Genomics and the Continuum of Cancer Care

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The provision of the human genome sequence in 2000 set in motion several waves of cancer research. The identification of an essentially complete set of protein-coding genes, coupled with the discovery of novel transcribed elements such as microRNAs (see the Glossary), has fostered an explosion of investigation using array-based approaches into patterns of gene expression in most cancer types. Similarly, the development of systematic approaches to identify somatic mutations has prompted exhaustive analyses of changes in cancer genomes, including copy-number changes (deletions and amplifications of DNA), rearrangements, small insertions and deletions, and point mutations. Recently, these efforts have culminated in the sequencing of complete genomes of human cancers, providing comprehensive catalogues of somatic mutations. These studies have yielded insights into the genes that contribute to cellular transformation. In parallel, the characterization of inherited variation in human populations has unleashed a surge of exploration into cancer susceptibility, focusing mainly on DNA variants that are common in the general population and that confer small increases in cancer risk. Finally, sets of biologic reagents have been developed that interfere with the function of essentially all genes in living cells, the most widely used being small interfering RNAs. These are being used in myriad ways—for example, to systematically determine which genes are required for cancer cells to survive and which genes confer sensitivity to particular drugs.

Some of the early fruits of this research, along with the techniques needed to implement them, are already being incorporated into clinical oncology. Here, we review the effects that genomic approaches are having on tumor classification, prognostic markers, predictive indicators of drug response, the development of new drug therapies, strategies for monitoring disease, and the management of susceptibility to cancer.

Biologic Classification

For most cancers, we still rely on histologic analysis of stained tissue sections or cells for diagnosis and subclassification. In some tumor types (e.g., breast cancers and the leukemias), molecular markers have been adjuncts to histologic classification for decades. The advent of microarray-based profiling, which measures the expression level of thousands of messenger RNA (mRNA) transcripts in a single experiment, has substantially increased the power to subclassify cancers. Possibly the most celebrated example has been the contribution of expression profiling to the classification of breast tumors. Although pathologists have long been aware of...
the heterogeneity of this disease, expression profiling has contributed to the development of a classification that usually includes the major molecular subtypes of basallike, positive for human epidermal growth factor receptor 2 (HER2), normal breastlike, luminal A, and luminal B. This classification is still evolving but has become a widely used conceptual framework in clinical breast oncology, with the different subtypes having markedly different clinical and biologic features, including patient survival. In routine clinical practice, however, classification is still based on conventional histologic analysis, coupled with immunohistochemical staining for estrogen receptor (ER), progesterone receptor (PR), and HER2, which when combined can reconstruct most of the subclasses defined by mRNA expression.

Beyond refinement of tumor classification, how might these advances be used? An example of a standard clinical classification problem that conventional histologic analysis has often struggled to address is ascertainment of the primary tissue of origin of a metastatic cancer. Gene-expression signatures, however, can provide acuity of resolution beyond that of the microscope-aided human eye, and since elements of the expression pattern of the tissue of origin are often retained in the cancer, analysis of expression profiles, particularly those that include expressed microRNAs, often provide additional insight, although they are not currently used in routine clinical practice.

**PROGNOSTIC INDICATORS**

The use of gene-expression signatures has empowered the identification of prognostic subclasses. For example, gene-expression profiles have been used to define the risk of relapse in patients with early-stage breast cancer. Three profiles have shown prognostic ability: the 70-gene profile (MammaPrint), approved by the Food and Drug Administration (FDA); the 21-gene recurrence score (Oncotype DX); and the 76-gene outcome Rotterdam signature. These profiles, which are obtained with the use of tumor-derived mRNA assayed on either DNA microarrays or by quantitative reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay, are being used in clinical practice to predict prognosis and hence to influence therapeutic intervention. The use of the Oncotype DX assay is included in the 2007 guidelines of the American Society of Clinical Oncology for the evaluation of patients with node-negative, ER-positive disease to identify those who may obtain the most benefit from adjuvant tamoxifen and who may not require chemotherapy. Remarkably, a recent multicenter study of physician practice showed that the medical-oncologist treatment recommendation has changed for almost a third of patients in this subgroup on the basis of this assay.

