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Will pharmacogenomics guide clinical practice?

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Very seldom has a field been launched at a more auspicious time. Pharmacogenomics emerged as the sequencing of the human genome was nearly complete, as DNA arrays were becoming everyday tools for the assessment of the expression of thousands of genes in one rapid experiment, and when proteomics makes it possible to efficiently pair up transcriptional and translational data. Yet, the powerful techniques used today have not led to conclusive pharmacogenomic data in many areas. Personalized medicines are still a promise, not a reality.

A specific case of inadequate translation of research into clinical medicine is presented by the cytochrome P450 genes, particularly CYP2D6 (located on human chromosome 22), which modulates the pharmacokinetics of multiple widely used drugs, including analgesics (fentanyl, meperidine, codeine, oxycodone, propoxyphene), beta-blockers (timolol, pindolol, propanolol, labetalol, metoprolol), antidepressants (amitriptyline, fluoxetine, paroxetine, venlafaxine, trazadone), antipsychotics (clorpromazine, haloperidol), antiarrhythmics (flecainide, propafenone), antialergics, and others. CYP2D6 contributes to the metabolism of a fourth of all drugs, including half of the 100 best selling medicines. The CYP2D6 gene has been well studied and shown to have at least 53 alleles. More than 20 of those alleles significantly alter the metabolism of CYP2D6 substrates. A sizeable minority of individuals has CYP2D6 gene deletion or gene duplication. CYP2D6 gene deletion, which occurs in 6–10% of Caucasians, 0.5% of Japanese, 0.7% of Chinese and 6% of African-Americans, can lead to increased levels of drugs that are metabolized by that pathway and can result in severe adverse drug reactions.

The number of Americans who died in hospitals from adverse reactions (ADRs) to FDA-approved drugs properly administered by licensed medical professionals has been estimated to range from 30 000 to 108 000 per year. ADRs are thought to be the fourth leading cause of death and the single largest source of malpractice payouts in the US. In comparison to the death toll of ADRs, the total number of American casualties in the Vietnam War was 58 135, and in World War II it was 300 000. In summary, the testing for CYP2D6 genotype can be rapidly and reliably done; it is of considerable public health relevance. Yet such testing is not routinely performed, and it does not guide clinical therapeutics today. Meanwhile, enormous amounts of time and resources are spent in our efforts to discover predictors of outcome for various drugs, with the long-term objective of developing tests that would identify *a priori* patients' drug responses. In this context it is hard to understand that as new knowledge and technologies are sought in pharmacogenomics, knowledge and technologies that are already available are not routinely used to guide clinical practice.

Why is there such a disconnect between research and clinical practice in this field? Possible reasons may include lack of physician awareness of the importance of certain genotypes in the practice of clinical pharmacology and therapeutics. Additionally, because CYP2D6 is involved in the metabolism of so many drugs, it is not the major focus of a single specific, disease-based subspecialty. It is also unclear who would cover the costs of such tests. Would those be covered by medical insurance or would they be considered 'research'? It may very well be that the lack of application of existing pharmacogenetic testing in clinical practice is overdetermined by a combination of the need to contain escalating medical costs and intense competition for physician's time as medical encounters become shorter, while the availability of medical data, including new drugs, explodes.

As we attempt to elucidate genomic predictors of drug response, we must also identify the reasons why known genotypes are not tested in the clinic, and actively pursue efforts to translate existing knowledge into practice.

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