Personalized Medicine: Marking a New Epoch in Cancer Patient Management

Maria Diamandis¹, Nicole M.A. White¹,², and George M. Yousef¹,²

Abstract

Personalized medicine (PM) is defined as “a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.” The promise of PM has been on us for years. The suite of clinical applications of PM in cancer is broad, encompassing screening, diagnosis, prognosis, prediction of treatment efficacy, patient follow-up after surgery for early detection of recurrence, and the stratification of patients into cancer subgroup categories, allowing for individualized therapy. PM aims to eliminate the “one size fits all” model of medicine, which has centered on reaction to disease based on average responses to care. By dividing patients into unique cancer subgroups, treatment and follow-up can be tailored for each individual according to disease aggressiveness and the ability to respond to a certain treatment. PM is also shifting the emphasis of patient management from primary patient care to prevention and early intervention for high-risk individuals. In addition to classic single molecular markers, high-throughput approaches can be used for PM including whole genome sequencing, single-nucleotide polymorphism analysis, microarray analysis, and mass spectrometry. A common trend among these tools is their ability to analyze many targets simultaneously, thus increasing the sensitivity, specificity, and accuracy of biomarker discovery. Certain challenges need to be addressed in our transition to PM including assessment of cost, test standardization, and ethical issues. It is clear that PM will gradually continue to be incorporated into cancer patient management and will have a significant impact on our health care in the future. Mol Cancer Res; 8(9); 1175–87. ©2010 AACR.

Introduction

The field of medicine has seen many new advances in the last several decades. With the completion of the human genome project (1), an enormous amount of new information has been gained about the human genome and the genetic variations between individuals. Added to this is the emergence of new technologies for global genomic analysis, including high-throughput sequencing, single-nucleotide polymorphism (SNP) genotyping, and transcript profiling. The construction of haplotype maps of the genome (2, 3) is now allowing us to view DNA in a much bigger picture than ever before. This, coupled with enormous advances in computer systems and bioinformatics, has resulted in a revolutionary shift in medical care to the era of personalized medicine (PM).

PM is defined by the U.S. National Cancer Institute as “a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.” The promise of PM has been on us for some years and is rapidly gaining momentum. The concept of PM is to use clinical, genomic, transcriptomic, proteomic, and other information sources to plot the optimal course for an individual in terms of disease risk assessment, prevention, treatment, or palliation. Thus, PM aims to eliminate the “one size fits all” model of medicine, which has mainly centered on reaction to a disease (treating the symptoms) based on average responses to care, by shifting the emphasis of patient care to cancer prevention and early intervention for high-risk individuals (4, 5). Moreover, understanding the molecular profiles of individuals and how these can cause variations in disease susceptibility, symptoms, progression, and responses to treatment will lead to tailoring medical care to fit each individual patient (6-8).

The objectives of this review are to provide a simplified yet comprehensive overview of the scope of applications of PM and their effect on cancer patient management. We also summarize the basic principles of the most promising approaches for PM. Finally, we address the challenges and controversies that face our transition into an era of PM and provide a vision of how PM can be incorporated into clinical practice. We will avoid technical details and sophistications about specific applications when possible, referring the reader to more specialized articles in this regard. For a number of excellent reviews covering many aspects of PM, please refer to the April 1, 2010 issue of Nature.
The Scope of Clinical Applications of Personalized Medicine

Cancer is a heterogeneous group of diseases whose causes, pathogenesis, metastatic potential, and responses to treatment can be very different among individuals (9). Great variations exist, even between individuals with the same type of cancer, suggesting that genetic factors play an important role in cancer pathogenesis. These differences make cancer an ideal target for the application of PM. The suite of clinical applications of PM in cancer is broad, encompassing a wide variety of fields. Constituting some of these clinical applications are screening, diagnosis, prognosis, prediction of treatment efficacy, patient follow-up after surgery for early detection of recurrence, and the stratification of patients into specific smaller subgroups, thus allowing for individualization of treatment (ref. 10; Fig. 1).