In a similar vein, a 12-gene expression signature has been developed for colon cancer. It is an independent predictor of recurrence in patients with stage II disease and may help to define more accurately patients who will not benefit from chemotherapy. Among hematologic cancers, gene-expression profiling identified a 133-gene signature in adult patients with acute myeloid leukemia of normal karyotype that provides prognostic information independent of other known adverse features. Similarly, gene-expression analyses have identified new prognostic subtypes in diffuse large-B-cell lymphoma (DLBCL),

<table>
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<th>Glossary</th>
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<tr>
<td><strong>Cancer genome:</strong> The entire set of unique DNA that makes up a specific cancer.</td>
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<td><strong>Deep sequencing:</strong> Genetic sequencing at sufficiently high coverage to identify low-frequency mutations.</td>
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<td><strong>Epigenomic:</strong> Pertaining to changes in the regulation of the expression of gene activity without alteration of genetic structure.</td>
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<td><strong>Genomewide association study:</strong> An approach used in genetics research to look for associations between many (typically hundreds of thousands) specific genetic variations (most commonly single-nucleotide polymorphisms) and particular diseases.</td>
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<td><strong>Inactivating mutation:</strong> A change in the DNA sequence of a specific gene that results in loss of biologic function.</td>
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<td><strong>Gene knock-down:</strong> Techniques by which the expression of one or more of an organism’s genes are reduced by treatment with a specific sequence of RNA that targets a specific gene.</td>
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<td><strong>Messenger RNA (mRNA):</strong> RNA that serves as a template for protein synthesis.</td>
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<td><strong>Microarray-based profiling:</strong> The use of gene-expression signatures from cancer samples to define some aspect of outcome (e.g., recurrence rates and drug response).</td>
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<td><strong>MicroRNA:</strong> A short regulatory form of RNA that binds to a target RNA and generally suppresses its translation by ribosomes.</td>
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<td><strong>Next-generation sequencing:</strong> DNA sequencing that harnesses advances in miniaturization technology to simultaneously sequence multiple areas of the genome rapidly and at low cost.</td>
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<td><strong>Quantitative reverse-transcriptase polymerase chain reaction (RT-PCR):</strong> A laboratory technique based on the polymerase chain reaction, which enables both detection and quantification of gene expression.</td>
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<td><strong>Small interfering RNA:</strong> A short, double-stranded regulatory RNA molecule that binds to and induces the degradation of target RNA molecules.</td>
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<td><strong>Transcriptomic:</strong> Pertaining to the study of the transcriptome, the set of all RNA molecules in any population of cells; the examination of the expression level of messenger RNA is typically carried out with the use of DNA microarray platforms.</td>
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which improves the difficult discrimination between Burkitt’s lymphoma and DLBCL.\textsuperscript{14,15}

There is concern, however, about the incorporation of gene-expression signatures into routine clinical practice before confirmation of their efficacy from suitably powered, randomized, controlled trials. This has prompted large trials to test the efficacy of MammaPrint and Oncotype DX in predicting the benefit of adjuvant chemotherapy in patients with node-negative breast cancer or 1 to 3 positive nodes for adjuvant chemotherapy. In cases in which the clinicopathological risk and the 70-signature risk are discordant, patients are randomly assigned to a treatment strategy on the basis of either set of criteria. The study shows how gene-expression signatures can be incorporated with clinical decision making in the design of clinical trials that address questions such as the utility of adjuvant treatment in patients with cancer after resection of the primary tumor. ER denotes estrogen receptor, and PR progesterone receptor.

\textbf{Figure 1. Use of a Gene-Expression Profile to Define the Risk of Relapse in Patients with Early-Stage Breast Cancer.}

In the ongoing MINDACT (Microarray in Node Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy Trial), investigators are comparing a 70-gene–expression signature (MammaPrint) and common clinicopathological criteria in selecting patients with node-negative breast cancer or 1 to 3 positive nodes for adjuvant chemotherapy. In cases in which the clinicopathological risk and the 70-signature risk are discordant, patients are randomly assigned to a treatment strategy on the basis of either set of criteria. The study shows how gene-expression signatures can be incorporated with clinical decision making in the design of clinical trials that address questions such as the utility of adjuvant treatment in patients with cancer after resection of the primary tumor. ER denotes estrogen receptor, and PR progesterone receptor.

