences System (MCLSS), designed to include detailed genetic information of patients. IBM is digitalizing the genetic profiles in millions of the clinic's patient records. This will help physicians understand how individuals are likely to respond to disease by making it easy to compare them with others of similar genetic profiles and help the development of personalized medicine. Several projects in various therapeutic areas such as management of hypertension and chronic lymphocytic leukemia have already applied a personalized medicine approach. The Mayo Clinic is hoping the database will blend the practice and research of medicine to the benefit of both. In 2007, the AT&T Foundation gave $900,000 to the Mayo Clinic to expand the database of patients' clinical and genomic information. The funds will be used to increase the MCLSS's genomic and prescription data capacities and to make this information retrievable by Mayo Clinic scientists.

### Research Center for Personalized Medicine at Mt. Sinai Medical Center

The Mount Sinai Medical Center in New York received a $12.5-million donation from Andrea and Charles Bronfman Philanthropies in 2007 which it will use over 10 years, to start the Charles Bronfman Institute for Personalized Medicine. The research center will study personalized medicine, and the medical center plans to use the funds to start "an institution-wide biobank" and a "translational biomedical informatics center." The grant will also go toward what will become a $30-million personalized medicine initiative. The Institute will bridge the gap between genomics research and clinical patient care in the area of personalized medicine.

The Personalized Medicine Research Program will develop and provide essential core technologies that will enable genome-wide analysis of genetic variations and functions in human DNA, and quantitative biology at the single-molecule level for large-scale studies of genetic associations and predictive biomarkers. Access and training in these resources will be critical to overcoming current research infrastructure barriers that limit our disease-oriented research centers in deciphering the genetic underpinnings of, and developing personalized approaches to, complex diseases.

## *Role of the Medical Profession*

Substantial advances that are being made in the area of genomics and the results are beginning to play an important role in the general practice of clinical medicine. The practice of medicine is already being influenced by genomics. It is imperative that physicians involved in clinical practice become more aware of emerging genomic data and participate in integrating medical genomic information into current standard clinical practice.

### Education of the Physicians

As personalized medicine is being developed by the pharmaceutical industry, there should be a parallel education of the public and physicians on these issues. The present generation of physicians does not have any formal education in molecular medicine and this can be remedied by continuing education. This can be accomplished by conferences and symposia sponsored by the industry. For the busy physician who is unable to attend such conferences, the Internet educational programs offer an alternative. Extra courses need to be incorporated in the medical curricula and the pharmaceutical industry may invest in endowing chairs and supporting courses on clinical pharmacology that include pharmacogenetics, pharmacogenomics and personalized medicine. The ethical objection to involvement of pharmaceutical companies that occurs while conducting symposia for pharmaceutical products does not apply to industrial sponsorship of education in techniques

on the frontiers of modern medicine. Apart from the education of the physicians, active steps are needed to encourage the incorporation of personalized medicine into clinical practice.

The mere availability of new tests, new knowledge, and personalized medicines is no guarantee that these will be incorporated in clinical practice. The ability and willingness of physicians to adopt personalized medicine into practice is an important factor in realizing its potential benefits. However, studies in the field of innovation adoption as well as physician clinical reasoning processes indicate that all physicians do not incorporate new techniques into their practices at the same rate and some fail do so. The concern that personalized medicine will not be readily or proficiently integrated into practice is suggested by evidence that primary care physicians do not have significantly increased referrals for genetic services, nor have they increased identification of candidates who are appropriate for genetic testing.

An understanding of the physicians' clinical reasoning processes or habits of diagnostic decision making may help to identify and remove the barriers in assimilating genetics related innovations into clinical practice. Focused training and educational materials need to be developed to address not only the substance of new information but also the assumptions and diagnostic strategies that drive the practice of medicine.

## Off-Label Prescribing and Personalized Medicine

The term "off-label" is used when a drug or medical device is used to treat a disease or condition not listed on its label, or used in such a way that's not outlined in the label, it is said to be used off-label. This off-label use is also sometimes referred to as extra-label use, nonapproved use or unapproved use. Off-label prescription is a common practice because new indications for approved drugs may not be tested in clinical trials due to heavy cost involved or may be in the long process of approval. However, policy forces inside the US government discourage the use of genomic technologies to help physicians make off-label prescribing decisions. Physicians will not be able to always wait for FDA to approve a new label for every one of their patients, and drug companies will not be able to conduct a trial to explore every possible contingency. In the future, personalization of care could mean much more off-label use of new medicines, guided by the latest literature, at least until the regulatory approaches are able to fully adapt to a different paradigm where treatment is highly specific to individual patients.