Incorporation of the concept of PM into our health care system will allow patients and doctors to become aware of an underlying disease state, even before clinical signs and symptoms become apparent. In turn, treatment or preventive measures could be taken, even before the disease manifests, which can delay disease onset and symptom severity. PM will also guide treatment decisions by stratifying patients into unique subgroups based on their specific molecular characteristics. Subgroups would preferentially receive targeted therapies to which they are more likely to respond, with the goal of improving response rates and survival outcomes (6). Unnecessary side effects and toxicity of treatment will be reduced, especially in individuals predicted to be “nonresponders” to a particular targeted therapy. Nonresponders would be stratified into alternate subgroups for personalized therapy. Furthermore, an expectation of who will and will not respond to a particular treatment will have an effect on how clinical trials are designed and carried out, reducing their costs and failures. Ultimately, PM is expected to result in an overall reduction in the cost of health care (10). A summary of the currently available commercial tests for the different aspects of PM is shown in Table 1.

PM can also benefit pharmaceutical companies looking to identify unique molecular targets for drug design. Such strategies will reduce the cost of lead discovery, reduce the timeline and costs of clinical trials, and potentially revive drugs that were previously thought to be ineffective (10). The benefits of PM for the pharmaceutical industry are summarized in Fig. 2. Some of the methods currently being used for screening of cancer mutations are described in the succeeding paragraphs.

Cancer screening

A combination of genetic and environmental factors is thought to contribute to an individual’s predisposition to cancer (11). Knowledge of the precise nature of these contributors is important because it can affect the course of action for disease prevention (modifications to behavior and lifestyle) and monitoring of high-risk patients (10). In some cases, the association between genetic factors and cancer is very clear and has a significant effect on clinical intervention. For example, individuals with mutations in the tumor suppressor genes breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2) have a significant risk of developing breast cancer (12) and may choose to take early preventive surgical measures (e.g., prophylactic mastectomy; refs. 13, 14), undergo regular screening, or receive adjuvant therapies (15, 16). BRCA1 and BRCA2 mutations are also associated with other cancers, including ovarian (17), hematologic (18), and early-onset prostate cancers (19), and knowledge about these mutations may affect strategies for clinical management of these cancers (e.g., prophylactic salpingo-oophorectomy; refs. 20, 21). Genetic testing has also been used to identify individuals with inherited mutations in the DNA mismatch repair genes, MLH1 and MSH2, who have a higher risk of developing colon cancer (22). Knowledge of their predispositions can promote early screening colonoscopy for colon cancer, with more frequent testing, to enable early cancer detection and treatment. In addition, screening for RET gene mutations can identify individuals who are at a higher risk of developing multiple endocrine neoplasia type 2 (23) and allows for closer follow-up or prophylactic thyroidectomy. Public databases are constantly being updated with new mutations and polymorphisms associated with cancer (24). These databases can be useful resources for identifying new biomarkers for screening.

Tumor classification and subtyping

One of the revolutionary aspects of PM is that it changes the traditional paradigm of classifying cancers. With PM,
pathologic classification can shift from the histologic scale, which often gives little information on prognosis, individualized treatment options, and chance of recurrence, overlooking the fact that many patients with similar histologic types might experience markedly different disease courses, to the molecular scale, which offers a highly detailed, global perspective of the disease process and promises superior performance over traditional classifications (25-28). Molecular analyses at the protein, DNA, RNA, or microRNA (miRNA) levels can contribute to the identification of novel tumor subclasses, each with unique prognostic outcome or response to treatment, which could not be identified by traditional morphologic methods (10). Recently, molecular classification has been used to identify unique subclasses of cancers, including acute myeloid leukemia (29, 30), glioblastoma (31), breast cancer (32, 33), and renal cell carcinoma (34, 35), and to differentiate between Burkitt’s lymphoma and diffuse B-cell lymphoma (36). Subclassification of cancers into unique molecular groups with distinct prognosis or treatment options will significantly improve patient management.

