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Genetics and Genomics: Novel Approaches in Cardiovascular Medicine

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Abstract

Significant advances have been made in clinical medicine in the past half century. The application of epidemiology has resulted in the identification of disease risk factors leading to preventive measures. Research in physiology, biochemistry, molecular and all biology has increased our understanding of pathophysiology and mechanisms of diseases leading to rationale strategies for therapy. The discoveries of new drugs and devices, and the extensive evaluation by clinical trials have improved significantly the management of diseases. As we approach the next millennium, we are at the verge of a genomic revolution. When the human genomic map is completed in the year 2004, and becomes readily available for clinical use, one may anticipate an explosion of new information as well as an enormous opportunity for investigating the genetic/genomic basis of diseases.

Genomic Medicine will involve the application of the genome science to the diagnosis, prognosis and therapy of diseases. Accordingly, clinical diagnosis will not be defined by phenotype only imaging, markers, morphology), but by specific genetic mutations and genomic variances. The natural history and the progress of specific diseases may be predicted by genomic analysis. Accordingly, treatment strategies (i.e. early intervention specific therapies in specific subgroups of patients) may also be based on genomic data.

Variances in drug target gene can influence binding affinity, dissociations, kinetics, conformational change, intracellular signaling, thereby affecting efficacy and/or pharmacokinetics. Differences in disease gene abnormalities can influence the overall natural history and prognosis, as well as drug response. Variances in metabolism genes, e.g. the cytochrome P450 system, may alter drug metabolism thereby affecting pharmacokinetics and safety. Accordingly, profiling of these genomic factors can result in population segmentation into responders vs. non-responders, severe vs. mild disease phenotype, likelihood of remission vs. recurrence, and poor vs. extrinsic metabolizers.

A crucial element in pharmacogenomic research is patient resources. Genetic analysis requires appropriate patient DNAs and phenotypes. Thus, a pharmacogenomic program should ideally have an existing patient data base, a DNA repository, disease phenotyping expertise as well as clinical trials data management capabilities. High-through-put technologies with process automation, rapid DNA and protein sequencing, transcription profiling with micro array DNA chip technology, computational biology and bio-informatics are essential ingredients for success. Thus, pharmacogenomic research will involve the interactions and collaborations of multiple disciplines and organizations, e.g. molecular

geneticists, clinical investigators, biostatisticians, bio technology, the pharmaceutical industry and possibly contract research organizations.

In the future, we can expect that each disease will be subclassified genetically, and not only by symptoms and phenotypes. Therefore, each patient's treatment will be individualized. The genomic stratification of patient populations will provide predictable and improved outcome. Another benefit is improved safety. Pharmaco-genomics will also improve cost effectiveness and may rescue drugs that failed clinical trial due to borderline efficacy and undesirable adverse effects. We believe that applied human genetics will revolutionize clinical medicine in the next millennium.