Exploring the Human Genome in Cancer with Genomic Approaches

John R. Scheel, PhD, and Michael D. Kuo, MD

J Vasc Interv Radiol 2006; 17:1225–1233

Abbreviations: ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CML = chronic myeloid leukemia, ER = estrogen receptor

CANCER is the second leading cause of death in the United States, and despite the overall decreasing trend in cancer mortality during the past 10 years, it is expected to become the leading cause of death in the next decade. The decrease in cancer mortality has been largely attributed to prevention through the identification of environmental and genetic risk factors, early detection through population-based screening programs, and advances in treatment (1,2). However, as environmental factors are identified and public exposure reduced, the identification of high-risk genes that result in susceptibility to cancer development has primarily been limited to forward genetics, wherein the functions of single genes are typically studied by creating a mutation or deletion in a rodent model. Although most of what is known about the pathophysiology of cancer was learned through this approach, forward genetics is too time consuming and cost inefficient to be applied to every gene responsible for the characteristics of a single cancer, and it is unknown whether the results would be applicable to human cancer. Recently, DNA microarrays have been used to profile and compare the global gene expression patterns of different cancers in human patients. Surprisingly, despite the diversification of gene expression that accompanies unregulated cell division, many similar changes were detected across the same types of cancer.

This report focuses on the advances that have been made in our understanding of cancer biology with the use of functional genomics and how this knowledge translates into determining the diagnosis, prognosis, and treatment of different types of cancers. Additionally, specific areas are identified in which knowledge is deficient and further research is needed. Finally, we briefly discuss how the science of cancer genomics, also known as oncogenomics, could potentially impact the practice of interventional radiology. Although individually tailored medicine is currently economically infeasible and time inefficient, oncogenomics could allow individual patients with cancer to be categorized into molecular subgroups to optimize their treatment and improve overall patient care.

CANCER AND MICROARRAYS

Cancer represents a heterogeneous collection of diseases that all develop by a similar mechanism and share many characteristics. The spectrum of normal to malignant cells is typified by an accumulation of defects in genes directly involved in cell proliferation, differentiation, survival, and death or indirectly involved through cell-signaling pathways (3,4). Signaling pathways are the mechanisms that translate changes in the extracellular environment into changes in intracellular function, primarily through changes in gene expression. Through a process termed clonal selection, cells accumulating mutations and gene expression changes that confer the best survival and proliferative properties "outcompete" and outgrow the other cells. Although the time required to accumulate the number of mutations sufficient for cells to become malignant is variable, cancer is by definition a disease of genetic instability. Therefore, although environmental and dietary factors are important in cancer development, cancer is a genetic disease caused by an accumulation of mutations that ultimately result in large-scale changes in gene expression.

Surprisingly, despite the diversity of mutations found in cancers, the defects appear to affect only a limited number of cell-signaling pathways. Knowledge of these signaling pathways or genetic defects underlying cancer has led to unique targets for drug development and has improved the survival of cancer patients (5). One example is the discovery of the hybrid Philadelphia chromosome t(9;22) in chronic myeloid leukemia (CML) and how this translocation results in the constitutive activation of a tyrosine kinase fusion protein, BCR/ABL (6). The

From the Department of Radiology (J.R.S., M.D.K.) and Center for Translational Medical Systems (M.D.K.), University of California San Diego Medical Center, 200 West Arbor Drive, San Diego, California 92103. Received February 22, 2006; and accepted May 31. **Address correspondence to** M.D.K.; E-mail: mkuo@ucsd.edu

Neither author has identified a conflict of interest.