**Targeted therapy and predictive markers for treatment efficiency**

The ultimate goal of PM is to define the disease at the molecular level so that therapy can be directed at the right population of patients (the predicted “responders”). Thus, elucidating the molecular differences between individuals will have an impact on how new treatments are developed and would be of great benefit to pharmaceutical companies looking to market new cancer drugs. It is now known that even in individuals with similar clinical phenotypes (clinical manifestations and pathologic type), drug therapy is usually only effective in a fraction of those treated, suggesting that other differences account for individual drug responses (7). Being able to predict which patients will

<table>
<thead>
<tr>
<th>Table 1. A partial list of commercial tests currently available for PM in cancer patients</th>
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<td><strong>Test</strong></td>
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<td>-----------------------------------------------</td>
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<tr>
<td>Oncotype Dx Breast Cancer Assay</td>
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<td>Oncotype Dx Colon Cancer Assay</td>
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<td>MammaPrint</td>
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<tr>
<td>HercepTest</td>
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<tr>
<td>Ventana Pathway</td>
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<tr>
<td>TheraScreen: EGFR29 Mutation Kit</td>
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<tr>
<td>TheraScreen: KRAS Mutation Kit</td>
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<tr>
<td>CYP450 Test</td>
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<tr>
<td>BCR-ABL Mutation Analysis Test</td>
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<tr>
<td>EGFR Amplification Test</td>
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<td>EGFR Amplification Test</td>
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<tr>
<td>ALK Gene Rearrangement Test</td>
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<td>EGFR Mutation</td>
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Abbreviations: RT-PCR, real-time PCR; IHC, immunohistochemistry; NSCLC, non–small cell lung cancer; mCRC, metastatic colorectal cancer; CML, chronic myelogenous leukemia; CRC, colorectal cancer; FISH, fluorescence in situ hybridization.
benefit from a drug would promote a shift to identify alternative therapies to improve outcomes in the predicted “nonresponders,” in turn reducing the administration of costly and potentially toxic treatments to them. Furthermore, clinical trials of new drugs could focus on enrolling patient populations in which treatment is predicted to be most efficacious, thus increasing the likelihood of positive outcomes (7).

The concept of PM gained much positive momentum from the development of highly successful U.S. Food and Drug Administration–approved targeted therapies, such as imatinib mesylate (Gleevec) for chronic myeloid leukemia and gastrointestinal stromal tumor (37, 38) and trastuzumab (Herceptin) for breast cancer (39). Using specific molecular characteristics of these cancers as predictive markers for treatment response (abnormal protein tyrosine kinase activity in chronic myeloid leukemia and gastrointestinal stromal tumor and overexpression of the HER-2 receptor in breast cancer), only those individuals who harbor the appropriate molecular alterations are eligible for treatment. It is this subclassification of cancers, and the consequent customization of therapy, that has resulted in the remarkable surge in survival rates for some cancers from zero to 70% (7).

This application of PM has been further shown by the use of mutation screening in the treatment of patients with lung cancer who received the tyrosine kinase inhibitors gefitinib (Iressa) or erlotinib (Tarceva; ref. 40). Non–small cell lung cancers with mutations in the kinase domain of epidermal growth factor receptor (EGFR) are much more responsive to treatment with gefitinib/erlotinib, and more specifically, these drugs are especially effective in subgroups of Asian female never-smokers with adenocarcinomas (41, 42). In contrast, individuals with mutations in the downstream effector KRAS are resistant to erlotinib (43). Activating mutations in KRAS also cause resistance to the drugs cetuximab (Erbitux) and panitumumab (Vectibix) in colon cancer patients, whereas these drugs are effective in cancers with wild-type KRAS (44, 45). Specific responses to drugs based on one’s molecular profile has led to the recent recommendation by the American Society of Clinical Oncology that molecular testing of KRAS be done before the administration of cetuximab or panitumumab to colon cancer patients (46).

Insurance companies have even offered to pay for medication for those individuals with wild-type KRAS (knowing they will respond well to therapy), adding a layer of complexity to the concept of PM. Targeted therapy, as in the cases of lung and colon cancers, highlights the potential for PM to guide patient care and gives hope for the development of new or combination treatments for other cancers based on an understanding of their pathogenesis (47). Additionally, old drugs that may have been dismissed as ineffective in a broader category of cancer patients, or drugs being used to treat other diseases, could be reintroduced into clinical trials that are focused on a specific cancer subgroup to investigate novel effects.

