left ventricular systolic and/or diastolic dysfunction either in asymptomatic or symptomatic patients, that is, stage B or C of the definition of heart failure, according to the classification of the American Heart Association/American College of Cardiology task force for the diagnosis and management of chronic heart failure (3).

One important finding of our metaanalysis (1) is represented by the heterogeneity of data published on the comparison of diagnostic accuracies of BNP and NT-proBNP, especially for studies concerning chronic heart failure. Evidently, the large variability of these data may be decreased if statistical analyses are performed separately for specific clinical conditions (e.g., systolic or diastolic dysfunction), as suggested by Mueller. However, this approach may not be feasible at this time, considering the small number of studies comparing the diagnostic accuracies of BNP and NT-proBNP. In conclusion, further studies are needed to evaluate differences in diagnostic accuracy of BNP and NT-proBNP assay in patients with heart failure.

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Genetic Factors for Warfarin Dose Prediction

To the Editor:

Warfarin, a commonly prescribed anticoagulant drug used to prevent thrombosis, has a narrow therapeutic range, and small dose variations may result in hemorrhagic or thrombotic complications. The 2 key enzymes in the metabolism of warfarin are cytochrome P450 (CYP) 2C9 (CYP2C9 gene) and the C1 subunit of the vitamin K 2,3 epoxide reductase complex (VKORC1 gene). CYP2C9 accounts for up to 85% of the metabolism of the pharmacologically more potent S-warfarin enantiomer, and VKORC1, the 2nd key enzyme in warfarin metabolism, is responsible for recycling reduced vitamin K. In their recent article, Zhu et al. (1) concluded that genotyping both VKORC1 and CYP2C9, in conjunction with patient physical characteristics facilitated more precise estimation of warfarin dose and thus improved the efficiency of the dosage titration process. This conclusion was supported by the evidence that VKORC1 and CYP2C9 genotypes, age, sex, and body weight accounted for 61% of the variance in warfarin daily maintenance dose. The findings of Zhu et al. (1) are consistent with earlier findings of Caldwell et al. (2), which demonstrated that CYP2C9 and VKORC1 each contribute substantially to dose variability and, together with clinical factors, explain 56% of the individual variability in stable warfarin dose. Taken together, these studies support the hypothesis that the formulation of dense genetic maps on the basis of single-nucleotide polymorphisms is an important approach to elucidating polygenic traits of drug response and, in combination with appropriate nongenetic factors, might help to define a warfarin dose-response phenotype.

We wish to point out additional aspects in the challenging endeavor to individualize warfarin therapy. First, the single contribution of the VKORC1 and CYP2C9 gene polymorphisms accounts for approximately 27% and 22% of the variability of maintenance dosage, respectively (1). Therefore, the aggregate variability of warfarin dosage explained by these 2 genes approaches 50% provided that other nongenetic factors are maintained fairly steadily throughout the titration period. Second, synthetic preservative substances, such as benzethonium chloride, are potent inhibitors of CYP2C9 activity in vitro, producing unpredictable effects of warfarin therapy (3). Third, the effectiveness of therapy is affected by numerous variables including drug interactions, illnesses, dietary or gastrointestinal features that alter the bioavailability of vitamin K, and physiologic variables that modify the synthetic or metabolic fate of the vitamin K-dependent coagulation factors. Thus, genetic algorithms might be efficient only when all these variables are stable (4). Finally, CYP2C9 genotyping may not be useful in African-Americans or as a marker of long-term over-anticoagulation once a stable dose is reached (5).

Although individualization of therapy based on genetic factors has great potential to improve efficiency and safety of the dosage titration process, genetic variability explains only a large fraction, not all, of the interindi-
individual variation in warfarin dosage. Prospective studies that incorporate both gene testing and a variety of ethnic, clinical, pharmacological, and environmental variables, along with age, sex, and body weight, will be required to demonstrate the real safety, cost-effectiveness, and feasibility of individualized dosing regimens according to the statistical models for warfarin dose calculation.

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Evaluation of Analytical Performance of the Siemens ADVIA Tnl Ultra Immunoassay

To the Editor:

In light of recommendations on the quality (1) and clinical use (2) of troponin assays, we evaluated the analytical performance of the ADVIA Centaur and ADVIA CP® platforms (Tnl-Ultra, Siemens Medical Solutions Diagnostics SrL) for measurement of cardiac troponin I (cTnl). The chemiluminescent Tnl-Ultra method uses 2 monoclonal capture antibodies directed to epitopes at amino acids 41–49 and 87–91 and a tracer polyclonal goat antibody labeled with acridinium ester, directed against amino acids 27–40 (1, 3, 4).

Two clinical laboratories participated in the study: the CNR Institute of Physiology in Pisa and the San Bortolo Hospital in Vicenza.

The limit of detection (limit of the blank) for the Tnl-Ultra method was calculated as the concentration corresponding to a signal of 3 SD above the mean of 60 replicates (obtained in 4 different runs and pooled together) for the calibrator in which cTnl was absent; a mean cTnl concentration of 0.006 μg/L was found. The total imprecision (CV%) of the Tnl-Ultra method, assessed according to the NCCLS EP5-A protocol over 20 consecutive working days, was 11.6%, 5.6%, and 4.4% for 3 plasma samples with cTnl concentrations of 0.05, 0.25, and 2.68 μg/L, respectively. From plots of CV vs log-transformed concentrations that corresponded to 10% CV and so an arbitrary concentration of 0.006 μg/L was attributed to these samples. A highly significant correlation was found between cTnl values and age (R = 0.268, P < 0.0001 by Spearman rank correlation coefficient test). Moreover, a significant difference was found between the cTnl values found in men and women, respectively [mean (SD) 0.015 (0.018) μg/L, median 0.012 μg/L, range 0–0.196 μg/L, n = 204 for men; 0.009 (0.014) μg/L, 0.008 μg/L, 0–0.130 μg/L, n = 214 for women; P < 0.0001 by Mann–Whitney U-test]. We found that both sex (as a dummy independent variable with F = 1 and M = 2) and age (as a continuous independent variable) independently contributed to the regression with cTnl (as a dependent variable after log transformation of original values) by using a stepwise multiple regression analysis (log cTnl = −3.164 + 0.456 sex + 0.007 age; P < 0.0001, F-value = 71.962, R = 0.508, n = 416).

A close linear relationship was found between cTnl values measured by ADVIA Tnl-Ultra with the Centaur CP® platform and the Access AccuTnI method on the UniCell® DxI 800 platform (Beckman Coulter) in 318 plasma samples of 155 apparently healthy individuals and 163 cardiac patients (ADVIA = 0.016 + 1.272 Access; R = 0.936). The Tnl-Ultra method showed higher cTnl values than the Access AccuTnI.