DOI: 10.1097/01.RVI.0000232498.25928.A1

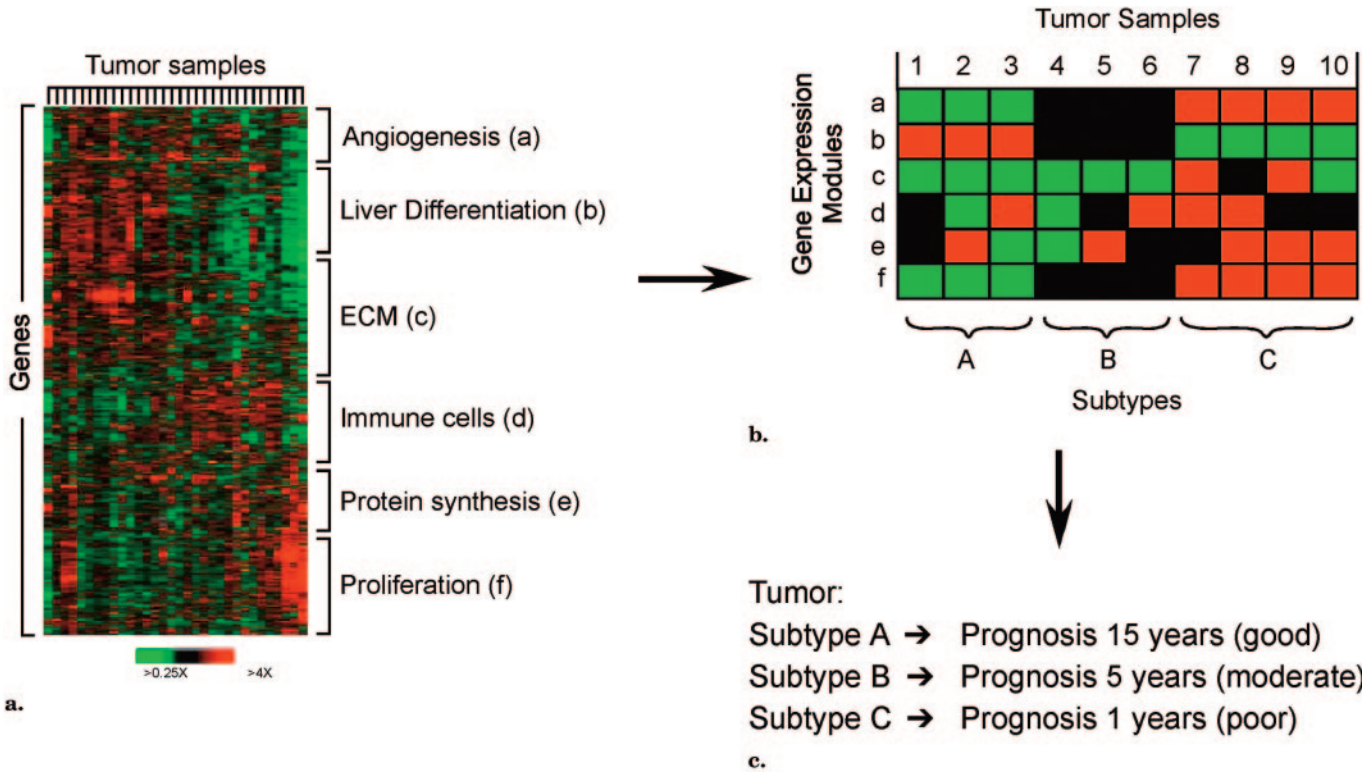

Figure 1. Use of gene expression profiling of cancer to predict patient prognosis. **(a)** In a hypothetical gene expression profile of liver cancer, each row represents a gene and each column represents a tumor sample. The level of expression of each gene in each sample is represented by a red/green scale as indicated in the key. Genes sharing a common biologic process are grouped together as "modules" and are annotated by their general function (angiogenesis, liver differentiation, extracellular matrix, immune cells, protein synthesis, and proliferation). **(b)** Composite matrix partitioning patients into subgroups A, B, and C on the basis of each tumor's average gene expression vector across each of the six liver cancer gene expression modules. **(c)** Each tumor is placed into subgroup A, B, or C on the basis of similar gene expression profiles, wherein the composite of gene module expression determines a good, moderate, or poor prognosis, respectively.

discovery of the primary genetic defect of CML led to the development of the tyrosine kinase inhibitor imatinib (STI571), which blocks the function of the BCR/ABL fusion protein. In addition to decreasing the mortality rate of patients with CML, imatinib has a reduced side-effect profile because it predominantly targets a chimeric protein that is not present in nonmalignant cells (7). Although CML can be successfully treated with allogenic bone marrow transplantation, matched donors are not always available, and the elderly population affected is not always composed of good candidates for this treatment. This example demonstrates how knowledge of gene expression in cancer can result in the development of a marker and treatment for a specific type of cancer.

Another example of how gene expression data can affect the treatment of cancer is the use of tamoxifen in the treatment of estrogen receptor (ER)–positive breast cancer. Approximately 50% of newly diagnosed breast cancers express the ER, which is a transcription factor that regulates the expression of several genes responsible for growth and proliferation. Before the development of the ER antagonist tamoxifen, the presence of ERs correlated to a worse prognosis compared with ER-negative breast cancer (8,9). The different survival rate between these two populations is attributed to a greater resistance to chemotherapy in the ER-positive group (10). Although the use of tamoxifen as adjuvant chemotherapy in patients with ER-positive breast cancer increases the 5-year disease-free survival rate only 4%–12% compared with the control group, when applied to the approximately 200,000 newly diagnosed cases of breast cancer per year, this translates to a significant reduction in the number of deaths (11). This example further demonstrates the potential for the analysis of gene expression data to help determine the prognosis and treatment of cancer.

Although the study of single genes and changes in their expression in cancer has contributed to our understanding of the pathophysiology of cancer, it is not without its limitations. For example, although single genes are important to the development of cancer, the vast majority of cancers are believed to be caused by a change in expression of many genes (3). Additionally, it is likely that an initial mutation in any of a diverse set of genes could allow the development of the same malignancy in different individuals, provided that the mutation allows the cell to escape apoptosis, divide independently of growth and inhibitory factors, or increase the rate of further mutations. In fact, the inter-