Pharmacogenomics and treatment safety
Genetic variations can also predict treatment dose and safety in different subgroups of cancer patients. Variations in genes that encode drug-metabolizing enzymes, drug transporters, or drug targets can have detrimental effects on patient outcomes following treatment (48). For example, polymorphisms in cytochrome P450 (CYP) enzymes can result in too slow or very fast metabolism of drugs, causing patients to exhibit symptoms of overdose or have no drug response at all (49, 50) by altering the pharmacokinetics of drug metabolism and distribution (48), and could also account for the common occurrence of adverse drug reactions (51). Thus, these polymorphisms could be used to predict optimal drug dosage, minimize harmful side effects, reduce the costs of “trial-and-error dosing,” and ensure more successful outcomes (50). In familial breast cancer, for example, genetic variations in CYP2D6 that confer “poor metabolizer” status have been shown to reduce survival in individuals treated with the chemotherapeutic drug tamoxifen (52). Genetic variability in P-glycoprotein, a drug transporter, affects the pharmacokinetics of the antineoplastic drug paclitaxel in ovarian cancer and is also associated with clinical outcomes (53, 54). The transition to PM already has some pharmaceutical companies placing information about genetic testing (including testing for CYP450 polymorphisms) on drug labels (8, 55).

Prognosis
Until recently, the clinicopathologic parameters of the patient (mainly tumor type, grade, and stage), along with biochemical testing for few tumor markers, were the sole indicators for prognosis and tumor aggressiveness and were consequently used for therapeutic decision-making for cancer patients. However, it has become increasingly clear that prognostic accuracy may greatly be improved by understanding the molecular basis of the different cancer subtypes. Genotyping or gene expression profiling by microarray (56) and protein analysis by mass spectrometry (discussed in the following sections; ref. 57) have already been used to identify numerous prognostic biomarkers.
Such markers can help, either alone or in combination with classic parameters, to substratify patients into smaller distinct prognostic risk groups and guide therapy decisions. Using tissue microarray analysis, Kim et al. (58) constructed a combined molecular and clinical prognostic model for survival that was significantly more accurate than standard clinical parameters for patients with renal cell carcinoma. The Oncotype Dx Breast Cancer Assay, which gives a gene expression profile of 21 genes known to be involved in breast cancer, has also been shown to be a good predictor of the risk of tumor recurrence (59).

Approaches and Tools for Personalized Medicine

Figure 3 summarizes the different approaches and tools available for molecular PM testing. A large array of techniques can be used for PM. Commonly used techniques include PCR, fluorescence in situ hybridization, immunohistochemistry, and sequencing. More recently, the completion of the human genome project opened a new horizon for PM analysis by using high-throughput analysis (60). These include microarray, mass spectrometry, second-generation sequencing, array comparative genomic hybridization, and high-throughput SNP analysis, among others. A common trend among these tools is their ability to simultaneously analyze hundreds or thousands of targets. This multiparametric approach is likely to improve the sensitivity, specificity, and accuracy of new biomarkers (35). In addition to acceleration of biomarker discovery, high-throughput analysis allows a better understanding of the “cross-talk” or interaction between different molecules in the pathogenesis of cancer. In the following discussions, we will highlight some of the commonly used techniques for global analysis.

High-throughput whole genome sequencing

The completion of the human genome project has motivated the development of “next-generation sequencing” technologies (61). High-throughput analyzers from Roche (454 Genome Analyzer), Life Technologies (SOLiD analyzer), and Illumina (Genome Analyzer IIe and HiSeq 2000) now make it possible to analyze millions of nucleotides at once, at a lower cost compared with the traditional Sanger method. These analyzers use pyrosequencing (62) or sequencing by ligation (61), rather than the traditional Sanger end-chain termination method. Table 2 summarizes the commonly used high-throughput sequencers with their features and applications for PM. The advantages of high-throughput sequencing include the capacity to perform multiplex reactions, reduced operating costs, and very fast acquisition of data.

