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Letters to the Editor

Considerations for the Utility of the CPIC Guideline for *CYP2D6* Genotype and Codeine Therapy

To the Editor:

We appreciate the recent Perspective from Nicholson and Formea *(1)* because it allows us to clarify the role of Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for clinicians. CPIC publishes genotype-based drug therapy guidelines to help clinicians understand how genetic test results could be used to optimize drug therapy. The underlying assumption for CPIC guidelines is that clinical high-throughput and preemptive genotyping will become common practice and clinicians will increasingly have patients' genotypes, such as a cytochrome P450, family 2, subfamily D, polypeptide 6 (*CYP2D6*) genotype test result, available before a prescription is written *(2, 3)*. Therefore, CPIC guidelines provide guidance on how to interpret available genetic test results to improve drug therapy. For example, patients carrying 2 nonfunctional alleles that give rise to CYP2D6 poor metabolizer status derive little or no pain relief from codeine and tramadol. Thus the CPIC guideline recommends avoiding their use in these patients due to lack of efficacy and to use alternative pain medications. The guideline discusses that although alternatives might include hydrocodone or oxycodone, both have limitations. The guideline states that "there is insufficient evidence to conclude whether poor metabolizers can be expected to have decreased analgesia or whether ultrarapid metabolizers have an increased risk of toxicity with normal doses of hydrocodone," and that "it is difficult to conclude whether CYP2D6 metabolizer phenotype affects oxycodone analgesia or risk of toxicity." However, we acknowledge that a quick read of Table 2 of the guidelines, rather than the text, might be taken as strong advice against the use of hydrocodone and oxycodone in patients with high-risk *CYP2D6* genotypes. Nonetheless, for the reasons stated in the text, and with the evidence provided in the supplement, we think it wise to alert prescribers to possible problems with hydrocodone and oxycodone in poor and ultrarapid metabolizers of CYP2D6.

Nicholson and Formea comment that "many healthcare providers follow a WHO ladder 'type' approach for the treatment of pain." They express valid concern that the entire second step includes opioids "commonly used for moderate pain (e.g., tramadol, codeine, hydrocodone, and possibly oxycodone)" that overlap with medicines that the CPIC guideline recommends avoiding (codeine and tramadol) or for which concerns are noted (oxycodone and hydrocodone). We agree with Nicholson and Formea that this creates a problem for prescribers, in that the third step includes opioids "usually reserved for severe pain presentation (e.g., morphine, oxymorphone, fentanyl, methadone, and hydromorphone)" and may be less familiar to practitioners.

However, the fact that these step 3 agents may be more difficult to use and prescribe does not negate the fact that they are alternatives to codeine and tramadol, and are not subject to concerns about *CYP2D6* genotype. Although we agree with Nicholson and Formea that for "moderate pain where an opioid might be required (e.g., musculoskeletal pain, toothache), it is unlikely that the provided alternatives would be an appropriate opioid choice for routine use," the CPIC guideline is recommending these alternatives for the minority of the population with a pharmacogenetic profile that poses them at risk of therapeutic failure or adverse effects. It is exactly these patients who may require step 3 analgesics. The fact that prescribing these agents is more difficult should not deter physicians from choosing more appropriate treatment to achieve pain relief in patients with at-risk *CYP2D6* genotypes.

Finally, Nicholson and Formea suggest that CPIC guideline recommendations for analgesic alternatives may be readily accepted without consideration of the complex interplay between clinical care and the proper application of pharmacogenomics. The guideline includes the caveat that "like all diagnostic tests, that for *CYP2D6* genotype is one of multiple pieces of information that clinicians should consider in guiding their therapeutic choice for each patient." The *CYP2D6* and codeine guideline, like all published CPIC guidelines, includes the statement that "Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for a patient."

We thank Nicholson and Formea for their valuable feedback about the applicability of the CPIC guideline for *CYP2D6* and codeine. When choosing analgesic therapy, healthcare providers must keep the whole patient in mind. We conclude that the goal of this CPIC guideline is to allow pharmacogenetic test results to serve as a tool to individualize analgesic prescribing for acute or chronic pain and thereby enable the clinician to make more rational treatment decisions.

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