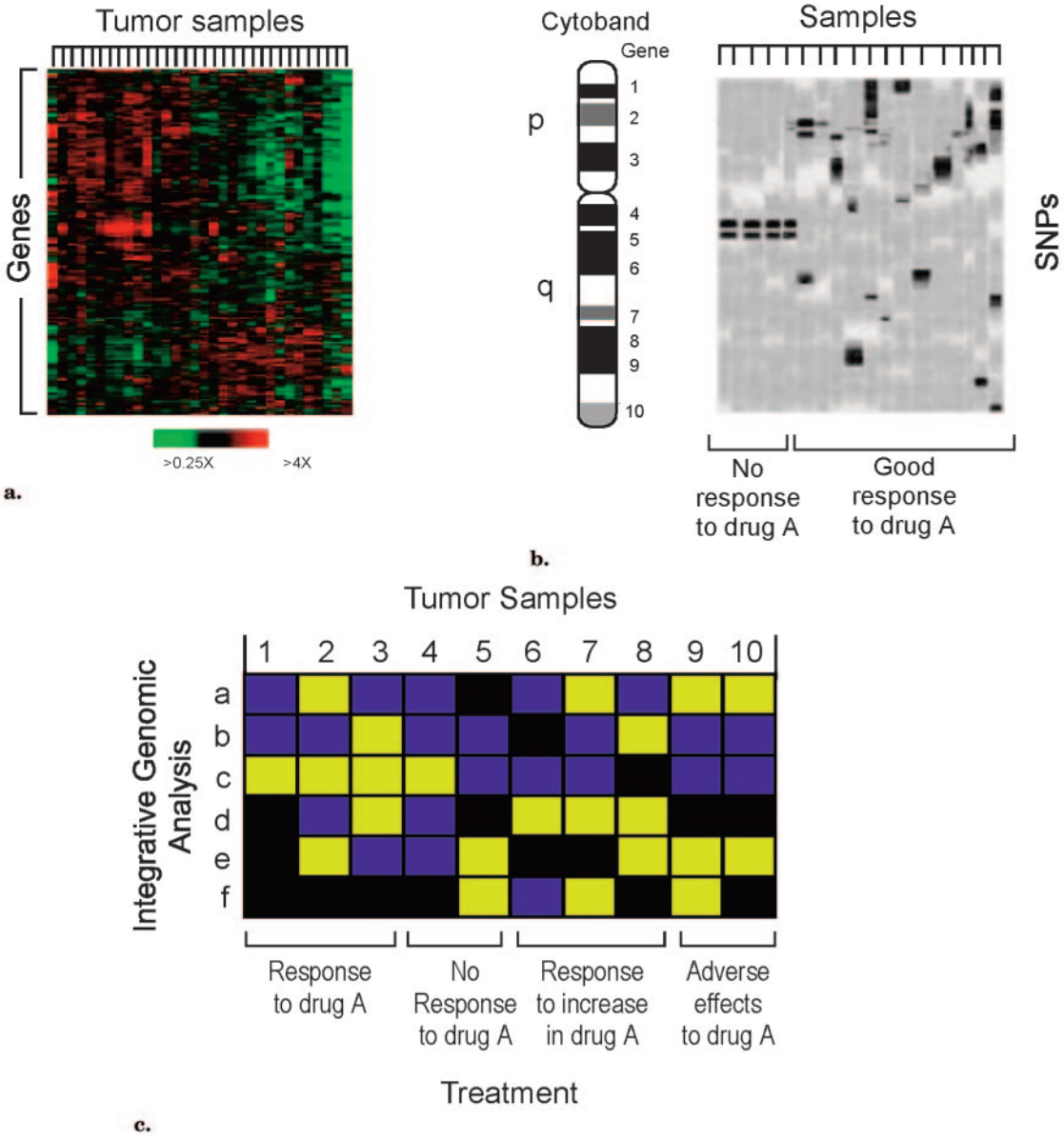

Figure 2. Integration of genome-wide studies to predict individual tumor drug response. **(a)** A hypothetical gene expression profile of liver cancer similar to that in **Figure 1a**, except that, in this example, genes are related to drug metabolism, sensitivity, and resistance. **(b)** Single-nucleotide polymorphism haplotype map of a hypothetical chromosome from the same patients in **a** demonstrating segregation of individuals into responders and nonresponders on the basis of the presence or absence of particular single nucleotide polymorphisms. **(c)** A final composite matrix integrates genome-wide information from gene expression and single nucleotide polymorphism profiling to collectively segregate patients into groups with different patterns of drug response.

val between the time when patients experience symptoms of cancer and the time when they seek medical attention is usually sufficient for a multitude of genetic mutations to accumulate and subsequent changes in gene expression to occur within the same cancer to make addressing these questions unrealistic. Therefore, to identify the genes responsible for the development and pathophysiology of cancer, global gene expression profiles of cancers must be determined from many different patients and compared with one another and with the expression levels of nonmalignant tissue.

Most, if not all, disease processes are accompanied by alterations in gene expression. Cancer is unique because it is driven by genomic instability that is reflected as fundamental alterations in gene expression programs. Microarray technology, described in our previous review, allows the measurement of global gene expression of cells and tissue (12). The use of microarrays to measure and compare the global gene expression profiles of hundreds of tumors derived from hundreds of patients has led to the discovery that tumors originating from the same cell type have several changes in gene expression in common, which

