As of 2012, CTC measurements and the relevant correlations have not yet been *validated* as a tool for making clinical decisions (190). For this reason, this author refrains from disclosing studies that have shown correlations that are merely promising.

e. Epigenetics

Current research is addressing the possible utility of epigenetics tests for the diagnosis of, for example, lung cancer (191), breast and ovarian cancer (192), hepatocellular carcinoma (193), and Alzheimer's disease (194). To provide an example, the analysis of methylation of about 40 genes has revealed that this methylation can be used as a biomarker for *renal cancer*. Increases and decreases in methylation of specific genes are both used to produce a score.

In a study of *multiple myeloma*, the degree of methylation of the *NFKB1* gene was found to be associated with response to treatment with a particular drug, where lower levels of NFKB1 methylation were associated with longer survival during chemotherapy (195). Epigenetic markers have also been proposed for use in autoimmune disease, such as multiple sclerosis and rheumatoid arthritis (196,197). In *rheumatoid arthritis*, loss of methylation (hypomethylation) has been observed in specific genes in T cells and in synovial fibroblasts in patients with rheumatoid arthritis. The methylation changes in T cells cause these cells to be autoreactive, while the methylation changes in synovial fibroblasts cause them to be more susceptible to autoimmune attack. To give an example of a specific gene, loss of methylation of the *MMP13* gene causes increased expression of this gene, leading to degradation of type II collagen in cartilage (198).

VI. SINGLE NUCLEOTIDE POLYMORPHISMS

a. Introduction

SNPs are variants in the genome occurring naturally in the human population. SNPs is often pronounced as "snips." Each individual inherits one allele copy from each parent, so that the individual genotype at an SNP site is *AA*, *BB*, or *AB*. The Human Genome Project, the SNP Consortium, and other groups, have

[190]Hayashi N, Yamauchi H. Role of circulating tumor cells and disseminated tumor cells in primary breast cancer. Breast Cancer 2012;19:110–7.

[191]Nikolaidis G, et al. DNA methylation biomarkers offer improved diagnostic efficiency in lung cancer. Cancer Res. 2012;72:5692–701.

[192]Wittenberger T, Sleigh S, Reisel D, et al. DNA methylation markers for early detection of women's cancer: promise and challenges. Epigenomics 2014;6:311–27.

[193]Villanueva A, Portela A, Sayols S, et al. DNA methylation-based prognosis and epidrivers in hepatocellular carcinoma. Hepatology; 2015. http://dx.doi.org/10.1002/hep.27732.

[194]De Jager PL, Srivastava G, Lunnon K, et al. Alzheimer's disease: early alterations in brain DNA methylation at ANK1, BIN1, RHBDF2 and other loci. Nat. Neurosci. 2014;17:1156–63.

[195]Fall DG, et al. Utilization of translational bioinformatics to identify novel biomarkers of bortezomib resistance in multiple myeloma. J. Cancer 2014;5:720–7.

[196]Gupta B, Hawkins RD. Epigenetics of autoimmune diseases. Immunol. Cell Biol. 2015;93:271–6.

[197]Van den Elsen P, et al. The epigenetics of multiple sclerosis and other related disorders. Multiple Sclerosis Relat. Disorders 2014;3:163–75.

[198]Gupta B, Hawkins RD. Epigenetics of autoimmune diseases. Immunol. Cell Biol. 2015;93:271–6.