Next-generation sequencing is now being used for global analysis of the genome. Previously, some cancer alleles could not be detected by Sanger sequencing because they were present in extremely low levels in cells. Now, the use of “deep sequencing” (extensive repeated coverage of the sequence of interest; ref. 63) and paired-end sequencing (64) has made their identification possible, thus expanding our understanding of the cancer genome. Laser capture microdissection (65) has also been useful for isolating and enriching cancer cell DNA and RNA obtained from a tissue sample, which can then be used for targeted sequencing. These methods enabled the identification of novel mutations, rearrangements, and other genomic alterations (66-68) that lead to tumorigenesis in acute myeloid leukemia (69, 70), chronic myeloid leukemia (67), and other cancers (71-74).

Methods for high-throughput sequencing continue to evolve. Biotechnology companies such as Complete Genomics, Helicos, and Pacific Biosciences are now working on “third-generation sequencing” methods, which are expected to further reduce cost, increase accuracy and length of reads, and provide even higher-throughput analysis of...
genomes (61, 75). As the reality of faster and cheaper high-
throughput analyses is becoming closer, several biotechnol-
ogy companies are racing to commercialize full genome
sequencing, which is expected within the next few years
(68, 75). Although currently too expensive (∼$48,000
USD for a full genome by Illumina), it is estimated that
the era of the “$1,000” genome is fast approaching (76).

There is no doubt that whole genome sequencing is a
powerful tool for digging deep into the genetic code to
look for influences on disease; however, with such a tool
comes the challenge of determining what information is
most important for analysis and interpretation, and this
is one challenge that will have to be addressed as we move
forward into the era of PM, as discussed later.

Table 2. Commercial analyzers for second-generation sequencing

<table>
<thead>
<tr>
<th>Analyzer</th>
<th>Company</th>
<th>Sequencing method</th>
<th>Throughput</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>454 Genome Sequencer</td>
<td>Roche</td>
<td>Pyrosequencing</td>
<td>&gt;1 million high-quality reads per run and read lengths of 400 bases per 10-h instrument run</td>
<td>De novo sequencing of whole genomes and transcriptomes of any size</td>
</tr>
<tr>
<td>Genome Analyzer IIe</td>
<td>Illumina</td>
<td>Reversible terminator-based sequencing</td>
<td>Combination of 2 × 100 bp read length and up to 500 million reads per flow cell</td>
<td>Genome DNA sequencing and gene regulation analysis, Epigenome ChIP-Seq, Methylation analysis, Transcriptome SNP discovery and structural variation analysis, Small RNA discovery and analysis</td>
</tr>
<tr>
<td>HiSeq 2000</td>
<td>Illumina</td>
<td>Reversible terminator-based sequencing</td>
<td>&gt;30× coverage of two human genomes in a single run</td>
<td>Genomic DNA sequencing, Gene regulation analysis, Epigenome ChIP-Seq, Methylation analysis, Transcriptome SNP discovery and structural variation analysis, Small RNA discovery and analysis</td>
</tr>
<tr>
<td>SOLiD</td>
<td>Applied Biosystems</td>
<td>Sequential ligation</td>
<td>100 Gb and 1.4 billion tags per run (extendable to 300 Gb and 2.4 billion tags per run)</td>
<td>De novo sequencing, Targeted resequencing, Whole genome sequencing, Epigenome ChIP-Seq, Methylation analysis, Transcriptome Gene expression profiling, Small RNA analysis, Whole transcriptome profiling</td>
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Abbreviation: ChIP-Seq, chromatin immunoprecipitation sequencing.
SNP analysis and haplotype mapping

The human genome is estimated to have more than 30 million SNPs, which are essentially the “fingerprints” of our genetic code (77, 78). Some of these have been thoroughly characterized by the International HapMap Project (2, 3) in various populations and made publicly available (79). These databases have provided the necessary tools for researchers to discover associations between disease risk and common SNPs (80). The advent of commercially available microarrays (SNP chips; ref. 81) has resulted in a shift from studying disease by linkage analysis to using genome-wide association studies (82). SNP arrays use allele-specific oligonucleotide probes that produce a fluorescent signal when a specific allele of a SNP is present and are capable of analyzing up to 1 million SNPs in a single sample (83, 84). Alternatively, SNP haplotypes, rather than single SNPs, can be analyzed. SNP arrays can also be used for screening for common features of cancer genomes, such as allelic imbalance, copy number variation, or loss of heterozygosity. SNP arrays have been used extensively to assess various aspects of cancer, including risk assessment (85-87), prognosis (88), survival (89), response to therapy (90), and progression and metastasis (91-93).

