

The medical directors of the organ-procurement organizations can determine the ABO compatibility of the exchange pairs and the proximity of their centers and note the date of the listings. Equipose should be achieved in terms of the medical characteristics of the donors and recipients; therefore, donors and recipients should be aware of the medical characteristics of their exchange partners, even if anonymity is preserved. This revelation should allay any understandable apprehension about whether the two kidney transplantations have similar prospects of success. Nevertheless, each transplantation center should reevaluate the medical information of the other donor and recipient in keeping with its own standards. As with any kidney transplantation from a living donor, both the donor and the recipient must realize that there is no guarantee that the exchange will yield a successful outcome. Finally, these exchange procedures must comply with the National Organ Transplant Act of 1984, which prohibits monetary transfers or transfers of valuable property among donors, recipients, and brokers in sales transactions.

In New England, the two transplantation procedures take place simultaneously by design, even when they are performed in different centers that may be at distant locations. Each donor travels to the recipient's center. When these elements of the procedure are maintained, the risk that one donor will withdraw his or her commitment after the other donor has undergone nephrectomy can be avoided.

Exchange transplants in instances in which there

was cross-match incompatibility between recipients and their intended donors have been particularly gratifying. For example, a brother with blood type A who was incompatible with his sibling because of an A-to-B blood-type disparity donated his kidney to a man with blood type A who was sensitized to the HLA antigens of his wife, who had blood type O. The wife simultaneously donated her kidney to the exchange donor's brother (see Figure). A father with blood type A who could not donate his kidney to his daughter, who had blood type B, gave his kidney to a teenager with blood type A, and the teenager's sister provided a kidney for the exchange donor's daughter.

Clearly, we have come a long way since the first living-donor transplantation between twins, which was performed after skin grafts had been exchanged between the prospective donor and the recipient in order to verify their genetic identity. Half a century later, irrespective of genetic relationships, we are no longer impeded by either blood-type or cross-match incompatibility if we transplant kidneys from living donors as part of donor-exchange programs.

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## Translating Cancer Genomics into Clinical Oncology

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Clinical medicine is in the midst of a revolution that is being driven by an increasing understanding of the human genome and advances in molecular biotechnology. This revolution promises to transform clinical practice from population-based risk assessment and empirical treatment to a predictive, individualized model based on the molecular classification of disease and targeted therapy. The expectation

is, of course, that personalized approaches to clinical care will increase the efficacy of treatment while decreasing its toxicity and cost.

Nowhere is this transformation more apparent than in oncology. Cancer is a complex disease. Our current taxonomy of cancers, which is based mostly on histopathology, includes more than 200 distinct entities arising from diverse types of cells. In addition,

tion, tumors have somatic mutations and epigenetic changes, many of which are specific to individual neoplasms; these molecular abnormalities influence the expression of genes that control a tumor's growth, invasiveness, metastatic potential, and responsiveness or resistance to chemotherapy. The genetic complexity of cancer probably explains the clinical diversity of histologically similar tumors, but it has been difficult to study this diversity with traditional methods, which are best suited to investigating one gene at a time. The advent of DNA microarray technology, however, permits the quantitative measurement of complex, multigene expression patterns in cancer.