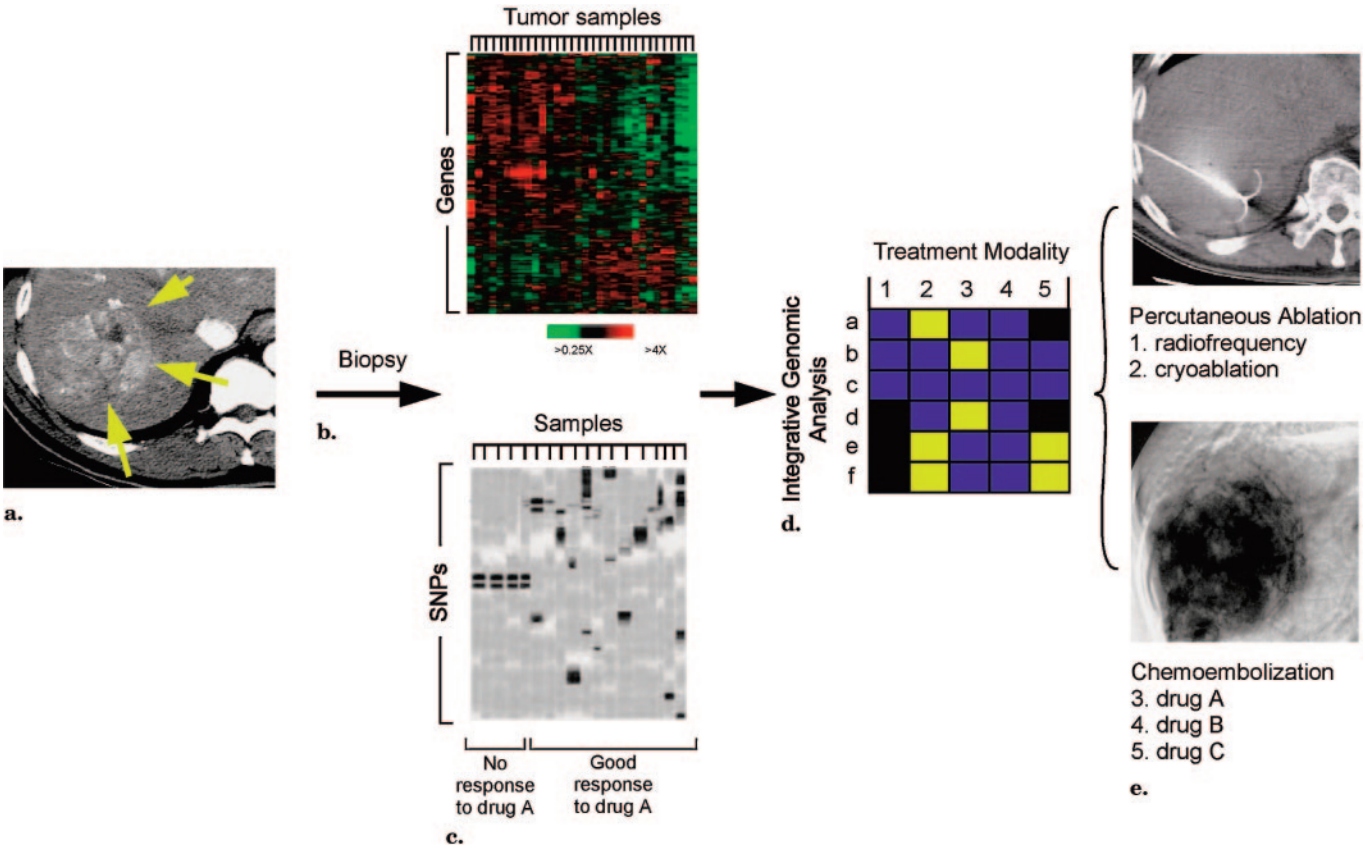

Figure 3. Potential use of interventional radiologic techniques to integrate oncogenomics information to optimize locoregional therapies. **(a)** A patient presenting with cancer first undergoes contrast medium–enhanced computed tomography that demonstrates a large hepatocellular carcinoma. **(b)** An image-guided biopsy is then performed. **(c)** Gene expression profiling and single nucleotide polymorphism analysis are performed on the tissue for classification and treatment response profile. **(d)** Integrative analysis is used to determine treatment possibilities. **(e)** The patient is then treated accordingly with the appropriate locoregional therapy based on the tumor's particular genomic profile.

will be described later in this article. Therefore, if patterns of gene expression changes are unique to specific cancers, one can reason that measurement of the global gene expression of the cancer could be used to identify the type of cancer, regardless of the individual or location at which the cancer specimen was obtained, and help determine a patient's prognosis and the optimal treatment.

GENE EXPRESSION PROFILES USED TO DIAGNOSE AND STAGE CANCER

Currently, there is no general unbiased approach for the classification of cancer in clinical practice. In fact, assigning a diagnosis and determining its subtype is often based on the interpretation of the tumor's morphology, histochemistry, immunohistochemistry, or cytogenetic analysis. Although this can be an effective approach, it is not without limitations, because many cancers can occur over wide age ranges and can present as masses distant from their sites of origin, resulting in a variety of symptoms. Histologic preparations have the benefit of including surrounding tissue, vascularity, and invasion, but they often lack specificity, because two cancers that appear histopathological similar can have significantly different clinical courses and treatment outcomes. By contrast, cytology uses cell markers to increase the specificity of diagnosis but gives no information about tumor invasion or vascularity, which provide important clinical information for solid tumors. Some undifferentiated or poorly differentiated solid tumors provide additional challenges because there are no current markers or characteristics to diagnose the type of cancer. Therefore, an optimal approach to diagnose cancer should be applicable to all types of cancer with a reasonable level of specificity and should include clinically relevant information about the subtype and other characteristics of the cancer.

One of the first groups to pioneer the use of microarrays for cancer class identification and differentiation was Golub et al (13). To design a systematic and unbiased approach for diagnosing cancer and determining its subtype, global gene expression profiles of 38 bone marrow samples derived from patients with known hematologic malignancies—acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)—were determined and analyzed for gene expression changes across 6,817 genes to identify genes whose changes in ex-

pression level were able to distinguish AML from ALL. Surprisingly, 1,100 genes met these criteria, and reanalysis of the tumors with the 50 genes with the strongest correlation to class prediction successfully identified the tumor type in 36 of the 38 samples. Additionally, when these 50 genes were used as criteria to classify 34 additional samples collected from patients of different age groups with different lengths of diagnosis and tissue origins, as well as from different reference laboratories, 29 of 34 samples were correctly classified as AML or ALL, with no incorrectly classified samples. The authors suggest that success could be improved with a standardization of sample preparation (13). Further analysis of these datasets showed that different criteria could be used to reclassify both types of cancers into subpopulations related to their response to chemotherapy and clinical outcome. Remarkably, several genes that were selected as markers for these subpopulations are known targets of currently used chemotherapeutic drugs or molecular markers for these types of cancers. Therefore, despite the diversity in gene expression changes that occur over time with cancer, global gene expression profiling can be used to successfully diagnose and classify tumors.