Microarray analysis

Microarrays are widely used for global analysis of gene expression in cancer because they are cost-effective and have high throughput (94). Microarrays are chips with immobilized capture molecules (such as oligonucleotides or cDNAs) that serve as probes for binding fluorescently labeled targets (e.g., cDNA) prepared from the two specimens to be compared (e.g., normal versus cancer). Using microarrays, it is possible to assess the expression levels of thousands of genes in a single experiment. There are several platforms for microarray analysis, including the most popular mRNA microarray, miRNA microarrays, DNA arrays (array comparative genomic hybridization), and protein arrays.

Microarrays have been extensively used to study the different aspects of malignancy, especially at the discovery phase. Gene expression profiling has been successfully used for the detection of cancer to categorize different subtypes of a cancer (95-98), identify invasive versus noninvasive phenotypes (99), predict prognosis (95, 96, 100-102), and predict responses to treatment (103-106) and early recurrence (107).

Newer microarray platforms, such as miRNA microarrays, are also showing encouraging preliminary data for their potential use as cancer biomarkers (108-113). MiRNA signatures have been used to stratify patients into prognostic cohorts and treatment subgroups. Finally, microarrays can be used to assess epigenetic changes in cancer (DNA methylation, histone acetylation, serine phosphorylation), which are implicated in tumorigenesis, and can be used to classify cancers and direct patient management (114).

Proteomics by mass spectrometry

Changes in the protein profiles of cancer cells can be important for determining new diagnostic biomarkers and may also aid in the classification of tumors into unique subtypes (115). Proteomic analysis can be advantageous over mRNA measurements because proteins are the final effector molecules and their levels do not always correlate with mRNA levels due to posttranscriptional modifications (116). Furthermore, protein-protein interactions are important contributors to cellular pathways and mechanisms that contribute to carcinogenesis. In mass spectrometry, proteins are ionized into smaller molecules with unique mass-to-charge ratios that can be used to quantify proteins (117). This has led to the identification of several new cancer biomarkers for different malignancies, including breast (118), ovarian (119), prostate (120), and kidney (121, 122) cancers. Proteomics can contribute to tumor classification (123), treatment selection, pharmacoproteomics, and identification of new drug targets and may also be used for therapeutic drug monitoring (124-126). Details of the principles of mass spectrometry are beyond the scope of this review and have recently been covered in a number of excellent reviews.

Genome-wide association studies

Recent technological advances have allowed the examination of genetic variations on a much larger scale than ever before. Genome-wide association studies (GWAS) allow for a complete picture of the genome rather than the smaller sections to which we were previously limited. High-throughput approaches allow for an unbiased examination of genetic variations in many different tumors. There are a number of ongoing GWAS and some of them are listed in Table 3. The Cancer Genetic Markers of Susceptibility project, an initiative of the National Cancer Institute, aims to identify genes involved in breast and prostate cancers by SNP analysis. The Human Genome Project will examine not only mutations but also other genetic abnormalities, such as gene silencing, through methylation and other epigenetic mechanisms, as well as gene translocation, amplifications, and deletions (127).

GWAS are all driven by the quest for future PM. Recent results of GWAS have identified 6q25.1 as a susceptibility locus for breast cancer (128) and two independent loci within 8q24 that contribute to prostate cancer in men of European ancestry (129, 130). GWAS have also indicated clear differences in susceptibility between cancer subtypes. For example, a lung cancer locus identified on 5p15.33 was strongly associated with adenocarcinoma but not squamous or other subtypes (131). Also, aberrations in the ovarian cancer locus BNC2 were associated with the serous subtype only (132). Recent findings indicate that certain mutations can predict patient response to treatment, as was shown for certain EGFR mutations that can predict patient response to the drug gefitinib (Iressa). Recently, a genome-wide scan of SNPs found 20 SNPs that were associated with the effectiveness of platinum-based chemotherapy in small-cell lung cancer patients (133). Also, a genome-wide methylation analysis in mantle cell lymphoma patients found that differentially methylated genes can be targeted for therapeutic benefit (134). Although the use of GWAS
has discovered many genetic loci and SNPs that are related to cancer, more studies are required to identify how these alterations contribute to disease risk (135).