## Medical Education

As knowledge in molecular genetics and cell biology accelerates, the biomedical community is finding it increasingly hard to harness the explosion of new information and translate it into medical practice. Biomedical scientists should be trained to apply new biological knowledge to human health. A better understanding of medicine can

also guide scientists in research directions that are most likely to benefit the diagnosis and treatment of human disease.

There is a growing need to incorporate the increasing body of knowledge of pharmacogenetics and pharmacogenomics in the standard curriculum of medical schools, so that the next generation of clinicians and researchers will be familiar with the latest developments in these areas, and will be capable of providing patients with the expected benefits of personalized medicine. As a first step, and in recognition of such emergent needs, the graduate school of the Sackler Faculty of Medicine at the Tel-Aviv University in Israel introduced a new course entitled 'Introduction to Pharmacogenomics: Towards Personalized Medicine' in the 2002–2003 academic year. The course is intended for graduate and undergraduate students who have a basic background in pharmacology and in human genetics (Gurwitz et al. 2003).

## *Education of the Public*

Public opinion is an important factor for the implementation of genotyping for pharmacogenetics and pharmacogenomics. There would be several ethical issues arising out of genotyping and detection of genetic diseases. Proper handling of this information will require education of the public about pharmacogenetics and pharmacogenomics. It is anticipated that healthcare companies will play an important role in sponsoring these educational activities.

The individual's right of access to his/her genetic information is well recognized. There is, however, a considerable concern about the application of new genetics approaches. It should be pointed out that application of genetic knowledge is nothing new. Genetic differences in susceptibility to diseases are well recognized in conventional medicine, which is accepted by the public. In public discussions on pharmacogenetics, the scientists and information providers of the industry should avoid getting sidetracked into discussions on the controversial areas of biotechnology.

### Role of the Internet in Development of Personalized Medicine

The Internet will play an important role in the development of personalized medicine and the important points are shown in Table 15.4.

An example of the commercial approach to online development of personalized medicine is GeneSage Inc. (www.genesage.com), the first company solely dedicated to developing online solutions to help educate consumers, patients and physicians about the genetic relevance of common and rare medical conditions. This Company has packaged its one-of-a-kind genetic health information system into a new platform that can now be easily and seamlessly adapted for use by healthcare content providers, disease management, pharmaceutical, and clinical testing companies. GeneSage's Rx Platform of detailed information on genetically related conditions,

**Table 15.4** Role of the Internet in development of personalized medicine

| |
|---|
| Education of the public about genetic testing |
| Information about diseases and early diagnosis for the public |
| Building of electronic databases and their utilization for research |
| Internet can reduce the cost and time of drug development |
| Facilitation of recruitment of patients in clinical trials |
| Internet would serve as a medium for exchange of ideas about personalized medicine between health professionals |



clinical testing and other features was developed to provide a standard framework to respond to the rapidly growing demand for expertise in genomic medicine and health risk assessments. The expert system database, catalogs up to 350 conditions with specific fact sheets covering the most common at two levels: one, designed for consumers or patients, and another for healthcare professionals. The databases can be easily searched by a variety of methods.

## Public Attitude Towards Personalized Medicine

It can be anticipated that the public, particularly in the USA, would be receptive to the concepts of personalized medicine as it would improve health care. However, several issues need to be addressed. The primary one is the education of the public. There are other issues such as public attitudes towards genetic testing that will affect the development of personalized medicine.

In 2007, a federal and private joint study started investigating the attitudes of young adults toward undergoing genetic testing for common diseases, and about how they would use information provided by such tests. The study, called the MultiPlex Initiative, aimed to understand how the development of personalized medicine would be affected by the attitudes towards genetic testing held by individuals aged 25–40 years. The study was conducted by the NHGRI, the NCI, the Group Health Cooperative in Seattle, and the Henry Ford Health System (Detroit, MI). The MultiPlex Initiative will study 1,000 individuals in the metropolitan Detroit area and will include tests based on 15 genes linked to type 2 diabetes, coronary heart disease, hypercholesterolemia, hypertension, osteoporosis, lung cancer, colorectal cancer, and malignant melanoma.(Is the the study yet to begin?or is it ongoing?) According to the NIH, the study will? look into the types of individuals who are and are not interested in receiving genetic testing, what influences their decisions, and how these individuals interact with the health care system. It will?? also aim to understand how people who decide to take the tests will interpret and use the results in making their own health care decisions in the future. The initiative will provide insights that will be a key to advancing the concept of personalized medicine. The NHGRI's Bioinformatics and Scientific Programming Core has designed an innovative system for data collection and analysis for the study.

