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Pharmacogenomics and Epigenetics: Update and Future Directions

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The goal of personalized medicine is to provide individualized treatment and to predict the clinical outcome of different treatments in different patients. Pharmacogenomics (PGx) is one of the core elements in personalized medicine. The basic concept is that interindividual variability in drug response is a consequence of multiple factors, including genomics, epigenomics, the environment and a patient's characteristics, such as gender, age and/or concomitant medication. PGx research has led to fundamental discoveries in the last decade, and a large resource of PGx traits has been generated in which variation in the gene sequence and/or variation in the expression of genes involved in the metabolism, transport and other drug targets are associated with alterations in drug response. Interindividual variability of expression and function with consequences on drug response is not only affected by genetic factors (e.g. clinical examples are the cancer drugs thiopurines, tamoxifen, methotrexate, irinotecan) but could be also explained by epigenomics (DNA methylation, histone modifications, regulation by miRNA). DNA hypermethylation results in gene silencing by direct inhibition of transcription-factor binding or by recruitment of methylated DNA-binding proteins. There is proof of principle for the clinical value of methylation markers for classification, prognosis and prediction of therapeutic response, and tissue-specific methylation alters the expression of selected ADME genes (Fisel et al. Clin Pharmacol Ther 2016, Clin Transl Sci 2018 in press). The large-scale, systematic epigenomic equivalents of GWAS, termed epigenome-wide associations studies (EWAS), are promising tools to determine specific drug-related phenotypes attributable to interindividual epigenomic variation. The new generation of -Omics technologies permits assessment of the entirety of the components of biological systems and produces an explosion of data and a major shift in our concepts of disease. These technologies will likely shape the future of health care. One aspect of these advances is that the data generated document the uniqueness of each human being in regard to disease risk and treatment response. These developments have reemphasized the concept of personalized medicine.

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