Databases/bioinformatics

An increasingly important new tool to achieve PM is the availability of repositories of freely accessible databases. Information obtained from genomic, transcriptomic, and proteomic analyses is now deposited into large databases for global access and data processing. Some of these include the Cancer Genome Anatomy Project (136), the Single Nucleotide Polymorphism Database (79), the Catalogue of Somatic Mutations in Cancer (24), the Mittleman Database of Chromosomal Aberrations in Cancer (137), the Stanford Microarray Database (138), the Roche Cancer Genome Database (139), the Protein Information Resource (140), and the Human Protein Reference Database (141), in addition to many others. Bioinformatic algorithms can then be used to integrate a patient’s clinical information and the genetic profiles of their tumor to predict the relationships of certain molecular changes to cancer, as discussed earlier.

Personalized Medicine in the Clinic: Challenges and Controversies

As we move into the era of PM, several challenges have to be addressed. The first is to establish a significant clinical utility that is superior to our existing parameters, and this will lead to a “real” improvement in cancer patient care. This requires a team approach, with collaborative efforts between clinicians, research scientists, computer experts, and biostatisticians, to achieve a clinically meaningful outcome. Full transparency in reporting results (especially the negative ones) should be emphasized to avoid selection bias for positive results reporting (35). It also has to be noted in this regard that statistically significant results in a research setting are not always equivalent to clinically significant results. Prospective trials on large patient cohorts are needed to solidify the clinical utility of new tests being offered to cancer patients. Care must be taken when interpreting published results due to the heterogeneity of the analyzed material, which can be obtained from tissues, cell lines, and biological fluids, and when comparing different histologic types, stages, and grades of tumors.

Another important issue is the need for standardization of testing. Standardization encompasses several aspects including the type of specimen to be analyzed, the appropriate methods of specimen collection and storage, the choice of the target genes/proteins to be tested, the platform to be used, optimal experimental conditions, and the clinical interpretation of tests (cutoff values for positive and negative results). There will be a need for quality standards for different laboratories, and test validations will be required with external quality assurance protocols. It may also be necessary to implement Clinical Laboratory Improvement Amendments–certified specialized laboratories to perform particular tests to ensure quality. A recent report by the National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines expounded on two main technologies commonly implemented for PM, microarray and mass spectrometry, and developed recommendations on what must be done before for their application into the clinical realm.

One of the most important considerations will be the higher cost of incorporating new, advanced technologies that will provide more detailed predictive and prognostic information about each individual patient. Setting up the infrastructure for PM will require significant spending. Prices are, however, becoming much more affordable compared with earlier years, as technology becomes more widespread. Following an initial capital investment, additional running costs will become much less. The increased cost of these advanced diagnostic systems will be partially compensated for by savings in patient care cost, such as reduced courses of unnecessary chemotherapy or radiotherapy and reduced hospital stays.

Ethical issues, including who will have access to this new detailed information, especially those at risk of developing cancer, should be adequately addressed. Individuals should

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<th>Table 3. A partial list of genome-wide association studies</th>
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<tr>
<td><strong>Project</strong></td>
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<tr>
<td>Cancer Genetic Markers of Susceptibility</td>
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<tr>
<td>The Consensus Coding Sequence of Human Breast and Colorectal Cancers</td>
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<tr>
<td>The Cancer Genome Atlas</td>
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<tr>
<td>The International Cancer Genome Consortium</td>
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<td>Human Proteome Project</td>
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be free to accept or decline susceptibility testing. The access for insurance companies, other family members, employers, and other agents will need to be clearly stated and new laws may have to be passed to ensure fair treatment, protection, and privacy of the tested individuals. Misuse of genetic information could take place at the expense of those tested. Patients with known risks for developing cancer, those who are expected to have poor outcomes, or those who will not respond well to treatments may be discriminated against or denied employment opportunities or health insurance coverage. Individuals who are expected to not respond to treatment may also be denied certain medications. Also, the cost of targeted therapies is high. In this case, although genetic testing may indicate one would receive benefits from a certain drug, they may have limited access due to wealth or insurance status. In this case, PM will add to the problem of socioeconomic divisions. Furthermore, genetic testing may reveal traits for other serious illnesses (regardless of whether an individual chooses to find out about them or not), which may also affect how they are treated by others. Good policy decisions will be crucial to reap the benefits of PM (142). Luckily, in the United States, laws are already in place to protect patients from these types of issues (8).

