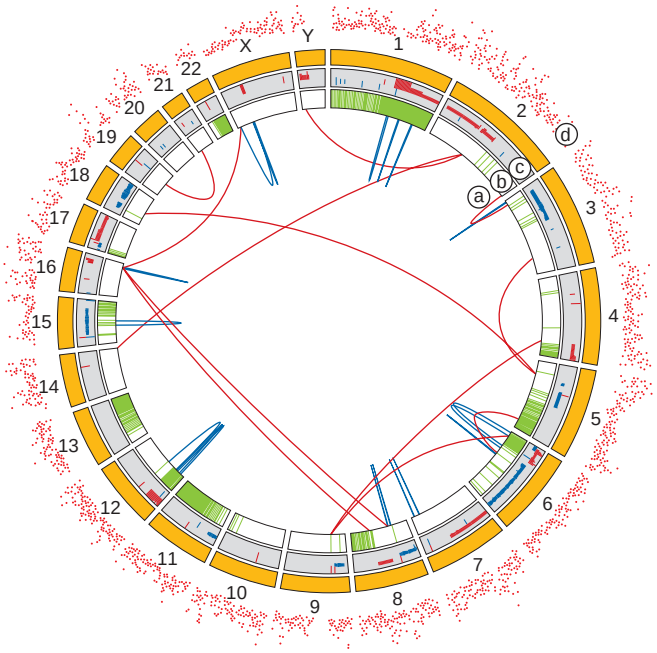

Figure 7-50 A circos plot showing genetic alterations in a single lung cancer in a male patient. Each of the 24 chromosomes in the cancer is displayed in a circle. The positions of various tumor-specific aberrations are mapped onto these chromosomes as follows: **a,** Structural rearrangements in chromosomes. The blue lines denote intrachromosomal rearrangements, while the red lines denote interchromosomal rearrangements. **b,** Regions of loss of heterozygosity and allelic imbalance (overrepresentation of one allele versus the second) are in green. **c,** Copy number profiles, showing copy number losses (in red), and copy gains (in blue). **d,** Point mutations, represented as red dots.

tumors such as lung carcinomas, which are genetically diverse and require a "personalized" approach if targeted therapy is to succeed. Thus, the current trend in molecular diagnostic laboratories is to develop methods that permit several hundred exons of key genes to be sequenced simultaneously at sufficient "depth" (fold coverage of the sequence in question) to reliably detect any mutations that might be present in as few as 5% of tumor cells. A second method that is moving rapidly into clinical practice involves the use of DNA arrays to identify changes in DNA copy number, such as amplifications and deletions. Arrays containing probes that span the entire genome at some standard spacing can detect all but the smallest copy number aberrations, providing information that is complementary to that obtained from DNA sequencing. Other "omics", such as proteomics and epigenomics, are currently being used mainly in the realm of clinical research, but with many drugs that target the cancer epigenome moving into the clinic, it can be anticipated that tests directed at assessing the state of the epigenome that predict response to such agents are soon to follow.

The excitement created by the development of new techniques for the global molecular analysis of tumors has led some scientists to predict that the end of histopathology is in sight. Indeed, with the advent of targeted therapies, it can be argued that we are in the midst of a paradigm shift in which the most important part of the work-up of a cancer sample is the identification of molecular targets, rather than histopathologic diagnosis (Fig. 7-51). For example, it is now appreciated that histopathologically distinct cancers all often harbor the same gain-of-function mutation in the serine/threonine kinase BRAF, a component of the RAS signaling pathway (Fig. 7-52). In principle, all of these diverse "BRAFomas" are candidates for treatment with BRAF inhibitors. However, early studies have shown that the effectiveness of BRAF inhibitors vary widely depending on histologic subtype: hairy cell leukemias with BRAF mutations appear to have sustained responses, melanomas respond transiently, and colon carcinomas respond little, if at all, for reasons that remain to be determined. In this specific case, one could argue that the lineage distinctions that seem to predict response to BRAF inhibitors could be made by expression profiling. However, histopathologic inspection of tumors also provides information about other important characteristics of cancers, such as anaplasia, invasiveness, and tumor heterogeneity. Histopathology coupled with in situ biomarker tests performed on tissue sections also remains the best way to assess tumor:stromal cell interactions, such angiogenesis and host immune responses; the latter may have an increasingly important role in guiding therapeutic interventions that are designed to counteract immune evasion by tumors. Thus, what lies ahead is not the replacement of one set of techniques by another. On the contrary, for the foreseeable future the most accurate diagnosis and assessment of prognosis in cancer patients will be arrived at by a combination of morphologic and molecular techniques.

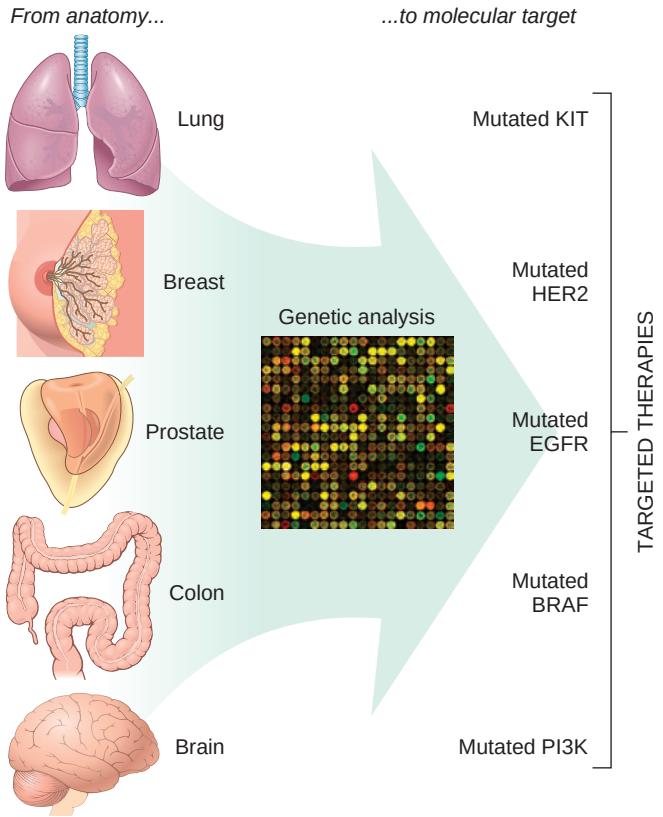

Figure 7-51 A paradigm shift: classification of cancer according to therapeutic targets rather than cell of origin and morphology. (Courtesy Dr. Levi Garraway, Dana Farber Cancer Institute.)