\textbf{Optimizing the Use of Therapeutics}

The common experience of practicing oncologists is that only a subgroup of patients with a specific type of cancer will derive substantial benefit from a particular therapy. Differences in responses to the same treatment among patients are unsurprising in light of the substantial ge-
nomic heterogeneity that exists among tumors. Some of these genomic differences have an important role in determining the likelihood of a clinical response to treatment. Notably, in instances in which the therapeutic agent is targeted at a particular cellular protein, genomic alterations in the gene encoding that protein can be major determinants of response. For example, overexpression and amplification of HER2 in breast cancer is a strong predictor of benefit from treatment with trastuzumab, an antibody directed against HER2. On the basis of such findings, the FDA approved trastuzumab in 1998 for use in the treatment of HER2-amplified metastatic breast cancer.

Following this and other examples, most new agents entering clinical trials over the past decade have been postulated to influence pathways important for the proliferation or survival of cancer cells. The genes involved in these cellular pathways are frequently mutated as a consequence of somatic alterations (point mutations, deletions, amplifications, and translocations) known as driver mutations, which directly contribute to the abnormal growth of the cancer cell. As a result, the presence or absence of mutations within these genes can have a profound effect on a patient’s response to a specific targeted therapy.

For example, small-molecule inhibitors of epidermal growth factor receptor (EGFR) kinase activity were originally developed for cancer treatment because of the known role of EGFR in regulating cellular proliferation and because the gene is overexpressed in many cancers. Subsequently, the discovery of activating somatic mutations of EGFR in non–small-cell lung cancer defined a subgroup of patients who had a particularly good response to EGFR inhibitors. A large prospective study has now shown that the response rate to targeted EGFR inhibitors in patients with non–small-cell lung cancer whose tumors harbor an activating EGFR mutation is 71%, as compared with 1% for those without a mutation. As a consequence of this and other similar trials, the analysis of tumor-biopsy samples for a subgroup of key mutations in cancer genes that confer sensitivity to targeted agents has been introduced as a routine diagnostic test in some centers.

In some instances, a therapeutic agent may have synergistic effects with a mutated gene even though the agent is not directly targeted at the protein encoded by the mutated gene. For example, inhibitors of protein poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP), which suppress a type of DNA repair, appear to be particularly effective in cancers defective in double-strand break repair because of inactivating mutations in BRCA1 or BRCA2. This synergy, often termed synthetic lethality, is thought to occur consequent to an overwhelming burden of unrepaired DNA damage in tumor cells rendered defective for both DNA-repair processes.

It is anticipated that many of the new therapeutic agents currently in development pipelines will enter the clinic accompanied by evidence implicating specific genetic alterations as predictive of response (Table 1). If this indeed transpires, an ever-increasing battery of diagnostic genetic tests to be performed on each cancer will be required to deploy these agents in the most effective and parsimonious manner. Recent sequencing studies of solid tumors have shown that many cancer genes are mutated in less than 10% of tumors of any single type. Therefore, for this targeting approach is to be generally effective, a much larger repertoire of drugs (and diagnostic tests) will be required to optimally treat most patients with a particular type of cancer.

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<th>DEVELOPMENT OF NEW THERAPEUTICS</th>
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<td>The development of inhibitors targeted to proteins encoded by mutated cancer genes has now been achieved with repeated success. The paradigm is best exemplified by imatinib (Gleevec), a potent inhibitor of the Abelson (ABL) kinase, in chronic myeloid leukemia (CML). The discovery of the Philadelphia chromosome in 1960 in a majority of patients with CML set the stage for a series of discoveries that ultimately revolutionized the treatment of this disease. This genomic alteration results in a reciprocal translocation between two genes on the long arms of chromosome 22 (where BCR is located) and chromosome 9 (where ABL resides), resulting in the formation of a chimeric, oncopgenic fusion protein (BCR-ABL) in which the ABL kinase is activated. Clinical trials of imatinib for the treatment of CML showed its substantial superiority over conventional chemotherapy, and in the United States, the FDA approved imatinib as first-line treatment...</td>
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In a 2006 study, the overall rate of 5-year survival for patients with newly diagnosed chronic-phase CML who were treated with imatinib was 89%.