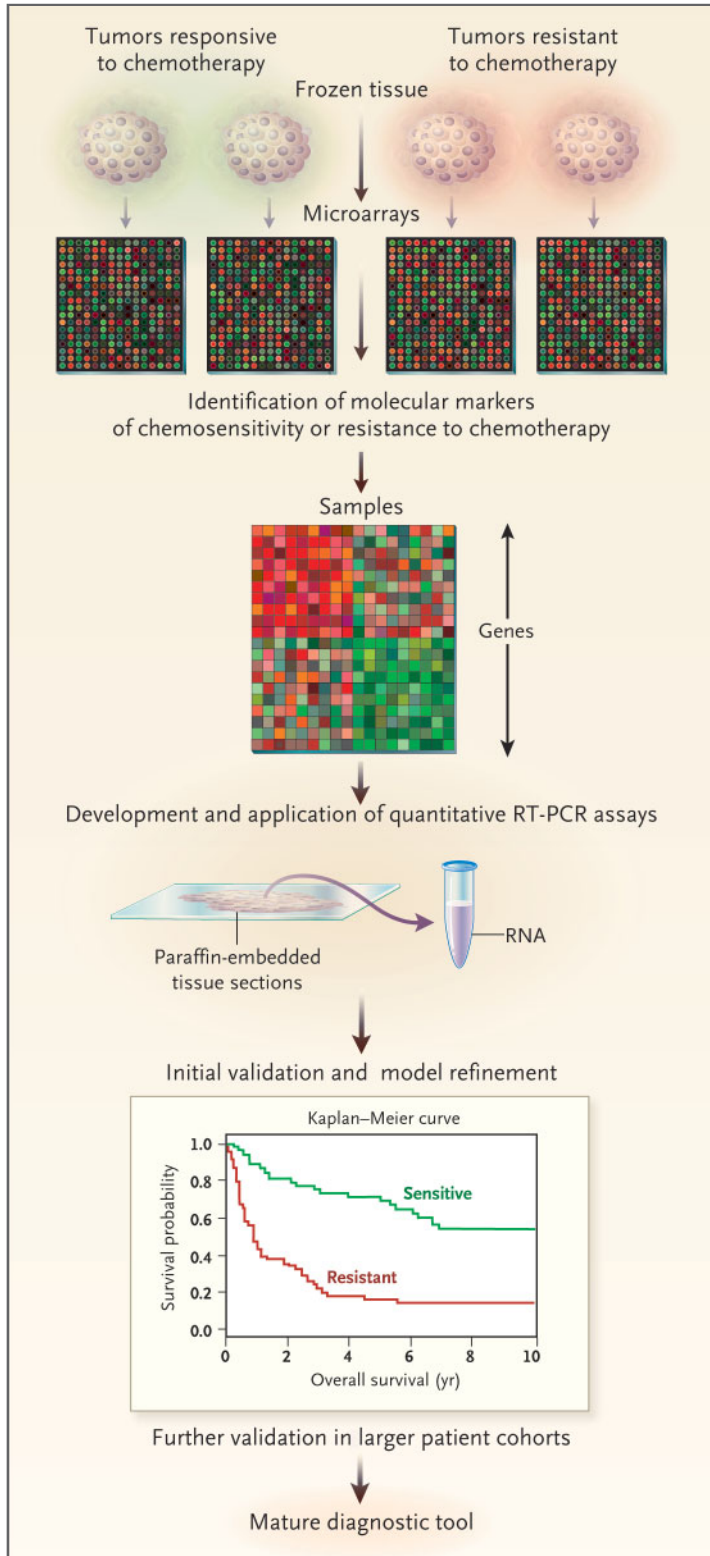
DNA microarrays display sets of nucleic acid polymers, immobilized on a solid surface, as probes for gene sequences. Microarrays are relatively easy to use, yield gene-expression measurements for thousands of genes simultaneously, and can be applied to large numbers of samples in parallel. The resulting gene-expression profiles can be used for the molecular classification of tumors according to their site of origin, their propensity to metastasize, and the likelihood that they will respond to treatment. Microarray-derived profiles can also yield insights into the molecular pathways that are associated with cancer. There is thus keen interest in creating a new generation of clinically useful diagnostic tests for cancer, based on gene-expression profiles, that can predict accurately the natural history of a tumor and the response to chemotherapy in individual patients.