The Center for Inherited Disease Research, operated by the NIH and the Johns Hopkins University, will handle the genetic testing for the study.

## Global Scope of Personalized Medicine

Development of personalized medicine needs to be considered against the background of current healthcare trends, which vary from one country to another. Basic healthcare depends on the economic resources, political systems, healthcare organization, government support and allocations of finances. There are differences in healthcare standards between the developing and the developed countries.

### *Personalized Medicine in the Developed Countries*

Personalized medicine will be initially introduced in the developed countries of the West. The USA is likely to be the first country to introduce personalized medicine on a large scale and some countries in the EU will follow.

#### US HHSs Supports Personalized Medicine

US Department of HHS is developing an agenda that will put extra emphasis on the development of personalized medicine, and will institute initiatives to ensure that genetic tests are safe and accurate. HHS, which oversees the NIH, has allocated a part of its budget for genetic research into a Genes and Environment Initiative, employing SNP analysis and technology development to understand the causes of common diseases. In addition, HHS has launched a public-private partnership called the Genetic Association Information Network (GAIN) to accelerate genome association studies. Entities in the partnership are NIH, Pfizer, and Affymetrix. The federal funding began in 2007 and will continue for several years. Initial funding was used for genetic analysis. Genotyping studies performed as part of the initiative will be done for several dozen common diseases to be selected by peer review. The genotyping is managed by an NIH coordinating committee under the usual government rules, subject to competition between research facilities. The primary private-sector contributor to the GAIN partnership is Pfizer, which donated $5 million to set up the project's management structure and committed $15 million worth of laboratory studies to determine the genetic contributions to five common diseases. Affymetrix will contribute laboratory resources for two additional diseases, expected to cost about $3 million each. Genotyping supported by Pfizer and donated to the GAIN project will be conducted by Perlagen. A similar arrangement was worked out with Affymetrix. The GAIN initiative proposes to raise $60 million in private

funding for additional genetic studies of common diseases and is actively seeking additional partners. Investigators may submit applications to have genotyping performed on existing DNA samples from patients with specific diseases and control individuals in case–control studies. The National Center for Biotechnology Information at NIH will develop databases to manage the genetic, medical and environmental information resulting from these initiatives. All data will be placed in the public domain.

The HHS already has an Office of Personalized Medicine and an advisory panel that meets regularly to consult and advise on gene-based medical issues. In 2007, HHS funded personalized health care projects with $277 million and the support is proposed to be increased to $352 million in 2008. The HHS initiative has three main goals: (1) to review structures for "ensuring that genetic tests are accurate, valid, and useful by seeing to it that HHS departments know their assignments in this area; (2) by developing consistent policies to guide HHS agencies in managing access to and security of federally supported research; and (3) by creating a network that pulls together health care information from the nation's major health data repositories to "enable researchers to match treatments and outcomes.

## Personalized Medicine in the USA

The US healthcare system is undergoing a second wave of change in the beginning of the 21st century similar to the managed care movement in the last decade of the twentieth century. This scenario will be favorable for the development of personalized medicine in which the well-informed public will be a driver. As mentioned earlier in this chapter, some leading clinics and healthcare providers in the USA are already embracing the concept of personalized healthcare.

## Personalized Medicine in the EU

There is a tremendous variation in the healthcare systems within the EU but there are some emerging patterns. All EU systems are converging around common denominators that include : more powerful patient organizations, stricter cost control measures, enhanced use of informatics. Patient bodies are a part of the decision-making in most EU systems, even the European Medicines Agency (EMEA), unlike the FDA in the USA. There is an increasing impact of EU regulatory bodies on national healthcare systems.

These trends in healthcare would be favorable for the development of personalized medicine. The following European countries appear likely to develop personalized medicine ahead of others: UK, Sweden, Spain and Germany. The current situation in the UK is more favorable to the development of personalized medicine than other EU countries. An example will be given of the introduction of genetics on National Health Service in the UK and how it will facilitate the development of personalized medicine.