The success of imatinib in CML was quickly extended to gastrointestinal stromal tumors (GIST), the majority of which sport a receptor tyrosine kinase (called c-Kit) that is activated by mutation. Because imatinib potently inhibits c-Kit, its therapeutic effect on GIST was tested in clinical trials, and objective response rates of more than 50% were obtained, comparing favorably to a response rate of less than 5% for conventional chemotherapy.

Although these are important examples of therapeutics targeting the products of genomic

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<th>Gene</th>
<th>Genetic Alteration</th>
<th>Tumor Type</th>
<th>Therapeutic Agent</th>
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<td>EGFR</td>
<td>Mutation, amplification</td>
<td>Lung cancer, glioblastoma</td>
<td>Gefitinib, erlotinib</td>
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<td>ERBB2</td>
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<td>FGFR1</td>
<td>Translocation</td>
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<td>PKC412, BIBF-1120</td>
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<tr>
<td>FGFR2</td>
<td>Amplification, mutation</td>
<td>Gastric, breast, endometrial cancer</td>
<td>PKC412, BIBF-1120</td>
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<td>FGFR3</td>
<td>Translocation, mutation</td>
<td>Multiple myeloma</td>
<td>PKC412, BIBF-1120</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>Mutation</td>
<td>Glioblastoma, gastrointestinal stromal tumor</td>
<td>Sunitinib, sorafenib, imatinib</td>
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<tr>
<td>PDGFRB</td>
<td>Translocation</td>
<td>Chronic myelomonocytic leukemia</td>
<td>Sunitinib, sorafenib, imatinib</td>
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<tr>
<td>ALK</td>
<td>Mutation or amplification</td>
<td>Lung cancer, neuroblastoma, anaplastic large-cell lymphoma</td>
<td>Crizotinib</td>
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<td>c-MET</td>
<td>Amplification</td>
<td>Gefitinib-resistant non–small-cell lung cancer, gastric cancer</td>
<td>Crizotinib, XL184, SU11274</td>
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<td>IGF1R</td>
<td>Activation by insulin-like growth factor II ligand</td>
<td>Colorectal, pancreatic cancer</td>
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<td>c-KIT</td>
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<td>Sunitinib, imatinib</td>
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<td>FLT3</td>
<td>Internal tandem duplication</td>
<td>Acute myeloid leukemia</td>
<td>Lestaurnitin, XL999</td>
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<td>RET</td>
<td>Mutation, translocation</td>
<td>Thyroid medullary carcinoma</td>
<td>XL184</td>
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<td>ABL</td>
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<td>JAK2</td>
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<td>Chronic myeloid leukemia, myeloproliferative disorders</td>
<td>Lestaurnitin, INCB018424</td>
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<td>SRC</td>
<td>Overexpression</td>
<td>Non–small-cell lung cancer; ovarian, breast cancer; sarcoma</td>
<td>KX2–391, dasatinib, AZD0530</td>
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<td>BRAF</td>
<td>Mutation (V600E)</td>
<td>Melanoma; colon, thyroid cancer</td>
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<td>Aurora A and B kinases</td>
<td>Overexpression</td>
<td>Breast, colon cancer; leukemia</td>
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<td>Polo-like kinases</td>
<td>Overexpression</td>
<td>Breast, lung, colon cancer; lymphoma</td>
<td>BI2536, GSK461364</td>
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<td>MTOR</td>
<td>Increased activation</td>
<td>Renal-cell carcinoma</td>
<td>Temsirolimus (CCI-779), BEZ235</td>
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<td>PI3K</td>
<td>PIK3CA mutations</td>
<td>Colorectal, breast, gastric cancer; glioblastoma</td>
<td>BEZ235</td>
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<tr>
<td>BRCA1 and BRCA2</td>
<td>Mutation (synthetic lethal effect)</td>
<td>Breast, ovarian cancer</td>
<td>Olaparib, MK-4827 (PARP inhibitors)</td>
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*PARP denotes poly(adenosine diphosphate–ribose) polymerase.