Further application of microarrays to other types of cancer has supported and extended these findings. Alizadeh et al (14) used global gene expression profiling to explore the molecular basis of the variability in clinical outcome among patients with the most common subtype of non-Hodgkin lymphoma, diffuse large B-cell lymphoma. Despite its current classification as a single subtype, diffuse large B-cell lymphoma has variable disease progression, and only 40% respond well to chemotherapy. To further subdivide this disease into classes that more accurately reflect their natural history, gene expression profiles of lymphocytes from patients with and without diffuse large B-cell lymphomas, as well as from a variety of lymphoma cell lines, were compared. Analysis of a subset of genes that demonstrated differential gene expression uncovered two molecularly distinct subtypes of diffuse large B-cell lymphoma that were associated with different stages of B cell activation and differentiation; namely, the germinal center and activated B-like subtypes. Remarkably, these two subtypes also showed significant differences in clinical outcome, with the group showing an activated b-like gene expression signature having a significantly worse 5-year survival than its germinal center b-like counterpart. Therefore, this study demonstrated that the molecular classification of tumors on the basis of global gene expression profiling could identify previously undiscovered biologically driven and clinically significant cancer subtypes that affected and predicted patient survival.

Although the results of the previously described studies demonstrated that hematopoietic malignancies could be diagnosed, classified, and even reclassified by global expression arrays, the application of this method to solid tumors has presented additional challenges. For example, the expression profiles of solid tumors may be affected by variability in the immune response and the amount of normal tissue that is removed with the tumor. Additionally, several properties of a tumor, such as vascularity, encapsulation, metastasis, and surrounding extracellular matrix, are important in determining the diagnosis, stage, and prognosis of a tumor, and it is unclear whether these characteristics can be reliably detected by gene expression arrays (15). Despite these obstacles, systematic investigations of the gene expression patterns of breast, liver, and brain cancer have been successful at determining gene expression profiles that can be used to classify these cancers into clinically relevant subtypes (16–18).

The results of gene expression studies in cancer have led to several important general concepts that have provided valuable insight into tumor biology and how malignancies might be more accurately diagnosed and classified. First, although considerable heterogeneity in gene expression exists among malignant cells, microarrays can be used to correctly diagnose and classify unknown malignancies. Gene expression data could also allow tumor samples to be classified into subgroups that reflect more clinically useful information, such as the natural history of the disease. Second, comparisons between gene expression profiles of paired samples from the same tumor and different tumors of the same subtype have shown that the dominant features of gene expression profiles are independent of intratumor histopathologic variation (19,20). This finding suggests that gene expression profiles of tumors more accurately reflect the pathologic and clinical differences between tumors than do current histologically based diagnostic criteria. Third, histopathologic features of tumors are often incorporated into their gene expression profiles. The use of microarrays in diagnosing and classifying tumors represents an important extension of our knowledge of cancer; however, further work is still necessary before this research can be applied in the clinical setting.

DETERMINATION OF PROGNOSIS BY GENE EXPRESSION

Microarray experiments comparing cancer and normal cells typically generate large sets of differentially expressed genes. A major challenge in the application of microarray data to clinical oncology is the differentiation of the few important gene expression differences that are specific to cancer from the other gene expression differences that represent cell variability not specific to the cancer (ie, background). However, exclusion of too many of the gene expression changes used to define a cancer subtype could potentially result in cancers with very different natural histories being grouped together. Therefore, the criteria used to define and subclassify a cancer need to be flexible enough to allow for normal variations among patients with the same cancer subtype to be grouped together while still being specific enough to be clinically useful (13).

One method of filtering the list of the hundreds of differentially expressed genes is to focus exclusively on genes with clinical importance, such as genes that correlate with patient prognosis (**Fig 1**). One study comparing the gene expression profiles from 117 patients with primary breast cancer examined this very question (21,22). The investigators initially analyzed a filtered dataset of approximately 5,000 differentially expressed genes. Initial hierarchical clustering of these 5,000 genes identified two major subgroups that began to reveal a struc-

ture related to prognosis. With supervised analysis, the investigators then reduced these initial 5,000 genes to a panel of 70 genes that strongly predicted the appearance of distant metastases within 5 years of diagnosis (23). This 70-gene profile was determined to be a stronger predictor of survival in young patients than the currently used system based on clinical and histologic criteria. Not surprisingly, tumors in the poor prognosis group were found to have increased expression of genes involved in cell cycle regulation, invasion, metastasis, and angiogenesis. Therefore, in breast cancer, an original list of 5,000 genes that are differentially expressed among different tumor samples can be further narrowed to a list of 70 genes that focus predominantly on the prognosis and indeed, in composite, are a very powerful independent predictor of patient outcome.

A similarly designed study comparing the gene expression profiles in glioblastoma multiforme tumors identified 70 genes that were differentially expressed between patients with a relatively good or poor prognosis (18). Overexpression of these 70 genes translated into a 4-month median survival time in the poor prognosis group, in contrast to a 25-month median survival time in the good prognosis group. In contrast to what was expected, the gene expression profiles defining these two subgroups did not necessarily correlate with the differences in tumor histology. Notably, many of the genes associated with a relatively short survival time (ie, poor prognosis signature) were involved in cell migration and invasion, suggesting a possible relation to glial or neural progenitor cells. One of these genes, *FABP7*, is involved in glial cell migration and was found to be strongly predictive of a poor prognosis in an independent dataset based on immunohistochemistry alone. In addition to suggesting a potential mechanism for glioblastoma multiforme pathogenesis, these results identify potential markers for determining a patient's prognosis that may be more clinically valuable than tumor histology alone.

