The cohabitation of art and genomic science

The art of medicine includes picking the right drug for the right patient, especially when we can choose between different classes of efficacious therapies. But, in view of our growing understanding of the human genome, can science replace art?

That question is part of the promise of pharmacogenetics, the study of how interindividual genetic differences influence a patient's response to a specific drug. A patient's genome dictates the expression of specific enzymes that metabolize a drug with various efficiencies: variant alleles may result in slightly different proteins that express different enzymatic activity, ie, different substrate affinities for a drug resulting in more or less efficient metabolism. Genomic differences may also dictate whether a specific biochemical pathway is dominant in generating a specific pathophysiologic response, in which case drugs that affect that pathway may be strikingly effective. This may partly explain the various responses to different antihypertensive drugs.

Another less well-understood example of pharmacogenetics is the link between specific *HLA* haplotypes and a dramatic increase in allergic reactions to specific medications, such as the link between *HLA-B*57:01* and abacavir hypersensitivity.

In this issue of the *Journal*, DiPiero et al (page 409) discuss thiopurine methyltransferase (TPMT), an enzyme responsible for the degradation of azathioprine, and how knowing the genetically determined relative activity of this enzyme should influence our initial dosing of this and related drugs. Patients with certain variant alleles of *TPMT* degrade azathioprine more slowly, and these patients are at higher risk of myelosuppressive toxicity from the drug when it is given at the full weight-based dose. The TPMT test is expensive but not prohibitively so, and it would seem that genomic testing is a reasonable clinical and cost-effective option.

As in the abacavir scenario noted above, genomic-based dosing of azathioprine makes scientific sense and offers proof of principle for the validity of pharmacogenomics. But is it truly a clinical game-changer?

The answer depends in part on how the prescribing physician doses the drug, which depends in part on what disease is being treated, how fast the drug needs to be at full dose, and whether there are equally effective alternatives. Recommendations have been offered that state if TPMT activity is normal, we can start at the usual maintenance dose of 1.5 to 2 mg/kg/day (or occasionally more). But if the patient is heterozygous for the wild-type gene and thus is a slower drug metabolizer, then initial dosing "should" be reduced to 25 to 50 mg/day, with close observation of the white blood cell count as the dose is slowly increased to the target. The very rare patient who is homozygous for a non–wild-type allele should not be given the drug.

My usual practice has been to start patients on 50 mg or less daily and slowly titrate up, asking them how they are tolerating the drug and watching the white count—notably, the same approach to be taken if I had done genotyping before starting the drug and had found the patient to be heterozygous for the *TPMT* gene.

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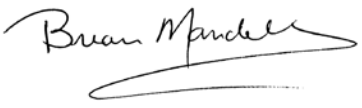
Interestingly, one pragmatic clinical trial tested whether genotyping patients before starting azathioprine—with subsequent suggested dosing of the drug based on the genotype as above—was safer and cheaper than letting physicians dose as they chose.[1] It turned out that physicians participating in this study still dosed their patients conservatively. Even knowing that they might be able to give full doses from the start in patients with normal TPMT activity, many chose not to. I assume that many of those physicians felt as I do that there was no urgency in reaching the presumed-to-be-effective full weight-based therapeutic dose. (We don't have a good clinical marker of azathioprine's efficacy). At 4 months, the maintenance dose was about the same in all groups.

We have robust evidence to support the role of pharmacogenetics in informing the dosing of several medications, more than just the ones I have mentioned here. And in the right settings, we should use pharmacogenetic testing to limit toxicity and perhaps enhance efficacy in our drug selection. As the field moves rapidly forward, we will have many opportunities to improve clinical care by using our patients' genomic information.

But like it or bemoan it, even when we have science in the house, the art of medicine still plays a role in our clinical decisions.



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1. **Thompson AJ, Newman WG, Elliott RA, Roberts SA, Tricker K, Payne K**. The cost-effectiveness of a pharmacogenetic test: a trial-based evaluation of TPMT genotyping for azathioprine. Value Health 2014; 17:22–33.