

June 4, 2009

Harold C. Sox, MD  
Annals of Internal Medicine  
190 North Independence Mall West  
Philadelphia, PA 19106-1572

Dear Dr. Sox:

Given the FDA's decision to include on warfarin labels a suggestion to consider genetic testing prior to dosing, we read with interest the thoughtful analysis of studies to date on genetic testing for warfarin sensitivity ("Cost-Effectiveness of Using Pharmacogenetic Information in Warfarin Dosing for Patients With Nonvalvular Atrial Fibrillation," 1/20/09, Volume 150, Issue 2, pp. 73-83). The authors' finding that warfarin testing is not cost-effective is reasonable based on the studies they examined, and we appreciate the inclusion of caveats that could potentially change that conclusion. We would like to highlight a few of those points, based on rapidly emerging developments in this field.

**Cost.** The authors assumed that genetic tests would cost \$400, the price that might be paid by a consumer who seeks an independent test from a lab. With more widespread use of the tests, costs for hospitals or clinics are now much lower, as low as \$50-\$75 per test, or about \$150 to \$225 if positive and negative controls are run with each test. As the authors note, a \$50 test is in fact cost-effective. Given the advances in technology, we suspect the price point will drop further and therefore, make this test not only cost-effective but also beneficial ("clinically worthy") to the patient.

**Timing.** In their analysis, the authors assume that it would take about three days to get a result from a genetic test. This time frame was reasonable when the underlying studies were done, given that few labs processed the tests at that time. Today, the tests can be turned around in as little as 45 minutes from patient to calculated dose, with most in the range of two to six hours and results obtainable in no more than 24 hours. While it is difficult to calculate the cost-effectiveness of a quicker test, some studies suggest that it will result in fewer adverse events, simply because patients could be given a more appropriate dose more quickly.<sup>i,ii,iii</sup>

Finally, we are concerned that the underlying studies, among others, examine the number of bleeding events as a way of determining whether treatment is effective. Bleeding is a relatively rare event, even more so in many of these studies, since it is unlikely that caregivers in state-of-the-art anti-coagulation clinics or clinical research (academic medical centers of excellence) settings would have failed to adjust a patient's warfarin dose

before bleeding could occur. Alternative measurements, that are possibly superior, are the number of dose adjustments (times a patient must get a new prescription filled or visit a clinic for an INR measurement), change between initial and final warfarin dose, or time to stable INR, in order to measure whether the genetic test resulted in more accurate initial dosing.

As we are all aware, these are serious issues. Errors in warfarin dosing result in 17,000 strokes and 85,000 serious bleeding events each year, and as many as 43,000 emergency room visits. If the 2 million people who start taking warfarin each year are able to receive a more accurate dose more quickly, the benefit to patients might be immense, with substantial healthcare cost savings.

Regards,

Charis Eng, M.D., Ph.D.

Chair, Genomic Medicine Institute  
Cleveland Clinic  
Co-chair, Clinical Science Committee  
Personalized Medicine Coalition

Jeffrey Cossman, M.D.

Chief Scientific Officer  
Critical Path Institute  
Co-chair, Clinical Science Committee  
Personalized Medicine Coalition

---

<sup>i</sup> Influence of CYP2C9 and VKORC1 on warfarin response during initiation of therapy. *Blood Cells Mos Dis*. 2009 Mar 16.

<sup>ii</sup> Effects of CYP2C9 and VKORC1 on INR variations and dose requirements during initial phase of anticoagulant therapy. *Pharmacogenomics*. 2008 Sept;9(9):1237-50.

<sup>iii</sup> Frequency of adverse events in patients with poor anticoagulation: a meta-analysis. *CMAJ*. 2007 May 22; 176(11): 1589–1594.