For CML in 2001. In a 2006 study, the overall rate of 5-year survival for patients with newly diagnosed chronic-phase CML who were treated with imatinib was 89%.

The success of imatinib in CML was quickly extended to gastrointestinal stromal tumors (GIST), the majority of which sport a receptor tyrosine kinase (called c-Kit) that is activated by mutation. Because imatinib potently inhibits c-Kit, its therapeutic effect on GIST was tested in clinical trials, and objective response rates of more than 50% were obtained, comparing favorably to a response rate of less than 5% for conventional chemotherapy.

Although these are important examples of therapeutics targeting the products of genomic
alterations specific to the cancer, the mutated genes that were involved were discovered well before sequencing of the reference human genome began in earnest. However, increasingly extensive systematic sequencing of cancer genomes over the past few years has identified several new mutated cancer genes. Some of these recommend the proteins that they encode as targets for new therapeutics, particularly those that encode enzymes such as kinases and in which the mutations result in constitutive activation. Examples include BRAF, PIK3CA, FGFR2, JAK2, AKT1, and IDH1, and searches for inhibitors of the proteins encoded by many of these mutated genes are in progress.

A notable example of a protein activated through somatic mutation in cancer is BRAF, a serine–threonine kinase. Activating mutations in BRAF were identified by a systematic search of candidate cancer genes in a panel of diverse cancers; BRAF was then shown to be mutated in about two thirds of malignant melanomas. Because of the limited treatment options for metastatic malignant melanoma, the discovery of BRAF mutations triggered multiple drug-discovery programs in the academic and pharmaceutical sectors. Preliminary results from phase 1 clinical trials of agents emerging from these programs have shown extraordinary activity, and further trials are in progress (Fig. 2). It has taken less than a decade to progress from discovery of mutated BRAF in melanoma to targeted therapies showing promise in clinical trials, illustrating the remarkable pace afforded by the coupling of drug development to genomics and biology.

Unfortunately, many mutated cancer genes do not make tractable targets for new-drug development. In this context, the development of agents that show synthetic lethality with mutated cancer genes seems like a sensible approach. For example, RAS gene family members are mutated and activated in 10 to 20% of human can-
cancers. Efforts to develop drugs that directly inhibit oncogenic RAS have been unsuccessful. However, the introduction of libraries of small interfering RNAs, each of which knocks down the expression of one of thousands of genes in cancer cells in vitro, has identified an interaction between mutated KRAS and a couple of protein kinases, STK33 and TBK1. Some cells with KRAS mutations are dependent on the expression of STK33 and TBK1 for survival, whereas cells with normal versions of KRAS are not. Since these kinases are likely to be more tractable drug targets than KRAS itself, the development of inhibitors of STK33 and TBK1 illustrates a potential therapeutic strategy that may apply to a broad spectrum of tumors.

Large-scale cancer genome studies, such as the International Cancer Genome Consortium and the Cancer Genome Atlas, are already applying next-generation sequencing technologies to tumors from 50 different cancer types to generate more than 25,000 cancer genomes at genomic, epigenomic, and transcriptomic levels and should generate a complete catalogue of oncogenic mutations, some of which may prove to be new therapeutic targets. Intriguingly, two recent studies suggest that genomes evolve as a cancer progresses. Deep sequencing of two primary breast cancers and subsequent metastases showed novel mutations or enrichment for low-frequency mutations in the metastases, pointing to the possibility that analysis of metastatic tissues of some cancers may identify additional mutations that may be important drug targets.

