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## Pharmacogenetic Testing—An Unfulfilled Promise

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The Human Genome Project heralded great hope that the clinical use of individual genetic information would result in improved care through treatments tailored to an individual patient's genotype. Such treatment would presumably reveal individual susceptibility to chronic diseases, thus preventing them, and lead to targeted pharmacotherapies based on an individual's metabolism and susceptibility to adverse drug effects.

Some say the influence of genetic testing is the next great paradigm shift in medicine, rivaling the changes that occurred after the discovery of microbes and their role in infectious diseases. However, progress has been much slower than anticipated.<sup>1</sup> There are few gene-based therapies in use, mostly in the area of cancer treatment, and even fewer have evidence of improved patient outcomes. Chronic disease prediction has resulted in marginal increases in odds ratios of questionable significance, and there is no evidence that this knowledge changes behavior to reduce risk.

Pharmacogenetics, up to now, has not been adopted in daily primary care practice in any meaningful way. Early on, the poster child for pharmacogenetic testing was warfarin (Coumadin). With its narrow therapeutic window, its high rate of complications from over and under dosing, and the discovery that physicians could predict individual metabolism rates through testing for specific gene variants, it seemed the perfect candidate for application of pharmacogenetics. Proponents of personalized medicine predicted that cytochrome P450 2C9 testing would lead to markedly reduced rates of adverse effects when used before starting warfarin therapy. Missing from all of the early enthusiasm was evidence in actual clinical practice, and as clinical trials were conducted and completed, it became

apparent that gene testing offered little to no clinical utility.<sup>2,3</sup> Although it helped make the initial warfarin dose estimate more accurate, leading to a slightly reduced time to reach steady-state international normalized ratio, it did not lead to a decrease in adverse events. Testing of international normalized ratio still has to be performed with regular dose adjustments, with or without gene testing. If widespread use of this test had been adopted before the clinical evidence had been accumulated, the result would have been no change in important outcomes and increased costs from an expensive and marginally useful test.

In this issue of *American Family Physician*, Chang and colleagues describe two possible pharmacogenetic tests and suggest when they could be useful.<sup>4</sup> The first is *CYP2D6*, which the authors say should be considered in patients who have no response to codeine or tramadol (possible poor metabolizers) or who have unexpected adverse effects (possible ultrarapid metabolizers). However, gene testing may not offer any advantage over simply switching to morphine, oxycodone, buprenorphine, fentanyl, or nonopioid analgesics for patients who do not respond well to codeine, tramadol, hydrocodone, and oxycodone. A review by the Clinical Pharmacogenetics Implementation Consortium recommends standard doses of codeine for those known to be extensive and intermediate metabolizers,<sup>5</sup> so it is not evident that genetic information is that clinically useful at either end of the spectrum, and it has not been demonstrated to be useful in controlled clinical trials.

Although *CYP2C19* testing before prescribing clopidogrel (Plavix) in patients undergoing percutaneous coronary intervention for acute coronary syndromes may be considered, no clinical practice guidelines currently recommend it, and clinical trials and systematic reviews have raised serious questions about its clinical utility.<sup>6,7</sup> The guideline that Chang and colleagues

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cite specifically states that it does not recommend *CYP2C19* testing before starting clopidogrel in every patient undergoing percutaneous coronary intervention.<sup>8</sup>

Chang and colleagues conclude with an acknowledgment that there is a paucity of randomized controlled trials on the use of pharmacogenetic testing. They are correct that family physicians need to learn more about the topic of pharmacogenetics, but the emphasis should be on how to assess tests and their utility, not on the adoption of testing based on low-level evidence.

Family physicians should not naively accept a new technology because it is the latest trend. We need to assess the clinical utility of potential applications of genetic information, adopting them when they improve patient-oriented outcomes and avoiding them when they simply add costs for little to no benefit.

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