### UK National Health Service and Medical Genetics

In the year 2000, an excellent report from Nuffield Trust in the UK explored the likely effects of genetics on human health and human health services, noting, "the medicine that has been practiced up to now, and the health services that we have become familiar with, will undoubtedly be subject to enormous changes" (Nuffield Trust Genetics Scenario Project 2000). UK genetic services are among the most highly developed in Europe, having evolved from academic departments into regional centers. Regional genetic centers are multidisciplinary, with clinical and laboratory services united or working closely together. Each centre includes specialist clinics and clinics in district hospitals and community facilities. Outreach staff from some centers may visit families at home. Genetic services help families with the risk of a genetic disorder to live as normally as possible. After a consultation and investigations patients are given information about the condition in their family, their risk of developing or transmitting the condition, and the options for dealing with it (genetic counseling).

The UK government awarded a package of £30m ($42m) in 2001 for measures to help bring the genetics revolution into everyday medical practice. A White Paper titled "Our Inheritance, Our future: realizing the potential of genetics in the NHS" was published in 2003 (www.tso.co.uk/bookshop). This document depicted the Government's strategy for maximizing the potential of genetics in NHS so that all patients can benefit from new genetic advances in disease prevention, diagnosis and treatment.

Under the UK government plan, the number of consultants specializing in genetics has nearly doubled to 150 currently. Support staff and genetic counselors have also doubled in number to approximately 500. Research and development in pharmacogenetics is being supported. The number of patients being seen by specialist genetic services has increased by about 80% -to 120,000 a year, and the waiting period to see a specialist has been reduced considerably.

The White Paper generally avoided the area of widespread population screening except in flagging up the antenatal and the newborn screening programs. The possibility of genetically profiling every newborn child to guide lifetime decisions has been considered. Overall, the White paper represented an important milestone in the development of a rational policy for the application of genetic science in healthcare services in the UK. With this background with the organization of the National Health Service in the UK may turn out to be an ideal place to introduce personalized medicine.

## *Personalized Medicine in the Developing Countries*

Poor persons in the developing countries and even in the developed countries of the West have not benefited from some of the advances in modern medicine. Would personalized medicine be applied to the economically deprived? It is unlikely that some of the basic problems of medical care for the poor will be resolved during the

next decade to consider personalizing the medical care. If patients in Africa have difficulties in getting anti-HIV drugs because of the high cost, genotyping for personalizing care and overcoming drug resistance is a secondary consideration. A concern has been expressed that as pre-emptive treatments become available, the rich in the developing and the developed nations will consume these to avoid genetically predisposing risks without having to change their lifestyle. Rather than worrying about such theoretical concerns, the emphasis should be on sharing genomic information with developing countries and using it to develop cost-effective population-based treatment for endemic diseases in the developing countries such as malaria and tuberculosis. Personalized medicine may eventually prove to be more economical than conventional medicine. One reason for investigating personalized medicine further in the developing countries would be ethnic variations in drug response based on pharmacogenetics.

Pharmacogenetic data currently available do not comprehensively explain drug response variation within the human populations. One of the many reasons as to why the solutions are incomplete is that they are focused on Western patient donors. The genetic causes for variable drug response are heterogeneous among the various nations of the world, and a classification/diagnostic kit that works very well for Caucasians may work poorly for individuals of Asian descent. To generate complete, broadly useful and sensitive drug–patient classification kits, population studies of international representation are required.

Southeast Asian populations and ethnic subgroups have been poorly represented in genomics research and product development efforts. The vast majority of pharmacogenomics research is conducted in North America and Europe primarily because of the difficulties in obtaining specimens from countries such as Malaysia, Indonesia and many other Southeastern Asian countries. To remedy this situation, a subsidiary was established by DNAPrint Genomics in collaboration with a Malaysian biotechnology company – DNAPRO SDN BHD (Kuala Lumpur, Malaysia), DNAPrint. The new company has secured access to a broad range of specimens that allow for the development of pharmacogenomics classification products for this specific population of Southeast Asian descent. The results would be available for application to healthcare of nearly 3.5 billion people worldwide who are of Southeast Asian descent. Currently, there is a considerable interest in personalized medicine in Japan, China and South Korea.

## Advantages and Limitations of Personalized Medicine

Advantages of personalized medicine for those involved are tabulated as follows: the biopharmaceutical industry (Table 15.5), the patients (Table 15.6), and the physicians (Table 15.7). Limitations of personalized medicine are shown in Table 15.8.

