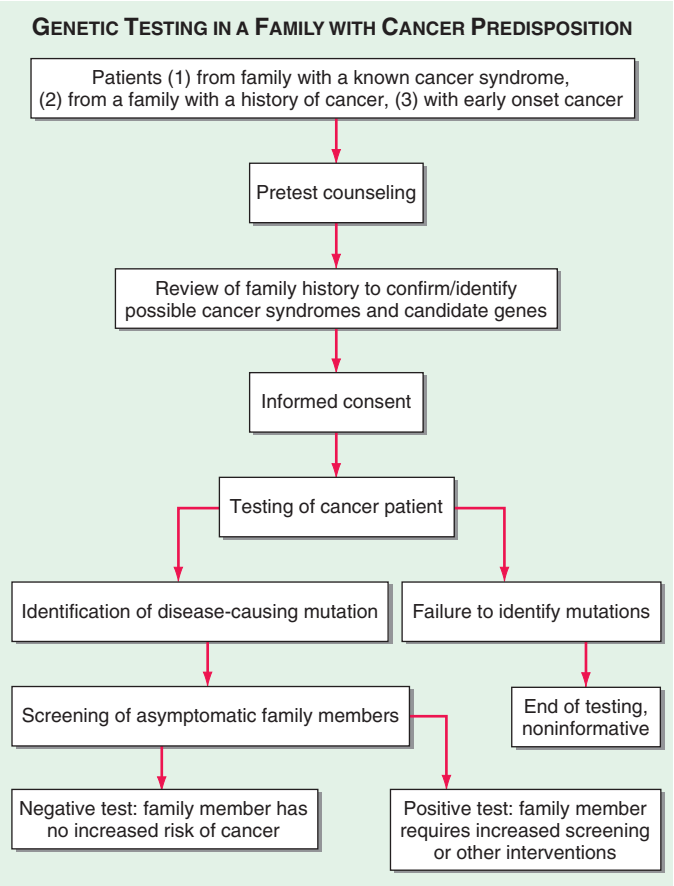

FIGURE 101e-6 Algorithm for genetic testing in a family with cancer predisposition. The key step is the identification of a mutation in a cancer patient, which allows testing of asymptomatic family members. Asymptomatic family members who test positive may require increased screening or surgery, whereas others are at no greater risk for cancer than the general population.