Some cancers, such as prostate carcinoma, already have a marker that can identify affected individuals within a population. In fact, despite being a nonspecific marker, the measurement of serum prostate-specific antigen levels in the United States has successfully identified early-stage cancers in many asymptomatic men. However, although prostate cancer is a leading cause of death in men, it is often an indolent disease. Additionally, although prostate-specific antigen levels can help alert physicians to underlying prostate pathologic processes that warrant biopsy, they cannot be used to determine the prognosis of the patient before treatment. Current methods for prediction of the natural history of the tumor are inadequate; as a result, many men undergo unnecessary and harmful procedures that result in little or no measurable benefit. To identify tumor markers that can distinguish between these two clinical phenotypes, Lapointe et al (24) compared the gene expression profiles of 112 prostate tissue samples (including 62 primary prostate cancers and nine unmatched lymph node metastases) and used the results to define three distinct subtypes of prostate tumors strictly on the basis of their gene expression profiles. Two of these three subtypes included a disproportionate number of tumors that had a more aggressive phenotype, including tumors that were more likely to be high-grade tumors, to metastasize to lymph nodes, and to recur. Despite the large number of genes that are differentially expressed among the three subtypes, some genes were identified as strong predictors of an aggressive or indolent phenotype, as well as tumors with an increased or a decrease risk of recurrence. The results of this study indicated that patients with prostate cancer will potentially benefit from further workup to classify their tumors into one of these three subgroups before they undergo potentially unnecessary and harmful treatment.

The use of gene expression profiles to diagnose and classify tumors based on the basis of prognosis has the potential to change the management of patient care. However, much work remains before microarray technology can be applied to the general population. Although several groups have successfully narrowed the number of genes needed to determine the subgroup or prognosis of a tumor, the list is still too extensive to screen in every patient. Additionally, the number of patients tested with the algorithms used to categorize patients is based on a relatively small sample of tumors. As the number of samples increases, tumors may be excluded from a group with a similar prognosis because the diversity of gene expression changes that result in the same prognosis may increase as the number of samples increase. Based on the cumulative research of microarray technology and algorithms to determine the prognosis of a tumor, this potential caveat appears less likely.

The enormous weight that patients, their families, and their physicians place on the diagnosis and prognosis of cancer makes the development of an accurate method that can be applied to the majority of cases paramount to patient care. Although a wide variety of gene expression changes occur in the development of cancer, the number of genes that predict prognosis appears to be relatively small. Further research in the gene expression changes that determine prognosis may suggest possible mechanisms for the development of cancer and improve the quality of patient care by differentiating patients in whom aggressive therapy would be futile and harmful from patients whose survival and quality of life would benefit from current therapy.

DETERMINATION OF THE OPTIMAL COMBINATION OF CHEMOTHERAPY

Current standards for effective cancer therapy are based on drug trials and years of clinical experience through trial and error. Although this approach has been successful in the treatment of some cancers, it is slow and time consuming. For example, ALL was a lethal disease in the majority of patients who received that diagnosis 25 years ago, but it is now curable in 90% of patients simply as a result of the optimization of combinations of existing drugs. Despite the success of this approach in ALL, some cancers, for unknown reasons, do not respond well to any known combination of chemotherapeutic agents currently available. Therefore, the development of new drugs and of methods to rapidly determine the appropriate chemotherapeutic drug or combination thereof are essential in the devel-

opment of effective treatment strategies for cancer (25,26).

Microarray technology allows the interrogation of thousands of genes simultaneously to generate a gene expression profile that details how a cell responds to its environment. The gene expression profile can then be used to facilitate drug development and optimize combination therapy for cancer (27). In addition to identifying tumors that are sensitive to a single drug or combination of drugs, microarray data can be used to identify individuals or subpopulations that are more likely to experience side effects or beneficial effects from a drug (28). Although this issue is beyond the scope of this review, gene expression data can also be used for therapeutic discovery by prioritizing genes as potential targets. Accordingly, microarray technology is rapidly emerging as a crucial step in the discovery, testing, and optimization phases of drug discovery.

Although age, organ function, and drug interactions have significant influences on the effects of a medication, it is estimated that 20%–95% of the variability in drug disposition and effects are inherited. The variability in the absorption, distribution, metabolism, excretion, and effects of many medications in a population is often coded for by single nucleotide polymorphisms found in the coding and noncoding regions of genes (29). Polymorphisms can affect the expression and function of a gene product and therefore help determine an individual's response and the side effects a drug will cause. As a result of the heterogeneity in the way individuals respond to drugs, a genome-wide approach, termed pharmacogenomics, is used to identify polymorphisms in genes and study how their products influence the pharmacodynamics and pharmacokinetics of a medication in individuals (30). A genome-wide approach allows the simultaneous study of genetic variation in the more than 30 families of drug-metabolizing enzymes found in the human population. It also identifies variations in drug target receptors and drug transport proteins. Although there are currently several examples of polymorphisms associated with an increase in the bioavailability of a drug, a decrease in signal transduction in response to a drug, and alterations in drug metabolism, there remains to be an example of this information changing the course of a patient's treatment (31).

