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Pharmacogenetics and clinical oncology: a new deal for personalized therapies

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The genetic basis of a differential response to drugs has been considered as the most challenging aspect of therapeutic evaluations on patients undergoing different treatments. This knowledge has generated hope that the individual basis for response to a wide range of drugs would be quickly known, and individualized drug selection and dosing would be possible for many or all disorders. Understanding the variable response to drugs seems particularly pressing in the field of oncology, being tumors as the most dangerous pathologic entity in which the stakes are high (failure to cure cancer usually leads to death) and where the drugs commonly used have a narrow therapeutic index. In addition, the toxicities of most chemotherapeutic agents can be severe and the need to better understand the correct posology is a crucial step point[1-3].

However, in common with many new technologies, the generalizability and clinical application of pharmacogenetics has proved more challenging than expected. Difficulties include, in many examples, a modest clinical effect relative to genotype, therapy-specific, not broad, applicability and the very major challenge of unraveling the complexity of gene-gene interactions. In addition, ethical and economic challenges to the application of pharmacogenetics have moved to the fore in recent years, particularly in the context of racial differences in outcome of therapy. However, greater understanding of the complexities of multiple gene modifiers of outcome, and the statistical challenge of understanding such data, will be needed before individualized therapy can be applied on a routine basis.

Differential response to the same drug in different patients is a common clinical experience. Many different factors may contribute to differential response including variable age and body size, diet, gastro-intestinal absorption, compliance with therapy and characteristics of the drug target, e.g., bacterial resistance to a specific antibiotic or mutation in the EGFR receptor in lung cancer treated with gefitinib. The heritable component of the variable response to gefitinib was recognized as a consequence of fast and slow metabolizers of drugs such as debrisoquine and isoniazid, and of a variable response to the anti-inflammatory phenylbutazone[4,5]. A significant genetic component in the metabolism of phenylbutazone was reported in a study published in *Science* in 1968[5]. This gloriously simple study used pairs of volunteer fraternal or monogenic twins, administered a dose of phenylbutazone and monitored clearance. The data showed close concordance of pharmacokinetic profiles between monogenic twins and significantly more variation between fraternal twins. Understanding the variable response to drugs seems particularly pressing in the field of oncology. In one of the first examples of pharmacogenetics in oncology, Weinshilboum and Sladek identified polymorphic responses to the key antileukemic drug, 6-mercaptopurine (6-MP) in 1980, and polymorphism of the gene thiopourine S-methyl transferase (TPMT) remains one of the best understood examples of pharmacogenetic variation[6]. It is of obvious interest to consider that in the last 10 years many new genetic approaches, understanding the functionality of polymorphisms affecting genes regulating drug metabolism, have boosted the application of personalised treatments for drugs. However, the capacity to completely overcome the variability on drug-related response applies on our capacity to fully understand the variability of human genome.

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