1. INTRODUCTION

The lack of clinical and laboratory markers that reliably predict response, side effects, or toxicity to therapeutic intervention poses a significant challenge in therapeutic decision-making. Consequently, rheumatologists and other physicians treating patients with rheumatoid arthritis (RA) must choose treatment regimens based on their own experience and assessment of the literature which usually consists of clinical trials of heterogeneous patient populations. With the US Food and Drug Administration's (FDA) approval of tumor necrosis factor (TNF) inhibitors such as etanercept (1) and infliximab (2), the era of targeted biological agents for the treatment of RA has begun. Biologic agents differ from traditional medications used for RA in their capacity to target specific pathophysiological pathways not previously accessible to focused therapeutic intervention. However, the expense of these medications (> $10,000/yr), their lack of universally positive clinical responses, and the risk of immunosuppression with regard to infections make the identification of markers for clinically significant responses both clinically and practically important.

Although the mechanism of action of biologic agents may be through molecular events "downstream" from those being directly inhibited, there is rationale for searching for genetic markers of disease within the targeted molecules or their ligands. By identifying genetic markers of treatment response (either positive or negative), rheumatologists hope to be able to stratify patients according to genetic determinants of likelihood of
response or toxicity. Genetic markers that can stratify patients based on their likelihood of response or toxicity may have an impact on clinical trials. For example, incorporation of pharmacogenetic analyses into clinical trials may reduce the number of patients required in phase III trials, but may increase the number of patients to be studied in postmarketing studies. Thus, an understanding of the genetics of clinical responsiveness has the potential to improve safety, cost-effectiveness, and clinical response rates by allowing treatment regimens to be individualized (3,4). It should be noted that although genetic tests may provide guidelines for pharmacologic management, they should not be used by medical insurers to disallow reimbursement for treatments with a particular drug.

GENETIC INFLUENCES ON TREATMENT RESPONSE AND TOXICITY IN HUMAN DISEASES

In the treatment of any disease, there are many factors that can influence response to drugs, including the severity and chronicity of the illness, liver and kidney function, patient age, concomitant treatment with other drugs, coexistent illnesses, and nutritional status (5). Genetic influences on response to drugs have been documented since the 1950s. For example, it was noted that inherited levels of erythrocyte glucose 6-phosphate dehydrogenase (G6PD) activity affected the likelihood of hemolysis after taking antimalarial medications (6). The explosive increase in human genetic information has influenced the field of pharmacology, fostering the burgeoning of pharmacogenetics and pharmacogenomics. For the purposes of this chapter, pharmacogenetics will be used in reference to the study of genetic variation underlying differential response to drugs; pharmacogenomics refers to the systematic application of genomics to discovery of drug-response markers (7).

Genetic markers useful in predicting treatment response or toxicity may lie in genes whose proteins are the target of the drug, are directly involved in the pathogenesis of the disease itself, or are enzymes that influence the metabolic or pharmacokinetic pathways of the drug (7). An example of a genetic marker in the drug target is the presence of coding and promoter polymorphisms in the serotonin receptor 5-HT2A gene, which influence response rates to the antipsychotic drug clozapine (8). For example, there is a polymorphism at position 452 of the 5-HT2A receptor in which either His or Tyr is encoded, based on the allele. In a sample of 153 schizophrenic patients, an association was found between the presence of the Tyr452 allele and poor clinical response to clozapine. A further analysis of multiple polymorphisms in the genes encoding adrenergic receptors, dopamine receptors, serotonin receptors, serotonin transporters, and histamine was performed. Genotypes at six polymorphisms (four in genes for serotonin receptors, one in a gene for serotonin transporter, and one in a histamine gene) yielded a sensitivity of 95% for predicting positive clinical response of schizophrenia to clozapine (9). In Alzheimer’s disease, the apolipoprotein E (apoE) gene is associated with neurofibrillary tangles and β-amyloid protein in the senile plaques. The presence of particular alleles of the apoE gene are associated with response of Alzheimer’s to treatment with tacrine (10). There are polymorphic variations in virtually all genes that encode enzymes involved in drug metabolism through modification of functional groups or through conjugation with endogenous substrates (reviewed in ref. 5).