**ACQUIRED RESISTANCE TO THERAPY**

The rational use of therapeutics that target the products of mutated genes has had considerable success, but many patients have a relapse because their tumors become resistant to the drugs. Genomic changes, originally present in small subclones of cancer cells, often underlie acquired resistance in these circumstances. These range from an additional point mutation within the gene encoding the protein to which the drug is targeted — such as ABL mutations in CML and EGFR mutations in non–small-cell lung cancer — to amplification of an entirely different cancer gene, such as MET in non–small-cell lung cancer.

The nature of the resistance mechanisms dictates the therapeutic approaches adopted in second-line therapy. These approaches may include the use of second-generation inhibitors capable of overcoming resistance mutations in target genes, as is the case in CML and non–small-cell lung cancer, or combination strategies that involve targeting the protein products of both the primary mutated gene and additional mutated genes.

If resistant clones are present at low frequency in the primary tumor, an important question is whether they could be detected at an early stage, thus influencing the choice of primary therapy. Deep sequencing of cancer genomes is capable of detecting small numbers of resistant cells and so could inform up-front combination-treatment strategies that might minimize the chances of the resistant clones ever expanding to dominate the tumor-cell population.

**MONITORING OF DISEASE BURDEN AND EARLY RECURRENCE**

For most solid tumors, monitoring of disease burden is achieved through various imaging methods, supplemented in a few cancer types by measurement of circulating tissue-specific markers (e.g., prostate-specific antigen in prostate cancer). For some cancers, however, detection of tumor-specific genetic abnormalities in blood samples has been used to quantify tumor load. This strategy has been particularly fruitful in hematologic cancers, in which treatment decisions are routinely based on the levels of certain genetic alterations. This success has depended on the recurrent gene rearrangements that are found in many hematologic cancers. Because of the possibility of designing PCR primers that specifically amplify the abnormally connected genomic segments, such rearrangements are ideal substrates for technically straightforward, highly sensitive and specific assays. For example, in patients with CML who have a reduction in quantitative BCR-ABL transcript levels by a factor of 100 after treatment, there is typically a durable response, and rising levels of BCR-ABL transcript often indicate the accelerated growth of neoplastic clones that have developed resistance to imatinib, triggering a switch to alternative therapies.

This strategy has not been routinely applied to the clinical management of most solid tumors,
primarily because of the absence of known recurrent genetic translocations or rearrangements. However, since dying cells in many solid tumors release naked DNA into the circulation, the tumor burden theoretically could be monitored by blood sampling similar to that done for hematologic neoplasms. Low levels of tumor-specific point mutations have been detected in the peripheral blood of patients with solid tumors. These mutations have been used to detect relapse of colorectal cancers and also the presence of a secondary resistance mutation in patients with non–small-cell lung cancer who are treated with EGFR kinase inhibitors. This strategy is difficult to implement widely in clinical practice because the detection of a small subpopulation of DNA fragments carrying a point mutation is technically challenging. However, most solid tumors carry genomic rearrangements that are specific to each individual patient. Indeed, recent studies have shown that rearrangements that are detected in primary cancers by next-generation sequencing can be used to detect circulating tumor DNA, the levels of which correlate with tumor load. Thus, it may be possible to monitor the cancer burden of almost all patients with solid tumors in a way similar to that used in monitoring hematologic cancers (Fig. 3, and an interactive graphic, available with the full text of this article at NEJM.org).

At present, the detection of early relapse for most cancers does not yield improvements in survival, and this will continue to be the case in the absence of more effective therapies. We would hope that such therapies will result from the generation of catalogues of recurrent somatic mutations among most of the major cancer types. However, early detection is currently likely to be important for cancers (e.g., colorectal cancer) for which surgical resection of relapsed disease translates into substantial improvements in survival. The utility of this strategy requires stringent evaluation through clinical trials.

**GENOMICS IN THE DESIGN OF CLINICAL TRIALS**

As described earlier, the targets of many new anticancer drugs are proteins encoded by genes with driver somatic mutations in cancer. Thus, many such agents may be efficacious only in a subgroup of patients whose tumors harbor these mutations. Since this subgroup may be relatively small, the effectiveness of some drugs may not be detected if the study group is composed of patients who are not selected on the basis of mutation status. This finding has prompted changes to standard clinical-trial design in which the study population is enriched with patients whose tumors carry a particular mutation, set of mutations, or other biomarker increasing the likelihood that such tumors will be sensitive to the intervention.