One of the limitations of pharmacogenomics-based medicine is that there is a lot more to drug response than genes. Drug treatment outcome represents a complex phenotype, encoded by dozens, if not hundreds of genes, and affected by many

**Table 15.5** Advantages of personalized medicine for the biopharmaceutical industry

| |
|---|
| Reduced costs of drug development |
| Reduced time for drug development |
| Monopoly in a specified segment of the market |
| Increase in the discovery of new drugs |
| Increased revenues from combination of diagnostics packaged with therapeutic products |
| Reduction of the need for black-box warnings |
| Rescue of failed drugs by matching them to patients for whom they are safe and effective |

**Table 15.6** Advantages of personalized medicine for the patients

| |
|---|
| Effective and specific therapies |
| Less risk of adverse effects |
| No time lost in trial and error with ineffective drugs |
| Lower cost of treatment |
| Facilitates personalized preventive healthcare |
| Improvement of Quality of Life |

**Table 15.7** Advantages of personalized medicine for the physicians

| |
|---|
| Avoidance of trial and error approach in selection of drugs |
| Rational therapeutic decisions based on pathomechanism of disease |
| Diagnostic guidance to treatment incorporated in personalized approach |
| Less complications of treatment |
| Increased professional satisfaction |

**Table 15.8** Limitations of personalized medicine

| |
|---|
| Factors other than genes also affect response to drugs |
| Not all the treatments can be personalized |
| Limited support from governments or healthcare organizations |
| Ethical, legal and social problems need to be addressed |
| Approval of new biomarkers from regulatory agencies is difficult |
| Shortage of bioinformatic manpower needed for management of huge amounts of data |
| Technologies required for implementation of personalized medicine still need refinement |
| Routine genetic testing revealing clinically non-relevant information – Incidentalome |



environmental factors; therefore, we will almost always see a gradient of response. Diet, general health, and drug–drug interactions are just some of the factors that alter a drug's performance in a given patient. The genome is not going to give us all the answers, just some of the answers. The other factors will need to be studied as well.

The laudable, longer term objective of personalized medicine cannot be fulfilled however, until one more element of diagnostic testing becomes feasible by the creation of reliable methods to predict how an individual's unique genetic status may predispose him/her to the development of future illness. The development of disease predisposition risk diagnostic tests that map the probability that an individual will

succumb to one or more of the complex late-onset, multigenic, non-Mendelian diseases that account for most patient morbidity and mortality is the most futuristic and technically the most complicated, element of the emerging diagnostic universe.

New genome-scale screening tests may lead to a phenomenon in which multiple abnormal genomic findings are incidentally discovered, analogous to the "incidentalomas" that are often discovered in radiological studies. The "Incidentalome" in radiology has some benefits resulting from discovery of unexpected potentially life-threatening conditions that can be treated prior to clinical manifestations. However, the incidentalome resulting from molecular diagnostics threatens to undermine the promise of molecular medicine in at least three ways (Kohane et al. 2006):

1. Physicians will be overwhelmed by the complexity of pursuing unexpected genomic measurements.
2. Patients will be subjected to unnecessary follow-up tests, causing additional morbidity.
3. The cost of genomic medicine will increase substantially with little benefit to patients.

Given the current limitations of sensitivity and specificity of many genomic tests, application of these for screening of large populations to detect conditions with low prevalence will result in large numbers of false positives. Even if genomic tests were to achieve 100% sensitivity and a false-positive rate of zero, the risk of the incidentalome still remains. Some pathology of disease discovered incidentally never reaches clinical significance and may not influence decision for management. For example, a large number of prostate carcinomas accurately diagnosed after the finding of an elevated prostate-specific antigen level in all likelihood would not contribute to an individual's death and may not be treated.

The role of a genome-wide panel (i.e., a panel of 500,000 genetic polymorphisms all ordered and measured together), however cost-effective to measure, needs to be compared with a series of more focused genomic-based panels with clear indications for use and proper protocols for workup of unexpected findings. The physicians need to be educated to ensure that there is appropriate clinical justification to perform and interpret these tests in a manner that ushers in the era of personalized medicine and does not allow the incidentalome to block its arrival.

## Summary

This chapter deals with the organization and development of personalized medicine. Role of academic as well as commercial players in this area is discussed. Healthcare providers as well as the patients are important factors. The US government is facilitating the development of personalized medicine through support of research as well as proposed reforms in the healthcare system. Prospects of personalized medicine in Europe and the rest of the world are described. Finally the advantages as well as drawbacks of personalized medicine are noted.