Microarrays are wonderful tools for discovery, allowing researchers to obtain unbiased surveys of gene expression in tissue samples, but some have questioned their direct clinical application for individualized diagnosis and treatment planning. Microarrays have an appreciable failure rate and occasionally show significant interreplicate and interbatch variability in measurement. A second concern is that in a single sample, microarrays measure thousands of variables, most of which are irrelevant to the clinical end point under investigation. Complex statistical and computational tools are thus required to extract informative patterns from raw microarray data. Current technology also requires snap-frozen tissue for microarray-based gene-expression profiling. It is usually possible for established tumor banks to provide small frozen specimens for the initial discovery of clinically useful gene-expression profiles, but validation studies are often limited by the availability of tissue, since

tumor specimens are generally fixed in formalin rather than frozen. These limitations pose considerable obstacles to the routine use of microarrays in the clinical laboratory, where tests must be highly reliable and easy to interpret.

One strategy for translating microarray profiles into clinical tests is first to identify small, diagnostic gene-expression profiles with microarrays and then to validate the clinical usefulness of these genes either retrospectively or prospectively with the use of a simple, robust, conventional assay such as the quantitative reverse-transcriptase polymerase chain reaction (RT-PCR) (see Figure). This particular strategy is based on the assumption that there are small gene-sets (that are amenable to multiplexed PCR assays) for all interesting diagnostic distinctions. Although this assumption might not always be valid, it appears to be reasonable at first glance. A major virtue of this approach is that potentially useful gene signatures, initially discovered in frozen tissue with microarrays, can be validated with multiplexed quantitative RT-PCR in formalin-fixed, paraffin-embedded tissue sections, which are the global standard for pathological studies.

In this issue of the *Journal*, Lossos et al. (pages 1828–1837) use such a strategy to identify and validate a gene-expression signature specific to diffuse large-B-cell lymphoma that predicts the response to standard combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Their six-gene, PCR-based diagnostic test is independent of the International Prognostic Index and adds to it as a clinical measure of the likely outcome of treatment in patients with diffuse large-B-cell lymphoma. Thus, Lossos and coworkers have passed a milestone in the development of clinical diagnostic tests for cancer by moving from unbiased, genome-scale surveys of gene expression in human tumors to the creation and initial validation of a novel diagnostic tool that should fit easily into clinical practice and might refine the currently available measures used for risk stratification. This predictive tool stratifies populations of patients on the basis of a high, medium, or low response to treatment—categories analogous to the subgroups of patients defined by the currently available clinical measures. The evaluation of larger cohorts of patients should permit the development of probabilistic models for more accurate prediction of the likelihood of a response to chemotherapy in an individual patient. There are also early indications that



**Figure. Development of Microarray-Based Diagnostic Tests for Cancer.**

Primary or metastatic tumors are resected from patients; DNA microarray profiling is used to obtain gene-expression profiles of the tumors. Next, genome-wide computational and statistical analyses are used to identify gene-expression markers of responsiveness or resistance to chemotherapy; multiplex quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays are developed for the best markers, and these assays are applied retrospectively or prospectively to formalin-fixed, paraffin-embedded tissue sections. On the basis of the results, researchers develop diagnostic and predictive models that can then be validated in large cohorts of patients, resulting in a mature diagnostic tool.

it might be possible to work directly with fixed, paraffin-embedded tissue to discover new diagnostic signatures, with the use of either highly multiplexed RT-PCR assays or microarrays. If these alternative strategies are demonstrated to be generally feasible, the translational landscape will shift very rapidly. Time will tell.

Why should these developments interest the busy clinician? Oncology is spearheading the movement to an era of personalized diagnosis and treatment planning with the development and implementation of increasingly accurate molecular diagnostic tools. Although clinical diagnostic tests have traditionally taken a backseat to therapeutic agents in cancer medicine, change is at hand. In principle, it should be possible to create molecular diagnostic tools that can predict the response of all human tumors to single agents or combination chemotherapy, thereby allowing for precise, individualized matching of molecular diagnosis with treatment. Moreover, early studies in cancer genomics have focused on microarray-based RNA-expression profiling, teaching us how to grapple with complex biological data sets in the genomic era. Lessons learned from this initial experience are already informing our use of newer techniques for obtaining system-wide molecular views of disease. These advances have profound implications for the development of new drugs, the design of clinical trials, and the planning of treatment during routine patient care.

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