In addition to variations in drug metabolism and effects, genome-wide platforms can be used to detect the presence of polymorphisms that identify tumors that are sensitive to specific chemotherapy regimens. The treatment of patients with cancers that are genetically unlikely to respond favorably to a particular chemotherapy regimen would delay the administration of a potentially beneficial treatment and unnecessarily expose patients to drugs with harmful side effects. For example, in a subset of patients with non–small-cell carcinoma of the lung, the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (Iressa; AstraZeneca, Wilmington, DE) induces tumor regression. High-throughput sequencing of receptor tyrosine kinase genes from genomic DNA of responders and nonresponders determined that the response to the drug correlated with the presence of a polymorphism that resulted in a somatic missense mutation in the epidermal growth factor receptor gene (32). Interestingly, this study also identified subpopulations with a higher prevalence of the mutated epidermal growth factor receptor gene (patients of Japanese decent, women, and patients with adenocarcinomas), further demonstrating the potential of genomic approaches to identify patients with tumors that will respond to specific therapy.

In many cases, tumors may initially respond favorably to a drug but develop resistance as the malignant cells divide. Although all cancers have the potential to develop resistance as a result of their inherent genomic instability, microarrays could be used to identify tumors with the potential to develop resistance to specific drugs, in addition to identifying alternative drugs or adjuvant therapies likely to be more effective (**Fig 2**). For example, a study comparing gene expression differences of ALL and their responses to prednisolone, vincristine, asparaginase, and daunorubicin (33) found that the resistance and sensitivity of the cancer cells was correlated with the expression and repression of a small number of genes. Therefore, the gene expression profile can be used to predict the response of individual cancers to various treatments.

The ultimate goal of pharmacogenomics is to individualize medicine. However, even short of this goal, its application to cancer can enhance drug discovery by identifying new drug targets for the development of subpopulation-specific drugs. The use of microarrays to identify polymorphisms that influence drug metabolism and its effects, as well as to increase the probability of successful chemotherapy treatment, is a way in which a genomic approach may influence clinical decision making in the future (34).

Despite the retrospective success of genomic technology in cancer treatment, few examples exist in which these advances have been translated to clinical practice. To translate the knowledge gained from research in human genomics into better therapeutic agents, prospective controlled trials are needed. Such trials should compare the current strategy of a standardized approach to the treatment of all patients with a type of cancer and then modifying the treatment of nonresponders according to trial and error versus a strategy that uses genomic data from the cancer and patient subpopulations to determine the appropriate treatment. Although a genomic approach would be very expensive to apply to individuals at the initiation of treatment, it might prove to be more cost effective than the current approach because an individual's genetic profile would need to be determined only once in his or her life, and several trials of different chemotherapeutic regimens would be abandoned in favor of the treatment with the greatest probability of success.

GENOMICS AND INTERVENTIONAL RADIOLOGY

As the scope of interventional oncology continues to expand, it will become increasingly important for interventional radiologists to be familiar with new technology that may affect cancer patient care. The use of microarrays to create gene expression profiles of different types of cancer is an example of such a technology that is beginning to influence how we think about the classification and

treatment of cancer. It is likely that the information learned from ongoing oncogenomic research will eventually find its way to the bedside. Therefore, it is important for interventional radiologists to understand how to integrate oncogenomics with the administration of care to patients with cancer, as well as recognize their potential role in contributing to this research.

Gene expression profiling of cancer promises to directly and indirectly revolutionize the way cancer is currently viewed, managed, and ultimately treated. However, to date, the vast majority of cancer gene expression microarray analyses have been performed on large surgically resected tissue specimens, making the practical adoption of this technology to every individual presenting with a potential cancer impractical. Alternatively, radiographic imaging provides a reliable method to noninvasively characterize the location, morphology, and tissue characteristics of the cancer in situ. Accordingly, the coupling of advances in image-guided interventions with advances in array technology and amplification techniques that significantly decrease the amount of tissue required to perform microarray analyses places interventional radiologists in an ideal position to procure tissue for microarray gene expression analysis. In this manner, patients could potentially be treated with a minimally invasive biopsy of their cancer by an interventional radiologist in an outpatient setting that could then be analyzed to provide an individualized genomic profile of their tumor (**Fig 3**). Additionally, it is possible that interventional radiologists could also provide tailored pharmacologic or ablative locoregional cancer therapies based on the prognostic and drug-response profile of the tumor's gene expression profile. For example, primary or metastatic liver tumors that exhibit gene expression signatures implicating susceptibility to certain chemotherapeutic drug regimens, such as antiangiogenic or DNA-stabilizing drugs, could be directly targeted with local intraarterial delivery of molecular-targeted drug regimens tailored to the gene expression profile of the underlying tumor. Alternatively, tumors that express different gene expression signatures may be better suited for ablative therapies. Therefore, interventional radiologists could find themselves actively involved in the transition to personalized medicine by providing the primary care team with the diagnosis, classification, and molecular subtyping of a cancer, as well as the locoregional and molecular-targeted treatment of these tumors.

CONCLUSION

In most if not all cases, the phenotype of a cell, whether normal or secondary to a disease process, can be correlated with a set of genes whose expression is governed by specific regulatory programs. The genetic regulatory programs of a cell are determined directly or indirectly by interactions of that cell with its microenvironment, including responses to pharmacologic, mechanical, and infectious stimuli or stressors. The gene expression profile of a cell is a reflection of its internal state and its local microenvironment. Therefore, the use of microarrays will facilitate our understanding of cancer by providing a detailed molecular window of each tumor at the level of gene expression.