For some drugs, however, there is no a priori indication of the biologic determinants underlying the responsiveness of a subgroup of patients, and therefore it is not possible to reconfigure trial design. Nevertheless, currently undiscovered determinants of sensitivity and resistance are likely to be buried within the genome and transcriptome of each tumor. With the costs of genome sequencing dropping precipitously, one could consider in the not-too-distant future the complete sequencing of cancer genomes and transcriptomes as routine accompaniments to clinical trials of cancer drugs in order to reveal these determinants.

**SUSCEPTIBILITY TO CANCER**

Several inherited abnormal genes that confer a substantially elevated risk of cancer and that are present in families with multiple affected members were discovered in the decades before 2000. Examples are BRCA1 and BRCA2, in which mutations confer an increased risk of breast and ovarian cancer, and MLH1 and MSH2, in which mutations confer an increased risk of colorectal cancer. Testing for mutations in these genes, which are rare in most populations, is now a conventional clinical approach. The results of these tests influence screening and other preventive measures.

Provision of the human genome sequence has recently allowed cataloguing of most commonly inherited DNA variants present in the normal population. Such work has led to the identification of a major new class of variants conferring cancer susceptibility. Genomewide association studies, which compare the prevalence of hundreds of thousands of inherited variants between large series of patients with disease and control subjects, have been applied to several cancer types. These studies have resulted in the
Figure 3. Identification of Cancer-Specific Chromosomal Rearrangements from Sequencing of a Cancer Genome.
On the basis of a tumor-biopsy sample, massively parallel paired-end sequencing detects chromosomal rearrangements that can be used to monitor relapse or response to treatment from serial blood samples from the patient.
identification of many new DNA variants conferring susceptibility to several different types of cancer, including cancer of the breast, prostate, colon and rectum, lung, and testis, along with chronic lymphocytic leukemia and other cancers. The inherited variants that are initially associated with a disease are not necessarily themselves the functional changes but are usually located adjacent in the genome to the true causative variants. In general, these common susceptibility variants, which may be present in the majority of the population, confer a very small increased risk of disease, rendering them of very limited utility in clinical practice. However, there may be opportunities in the future to test several such variants together at a population level, perhaps to identify persons who are at a relatively increased risk for entry into disease-screening programs or in the context of familial disease caused by high-risk susceptibility mutations, with the aim of further refining risk estimates.

Discoveries made through application of genomic technologies and the human genome sequence have already had an effect on several aspects of oncologic practice and have influenced the design of clinical trials. In the next few years, the pace of research into cancer genomes will increase markedly. Coordinated global initiatives will generate full genome sequences of tens of thousands of cancers, yielding complete catalogues of somatic mutations in each one. These studies will reveal essentially the full repertoire of mutated cancer genes, moving us closer to establishing a central metric of cancer development: how many and what combinations of mutated cancer genes are necessary to generate an individual cancer. This will clarify the challenges that we face in cancer treatment. Coupled with these advances, more systematic functional screening of living cancer cells to detect their biologic vulnerabilities will undoubtedly lead to new directions in targeted drug discovery.

The technologies that are research tools today are primed to become the diagnostics of tomorrow. We have already seen limited RNA profiling introduced into clinical practice and testing for a restricted series of somatic genetic abnormalities to select the appropriate targeted therapy for individual patients. The rapid development of next-generation sequencing technologies seems likely to be transformative. Within a few years, a complete cancer genome sequence will be obtainable for a few hundred dollars or less. As the number of informative genetic abnormalities to be searched for in an individual cancer continues to increase, it may ultimately be more parsimonious to sequence the whole genome rather than do a large battery of directed tests. However, in order to exploit the full clinical potential of information within the cancer genome, it will first be necessary to incorporate analysis of the genome and transcriptome more widely into clinical trials, generating new and unexpected predictors of drug responsiveness and prognosis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES