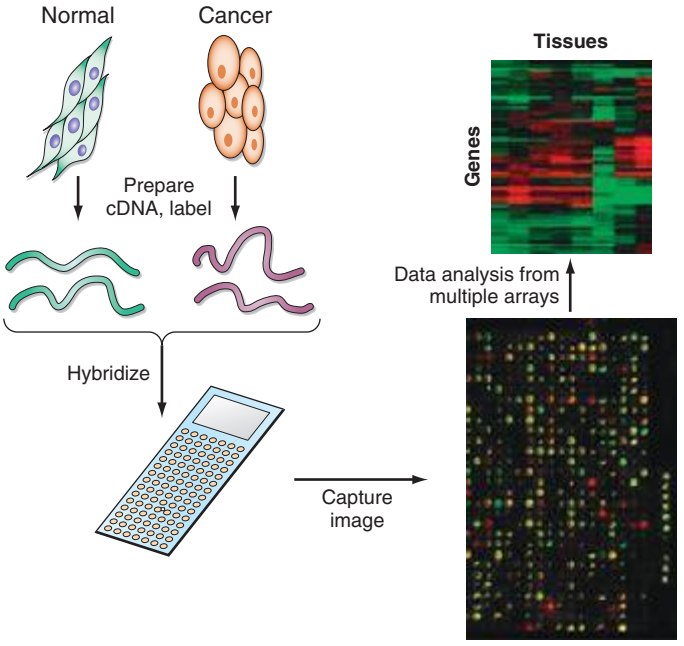

FIGURE 101e-7 A microarray experiment. RNA is prepared from cells, reverse transcribed to cDNA, and labeled with fluorescent dyes (typically green for normal cells and red for cancer cells). The fluorescent probes are mixed and hybridized to a cDNA array. Each spot on the array is an oligonucleotide (or cDNA fragment) that represents a different gene. The image is then captured with a fluorescence camera; red spots indicate higher expression in tumor cells compared with reference, while green spots represent the lower expression in tumor cells. Yellow signals indicate equal expression levels in normal and tumor specimens. After clustering analysis of multiple arrays, the results are typically represented graphically using a visualization software, which shows, for each sample, a color-coded representation of gene expression for every gene on the array.

revolutionize our approach to cancer prevention, diagnosis, and treatment. The International Cancer Genome Consortium (http://icgc.org/) was developed by leading cancer agencies worldwide, genome and cancer scientists, and statisticians with the goal to launch and coordinate cancer genomics research projects worldwide and to disseminate the data. Hundreds of cancer genomes from at least 25 cancer types have been sequenced through various collaborative efforts. In addition, exome sequencing (sequencing all the coding regions of the genome) has also been performed on a large number of tumors. These sequencing data have been used to elucidate the mutational profile of cancer, including the identification of driver mutations that are functionally involved in tumor development. There are generally 40 to 100 genetic alterations that affect protein sequence in a typical cancer, although statistical analyses suggest that only 8–15 are functionally involved in tumorigenesis. The picture that emerges from these studies is that most genes found mutated in tumors are actually mutated at relatively low frequencies (<5%), whereas a small number of genes (such as *p53*, *KRAS*) are mutated in a large proportion of tumors (Fig. 101e-8). In the past, the focus of research has been on the frequently mutated genes, but it appears that the large number of genes that are infrequently mutated in cancer are major contributors to the cancer phenotype. Understanding the signaling pathways altered by mutations in these genes, as well as the functional relevance of these different mutations, represents the next challenge in the field. Moreover, a detailed knowledge of the genes altered in a particular tumor may allow for a new era of personalized treatment in cancer medicine (see below). A major effort in the United States, The Cancer Genome Atlas (*http://cancergenome.nih.gov*) is a coordinated effort from the National Cancer Institute and the National Human Genome Research Institute to systematically characterize the entire spectrum of genomic changes involved in human cancers. Similarly, COSMIC (Catalogue of Somatic Mutations in Cancer) is an initiative from the Welcome Trust Sanger Institute to store and display somatic mutation information and related details regarding human cancers (*http://cancer.sanger.ac.uk/*).

PERSONALIZED CANCER TREATMENT BASED ON MOLECULAR PROFILES: PRECISION THERAPY

Gene expression profiling and genomewide sequencing approaches have allowed for an unprecedented understanding of cancer at the molecular level. It has been suggested that individualized knowledge of pathways or genes deregulated in a given tumor (personalized genomics) may provide a guide for therapeutic options on the tumor, thus leading to personalized therapy (also called precision medicine). Because tumor behavior is highly heterogeneous, even within a tumor type, personalized information-based medicine will likely supplement or perhaps one day supplant the current histology-based therapy, especially in the case of tumors resistant to conventional therapeutic approaches. Molecular nosology has revealed similarities in tumors of diverse histotype. The success of this approach will be dependent on the identification of sufficient actionable changes (mutations or pathways that can be targeted with a specific drug). Examples of currently actionable changes include mutations in *BRAF* (targeted by the drug vemurafenib) and *RET* (targeted by sunitinib and sorafenib), and *ALK* rearrangements (targeted by crizotinib). Interestingly, studies have reported that 20% of triple-negative breast cancers and 60% of lung cancers have potentially actionable genetic changes. Gene expression also offers the potential to predict drug sensitivities as well as provide prognostic information. Commercial diagnostic tests, such as Mammaprint and Oncotype DX for breast cancer, are available