As we enter the twenty-first century, early detection followed by surgical intervention is the basic paradigm for advances in cancer treatment strategies [1]. On the horizon are new therapeutic techniques incorporating our understanding about the molecular biology of cancer. Notions of gene therapy are already becoming reality, indicating the rapid advance in this area. At present, early detection and knowledge about the clinical and biologic significance of precursor states will dictate appropriate therapy, and will therefore be the focus of this chapter. For genitourinary (GU) malignancies, we will explore issues related to conventional as well as molecular screening and try to put them in perspective. This will involve a brief comment on the natural history of common neoplasms in each part of the genitourinary system (bladder, prostate, kidney, and testis), which will set the groundwork for further discussion regarding the significance of finding known genetic or molecular abnormalities. The statement by Dr. Sidransky in 1993, ‘Regardless of the ultimate technique used or the precise gene markers, the identification of gene mutations in cytologic specimens will become an intimate part of cancer diagnosis and screening,’ is rapidly becoming reality [2].

Neoplasia: molecular concepts

Cancer genetics

Cancer is the result of an accumulation of genetic alterations, either activation of proto-oncogenes or inactivation of tumor suppressor genes which leads to a cascade of cellular events and results in abnormal cellular proliferation. An oncogene can be defined as a gene that when overexpressed contributes to carcinogenesis, progression, invasion, or metastasis, and a tumor suppressor gene is a gene that when lost contributes to the same. Point mutations are commonly found in human neoplasms and involve both oncogenes and tumor suppressor genes, including ras, p53, and APC, to name a few. The accumulation of such genetic changes provides a selective growth advantage to the cell population that contains them [3,4]. The goal of current tumor biology re-
search is to identify the key combination of genetic changes for each tumor type that leads to clinically significant events such as invasion or metastasis.

Tumor heterogeneity

Even though tumors are of clonal origin, by the time most are discovered or analyzed they contain tremendous heterogeneity. Heterogeneity within a single tumor exists at many levels, including cellular morphology, protein or mRNA expression, and alterations of the DNA template. Each of these levels is interrelated and dependent to a certain extent on the others. Heterogeneity is a two-edged sword: it contains tremendous information, but sampling the entire tumor is impossible. The results of any analysis of a neoplastic process are highly dependent on the sampling method and should take tumor heterogeneity into account. Doing so can be exceedingly difficult, however, because pathologic techniques examine only a minuscule fraction of the entire tumor. This is even more the case for molecular analysis than traditional histopathology. The heterogeneity found in advanced tumors is a sign of genetic instability, which in itself is an important marker of biologic behavior. It logically follows that the analysis of individual precursor lesions will not contain quite the heterogeneity of a malignant tumor that might facilitate their analysis. Also, many early genetic alterations are present in all subsequent subclones — a point exploited in many current molecular genetic analyses.

Multifocality

Synchronous head and neck tumors have been shown to have different p53 mutations, indicating that they were separate primaries rather than multifocal disease or local metastasis. Using this technique, it is possible to determine the primary origin of a lymph node metastasis [5]. Similar work is under way in bladder and prostate, both of which tend to be multifocal diseases. Work by Sakr et al. has shown that the metastases in prostate cancer are not always from the index (largest) tumor but can be from much smaller lesions with distinct genetic changes. This finding is good evidence that analysis of genetic alterations will have a role in predicting biologic behavior of tumors.

Screening and early detection

Screening definitions

Cancer screening can be defined as the process of examining a population (usually at high risk) to detect and diagnose cancer. Screening for malignancy can take place at many levels: history, physical exam, imaging, and pathologic analysis of fluids or tissues. This analysis of fluid or tissue can be at the level of the DNA template, the RNA transcript, the protein product, or the posttrans-