We are already beginning to see potential ways in which the knowledge gained from gene expression profiling of cancer can be translated into clinical application. As we have demonstrated, expression profiling can be used to classify cancers into clinically relevant molecular-based subtypes that reveal underlying tumor biology and help predict prognosis and optimal treatment. Gene expression profiles can also be used to determine the likely side-effect profile and response of an individual to a given drug, and therefore potentially reduce unnecessary drug toxicity. In addition, because tissue is required for these analyses, it is evident that interventional radiologists can play a fundamental role in clinical cancer genomics by providing a simple and safe means of tissue procurement for genomic analysis. Even more so, interventional radiologists can also play a critical role in cancer therapy through delivery of targeted locoregional therapies based on the gene expression results. Therefore, it is clear that expression profiling of cancer will play a fundamental role in personalized medicine and that interventional radiologists can play an active role in its execution.

APPENDIX: GLOSSARY

Pharmacogenomics: the science of developing drug therapies to compensate for genetic differences in patients that cause varied responses to a single therapeutic regimen.

Pharmacodynamics: the study of the action and effects of drugs on living organisms.

Chimeric DNA: DNA that is composed of parts of different chromosomes.

Oncogenomics: the science of cancer genomics.

References

1. Breen N, Meissner HI. Toward a system of cancer screening in the United States: trends and opportunities. Annu Rev Public Health 2005; 26:561–582.
2. Buechler EJ. Pap tests and HPV infection: advances in screening and interpretation. Postgrad Med J 2005;118:37–40,43–46.
3. Alizadeh AA, Staudt LM. Genomic-scale gene expression profiling of normal and malignant immune cells. Curr Opin Immunol 2000; 12:219–225.
4. Chen X, Cheung ST, So S, et al. Gene expression patterns in human liver cancers. Mol Biol Cell 2002; 13:1929–1939.
5. Goldman JM, Melo JV. Chronic myeloid leukemia: advances in biology and new approaches to treatment. N Engl J Med 2003; 349:1451–1464.
6. Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999; 340:1330–1340.
7. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002; 346:645–652.
8. Hortobagyi GN. Treatment of breast cancer. N Engl J Med 1998; 339:974–984.
9. Osborne CK. Tamoxifen in the treatment of breast cancer. N Engl J Med 1998; 339:1609–1618.
10. Sigurdsson H, Baldetorp B, Borg A, et al. Indicators of prognosis in node-negative breast cancer. N Engl J Med 1990; 322:1045–1053.
11. Early Breast Cancer Trialists' Collaborative Group.Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 1992; 339:71–85.
12. Hsiao A, Kuo MD. High-throughput biology in the postgenomic era. J Vasc Interv Radiol 2006; 17:1077–1085.
13. Golub TR, Slonim DK, Tamayo P, et al. Molecular classification of cancer: class discovery and class prediction by gene

expression monitoring. Science 1999; 286:531–537.
14. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000; 403:503–511.
15. Ramaswamy S, Ross KN, Lander ES, et al. A molecular signature of metastasis in primary solid tumors. Nat Genet 2003; 33:49–54.
16. Lee JS, Chu IS, Heo J, et al. Classification and prediction of survival in hepatocellular carcinoma by gene expression profiling. Hepatology 2004; 40:667–676.
17. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003; 100:8418–8423.
18. Liang Y, Diehn M, Watson N, et al. Gene expression profiling reveals molecularly and clinically distinct subtypes of glioblastoma multiforme. Proc Natl Acad Sci U S A 2005; 102:5814–5819.
19. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature 2000; 406:747–752.
20. Garber ME, Troyanskaya OG, Schluens K, et al. Diversity of gene expression in adenocarcinoma of the lung. Proc Natl Acad Sci U S A 2001; 98:13784–13789.
21. van't Veer LJ, Dai H, van de Vijver MJ, et al. Expression profiling predicts outcome in breast cancer. Breast Cancer Res 2003; 5:57–58.
22. van't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002; 415:530–536.
23. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002; 347:1999–2009.
24. Lapointe J, Li C, Higgins JP, et al. Gene expression profiling identifies clinically relevant subtypes of prostate cancer. Proc Natl Acad Sci U S A 2004; 101:811–816.
25. Goldman B. Multidrug resistance: can new drugs help chemotherapy score against cancer? J Natl Cancer Inst 2003; 95:255–257.
26. Golub TR. Mining the genome for combination therapies. Nat Med 2003; 9:510–511.
27. Cheok MH, Yang W, Pui CH, et al. Treatment-specific changes in gene expression discriminate in vivo drug response in human leukemia cells. Nat Genet 2003; 34:85–90.
28. Gerhold DL, Jensen RV, Gullans SR. Better therapeutics through microarrays. Nat Genet 2002; 32(suppl):547–551.
29. Johnson JA, Evans WE. Molecular diagnostics as a predictive tool: genetics of drug efficacy and toxicity. Trends Mol Med 2002; 8:300–305.
30. Evans WE, McLeod HL. Pharmacogenomics: drug disposition, drug targets, and side effects. N Engl J Med 2003; 348:538–549.
31. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science 1999; 286:487–491.
32. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004; 304:1497–1500.
33. Holleman A, Cheok MH, den Boer ML, et al. Gene-expression patterns in drug-resistant acute lymphoblastic leukemia cells and response to treatment. N Engl J Med 2004; 351:533–542.
34. Evans WE, Relling MV. Moving towards individualized medicine with pharmacogenomics. Nature 2004; 429: 464–468.