**Personalized Medicine: Fantasy or Reality?**

The introduction of the concept of PM initially created a lot of promise in the scientific community. There was optimism for an imminent revolution in our medical practice whereby a molecular “fingerprint” for each cancer patient would replace the clinicopathologic designation system and would provide many pieces of information related to treatment simultaneously. This was, however, followed by a dormant period when promising research results did not cross the bridge to be adopted into clinical applications. One important reason for this is that the new classifiers created new “categories” of patients for which the clinical significance was unknown. One famous example of this is the basal-like phenotype of breast cancer that was created by microarray analysis (143). There are important reasons as to why there has not been a rapid change in the approach to cancer with the introduction of PM. The process of developing a tumor marker for “clinical” use is a tedious and multistep process requiring extensive testing, optimization, validation, and establishment of usefulness above other currently used methods (57).

After years of experience, we developed a more practical view of using molecular genetic information to complement, rather than replace, clinicopathologic parameters. Molecular profiling will be able to answer specific focused questions related to patient management for each particular cancer. In some respects, great leaps have been taken with the introduction of PM approaches to cancer. Several biomarkers have been very useful and are currently being marketed, as described earlier.

**A Future Prospective**

It is clear from recent literature that the concept of PM will have a significant impact on medical practice and is gradually being included as an integral component of our
cancer management plans. It will inevitably result in more effective treatment and fewer side effects for patients and will induce a proactive and participatory role for the patient in their own health care decisions. Patients will have the incentive to engage in lifestyle choices and health maintenance to compensate for their genetic susceptibilities.

Before the era of PM, cancer diagnosis, prognosis, and subsequent treatment decisions were based on histopathologic parameters including the tissue of origin and the stage and grade of the tumor. Experience has shown morphologic classification to be deficient in many aspects and that patients with the same histopathologic diagnosis can have unexplained variable outcomes. Individual molecular markers have been slowly added to ameliorate the accuracy of predicting prognosis and treatment efficiency. We now witness the accumulation of enormous amounts of genomic data generated by high-throughput analyses, which are augmented by tremendous advances in computer analytic systems. PM is a revolutionary concept that challenges our traditional classification and management of cancer. Although very appealing, it is unlikely that it will completely replace traditional approaches, at least in the near future. It will be essential to confirm the validity of new biomarkers generated by PM technologies using prospective clinical trials in independent patient cohorts. This will be an ongoing process that is expected to extend for many years to come.

The introduction of PM requires a very big initial investment, but with it comes the promise of a rewarding and cost-effective future for medical practice. Figure 4 shows one possible future scenario where molecular analysis can be incorporated with the various steps of cancer patient management, from early detection to time of treatment.

PM will be performed hand in hand with the usual histopathologic evaluation to bring together more specific details about every individual cancer, including assessment of risk, aggressiveness, and treatment options. This tumor “fingerprint” will reduce unnecessary treatments and could also extend to other family members who are at risk of developing the same or a related malignancy.

Following the establishment of molecular fingerprints, the examination and incorporation of one’s phenotype into individual disease assessment must be considered (144). Of course, this comes with its own challenges including the requirement of super-computers that can analyze these enormous amounts of data for one person. Integrating data from cancer genetics and functional data into molecular networks could potentially approach a genotypetype-phenotype map (145-147). Although this may be a reality in years to come, we need to approach PM in a stepwise manner and remember that the long-term benefits are yet to come.

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Maria Diamandis, Nicole M.A. White and George M. Yousef

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